Current thinking on PNH

David J. Araten, MD

Assistant Professor NYU School of Medicine
Agenda

• Introduction to blood cells, CBC, and PNH (David)

• Long Term Issues in PNH (Monica)

• Current Treatments (David)

• Case Presentations (Both, comments from audience)

• Questions from audience
Marrow

red cell

neutrophil (granulocyte)

platelets
Red blood cell

Oxygen from lungs

Hemoglobin molecules

Oxygen bonded with hemoglobin molecules

Oxygen released to tissue cells
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**DIFFERENTIAL**

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<td><strong>LYMPH</strong></td>
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<td><strong>MONO</strong></td>
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<tr>
<td><strong>EOS</strong></td>
<td>1.0</td>
<td>[0-7] %</td>
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**RETICULOCYTE COUNT** | **7.5** | **[0.5-2.0]** % |
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</tr>
<tr>
<td>MCV</td>
<td>113 [82-98] fl</td>
</tr>
<tr>
<td>MCH</td>
<td>35.2 [27-33] pg</td>
</tr>
<tr>
<td>PLATELETS</td>
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<tr>
<td>* 7.5</td>
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Many tests measuring the same thing (more or less)

Red blood cell count (RBC, number of red cells per volume)

Hemoglobin concentration (HGB)

Hematocrit (HCT, the percentage of blood by volume that is made up by the red cells)
Many tests measuring the same thing (more or less)

Red blood cell count (RBC, number of red cells per volume)

Hemoglobin concentration (HGB)

Hematocrit (HCT, the percentage of blood by volume that is made up by the red cells)

ANEMIA = low HBG, low HCT, low RBC (with a few exceptions)
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**RETICULOCYTE COUNT**  * 7.5  [0.5-2.0] %  

* (newly produced red cells)
Reticulocytes

Newly produced red cells
Larger, bluer than normal red cells
Requires a special test to measure
Not routinely reported on the CBC
Elevated: red cell loss (bleeding or hemolysis)
Decreased: Infection, Iron, B12 or folate deficiency, bone marrow failure
Anemia in PNH

• Hemolysis (break down of red cells)

• Lack of production of red cells
  -- aplastic anemia
  -- iron deficiency

Bleeding (e.g. in the stomach or lower bowel)

Tests: LDH, retic count, test of stool for blood
Why does the Lactate Dehydrogenase (LDH) go up in hemolysis?
RBC bursts......

[Diagram showing 'LDH' repeatedly within a red circle]
RBC bursts......
RBC bursts (hemolysis)......
LDH gets into the plasma
LDH

- Red Cells live 120 days, then break open, so some LDH is supposed to be in the plasma.

LDH is elevated whenever there is an increase in red cell bursting.
- Can be released from other tissues (heart, lung, liver).
- Almost always elevated in PNH.
Hemoglobin belongs inside the red cell....
Hemoglobinemia

Normal PNH

hemolysis
Hemoglobinuria
(Dark urine due to the presence of hemoglobin)
Hemolysis & Symptoms of PNH

THROMBOSIS
- Venous:
  - Liver
  - Dermal
  - Cerebral
  - Mesenteric
- Arterial:
  - MI
  - CVA

SMOOTH MUSCLE DYSTONIA
- Abdominal pain
- Dysphagia
- Erectile dysfunction

ANEMIA
- Transfusions
- Fatigue
- Dyspnea
- Angina

IMPAIRED QoL
- Disabling fatigue
- Poor physical functioning
- Pain
- Dyspnea

CHRONIC HEMOLYSIS IN PNH
Flow cytometry for PNH

Isotype

IgG\textsubscript{2}a-FITC

Normal

CD59-FITC

Small PNH clone

2.5%

CD59-FITC

Large PNH clone

33%

CD59-FITC
Flow analysis of red cells

Patient

Normal Control

IR CD59 FITC® FSC-H, SSC-H subset

PCV-Y CD59 FITC® rbc® FSC-H, SSC-H subset

# Cells

25%

65%

10%

# Events

PNH II

PNH III

CD59 Expression
More Typical PNH Patient

PNH III
The higher the % PNH red cells....

... the greater the LDH
... the greater the chance of blood clots (?)
... the more likely the patient will need a transfusion
... the more likely the patient will see dark urine

These are general, not absolute rules.
Many exceptions

Large PNH cell populations “Classic PNH”
Patients with very small PNH cell populations (e.g. 5%) will resemble patients with aplastic anemia (perhaps mild aplastic anemia)

Small PNH cell populations: “AA/PNH”
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**ANC** = % Neutrophils \( \times \) WBC

\( 1.5 = 59.8\% \times 2.5 \)

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Many words, same meaning

Neutrophils
Granulocytes
Polys
PMN’s
Polymorphonuclear leukocytes
Stem cell → Myeloblast → Promyelocyte → Myelocyte

Primary granules

Metamyelocyte → Band → Poly (PMN, Granulocyte)

Secondary granules

Myeloperoxidase
NADPH oxidase, respiratory burst
Chemotaxis (C5a)

Innate Immune System
Definition of Bone Marrow Failure

Low numbers of circulating cells in the blood due to a decreased number (or function) of stem cells in the marrow

Almost all cases in adults are acquired, and not inherited, and are not passed down to one’s children
Low numbers of circulating blood cells

- Anemia
- Thrombocytopenia
- Granulocytopenia, Neutropenia
Low blood counts

Red cells:
  anemia. Tired, “stress” on organs that require much oxygen (heart). No long term damage.

Platelets
  thrombocytopenia. Bleeding, bruising, problems during surgery

Neutrophils (polys, PMNs, granulocytes)
  neutropenia. Prone to bacterial or fungal infection (Medical emergency). Mouth sores, slow healing
Normal Marrow

HYPOcellular (Not enough cells)
Autoimmunity

The Immune System destroys the body’s own tissue rather than destroying viruses or other infections

Examples: Lupus, Rheumatoid Arthritis, Asthma, Thyroid diseases

In bone marrow failure syndromes: target of attack is the stem cell in the marrow
Blood Clot
Blood clot at the site of a broken vessel.
Dr. Bessler’s Slides
Treatment of PNH
• PNH *belongs in 3 chapters of the Hematology textbook*
  – Hemolysis (break down of red cells)
  – Bone marrow failure
  – Thrombosis (blood clots)

*Treatment…*
Bone marrow failure: low blood counts

Red cells:
Anemia. TRANFUSIONS

Platelets
thrombocytopenia. TRANFUSIONS, no aspirin or motrin, etc. AVOID HIGH RISK SPORTS & ACTIVITIES

Neutrophils (polys, PMNs, granulocytes)
neutropenia. BROAD SPECTRUM ANTIBIOTICS, IMMEDIATE MEDICAL ATTENTION IF FEVER (100.4 or 38). No raw meats or fish, no rectal exams, thermometers or suppository pills. Avoid fungal spores, don’t chop wood
Treatment of Bone Marrow Failure

- Careful attention to iron levels (can be too low or too high)
- Folic acid supplementation
- Vitamin B12 levels
Immunosuppression

**Kill or disable** the cells of the immune system (T cells)

Side effects: prone to infection

Examples: *anti-thymocyte globulin (ATG)*

* Cyclosporine
Aplastic Anemia: Treatment

Equine Anti-thymocyte Globulin (ATG)

40 mg/kg/day, 8 hour i.v. infusion x 4 days via central line
ATG from rabbits also available
Reactions to ATG

Immediate reactions
--Urticaria
--Fever
--Hypotension
--Tachycardia
--Anaphylaxis

Transient worsening of Cytopenias

Serum Sickness
Response to Immunosuppression

Response Rate

ATG + cyclosporine

ATG alone

Frickhofen & Rosenfeld 2000
Cyclosporine side effects

- Effects on kidney (reversible and irreversible)
- Prone to infection
- High blood pressure
- Gum swelling
- Loss of magnesium in the urine
- Tremor
Established immunosuppressive therapy: ATG (ALG in Europe) by vein and Cyclosporine (Sandimmune or Neoral) capsules.

There are other immunosuppressive therapies for other auto-immune diseases. None have been proven to be both safe and effective in the treatment of aplastic anemia.

Clinical Trials of new immunosuppressive therapies. [Can we do better than 80% success]
Traditional Treatments for Hemolysis

- Transfusions: irradiated filtered blood products

- Type Specific Blood Products
  (AB blood donor → AB recipient)

- Folic acid

- Steroids?
New Treatment for Hemolysis

• Eculizumab (Soliris) – the first and only medication that is FDA approved for the treatment of Hemolysis in PNH

• Blocks the proteins that break down red cells in PNH (complement)

• Eculizumab is an antibody protein, so it closely resembles proteins that the body makes itself
SOLIRIS (eculizumab) Humanized First in Class Anti - C5 Antibody

- **Human Framework Regions**
- **Complementarity Determining Regions** (murine origin)
- **Human IgG₂ Heavy Chain** Constant Region 1 and Hinge
- **Human IgG₄ Heavy Chain** Constant Regions 2 and 3
# Dosing Schedule

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Induction Phase</th>
<th>Maintenance Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 weeks before induction</td>
<td>Week</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
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<td>3</td>
<td>4</td>
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<td>5</td>
<td>6</td>
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<tr>
<td></td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>9 and every 2 weeks thereafter</td>
<td></td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em> vaccination</td>
<td>SOLIRIS dose, mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>600</td>
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<td></td>
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<td>900</td>
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</table>
Summary of Benefits of Eculizumab

• Hemoglobin level stabilizes
• Urine color returns to normal
• Symptoms of hemolysis improve: “stomach attacks”, male sexual function.
• LDH returns towards normal
• Fewer transfusions
• Many (most) patients completely avoid transfusions
• Patients feel better
• Thrombosis—decreased risk by a factor of about 10
• Renal function may improve in some patients
TRIUMPH: Time to First Transfusion

- By 14 weeks, all patients receiving placebo required a transfusion
- 51% of patients treated with SOLIRIS remained transfusion independent

\[ P < 0.001 \text{ (log-rank test)} \] for comparison of time to first transfusion between the two groups.


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TRIUMPH: Reduction in LDH With SOLIRIS

*P value based on mixed model analysis.

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TRIUMPH: SOLIRIS Improved Anemia – Reduced Transfusions Regardless of Historic Transfusion Requirements

Overall 4-14 Units 15-25 Units >25 Units

Median Units Packed RBCs Transfused

- Placebo
- SOLIRIS

(n = 44) (n = 43) (n = 15) (n = 18) (n = 11)

10 * 6 * 10 18
0 0 2 3

Overall 4-14 Units 15-25 Units >25 Units

*P < 0.001 based on rank sum test

TRIUMPH: Improvement in Fatigue With SOLIRIS

Mean Change in FACIT-Fatigue Score

Time, Weeks

FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue instrument.

*P < 0.001; †P < 0.01; values based on rank sum test.

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Fewer Thrombotic Events With SOLIRIS

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<thead>
<tr>
<th></th>
<th>Pre-Treatment</th>
<th>SOLIRIS Treatment</th>
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<tbody>
<tr>
<td>Patients, n</td>
<td>195*</td>
<td>195*</td>
</tr>
<tr>
<td>Thrombotic Events</td>
<td>39</td>
<td>3†</td>
</tr>
<tr>
<td>Cumulative Observation Period (patient-years)</td>
<td>272</td>
<td>281</td>
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- On an individual patient basis, pre-treatment and SOLIRIS-treatment periods were matched
  - Duration of SOLIRIS treatment was used to define the duration of the pre-treatment period
- Thrombotic events were defined by MAVE criteria based on an intent-to-treat analysis
- Majority of patients (63%) received concomitant anticoagulant therapy
- The effect of anticoagulant withdrawal was not studied

*N = 195 Soliris-treated patients: 11 Pilot; 43 TRIUMPH (SOLIRIS group); 44 TRIUMPH (placebo patients who crossed over to SOLIRIS treatment upon entering the extension); 97 SHEPHERD.
†P < 0.001.

MAVE = Major adverse vascular event.
Eculizumab Side Effects

- Headache on the first day of infusion
- About 0.5 to 1% incidence of infection per year
- Meningococccemia
Meningococcemia
WARNING: SERIOUS MENINGOCOCCAL INFECTION

- SOLIRIS increases the risk of meningococcal infections
  - Vaccinate patients with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of SOLIRIS
  - Revaccinate according to current medical guidelines for vaccine use
  - Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary
• Patients should be informed that they will be provided with a Patient Safety Card that they should carry with them at all times.
Questions regarding Eculizumab/Soliris

- How to further reduce transfusion requirements in patients who still require transfusions
- Comparison between complement blockade and coumadin for prevention of blood clots
- Safety in pregnancy
- Effects on iron stores
- Best way to reduce risk of meningococcus infection
- Impact on survival? Hopefully…
THE UNITED STATES OF AMERICA

FEDERAL RESERVE NOTE

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Almost all insurance companies will cover Eculizumab!
Treatment of Blood Clots

An ounce of prevention is worth a pound of cure
--Coumadin
--Low Molecular Weight Heparin (Lovenox)
--Fondaparinux (Arixtra)
--Eculizumab

Reversal of clots that have occurred
Clot busting drugs (tissue plasminogen activator)

Prevention of Second Clots
--Coumadin
--Low Molecular Weight Heparin (Lovenox)
--Fondaparinux (Arixtra)
--Eculizumab
Recent Improvement in Survival of PNH patients

De Latour et al. BLOOD June 2008
This is even before Eculizumab
Case Presentations
Case 1

- 43 year old woman
- 2 year history of low platelets
- Presents to an outside city hospital with a swollen abdomen filled with fluid, yellow eyes starting over Thanksgiving
- Found to have blood clots in the hepatic veins, inferior vena cava, portal vein
- LDH elevated
- PNH is diagnosed
- Plt count 50,000, Hemoglobin 10 WBC 5 retics 5%
Case 1 Continued

- Started on Heparin at the outside hospital
- Transferred to a referral center 2\textsuperscript{nd} week of January, worsening fluid in abdomen, very yellow eyes, can not move out of bed.
- No improvement in blood clots on heparin
- Platelet count is falling to 30,000
- Test for heparin dependent antibodies is positive
Case 1 Continued

• Liver transplant surgeons evaluate the patient to see if she is a candidate for liver transplantation, but the blood vessels into the liver are too clotted for this.

• What would you do.
• Break for DISCUSSION
Issues

Can blood clots be reversed 6 weeks after they occurred
Outcome

• Patient receives five 24 hour infusions of tissue plasminogen activator
• Gradual fall in the liver function test
• Large bruise on her side after the 5th infusion
• Small improvement on the sonogram: IVC clot resolves. Small amount of blood starts to flow in 1 out of 3 hepatic veins
Outcome continued

• The platelet count increases when the heparin is stopped
• The patient is maintained between infusions of TPA with Refludan
• The patient improves: less jaundice, less fluid in abdomen
• Sent home on coumadin
• 2 months later, completely improved, no sign of blood clots by sonogram of the abdomen

Case #1
Question

• Should this patient also be on Eculizumab/Soliris?
Case # 2

• Patient in her twenties with a history of thrombosis in the veins of the brain and abdomen, reversed with tissue plasminogen activator 5 years prior

• She had new blood clots while on coumadin which were again reversed with tissue plasminogen activator
Case # 2

• Patient is found to have the factor V Leyden allele, a common variant of the allele in the population (5%) that contributes to bleeding risk

• White blood count is 2.0, with 50% neutrophils. [ANC (absolute neutrophil count is 1.0)] Hemoglobin level is 9, platelets initially 80, now 40.
Case # 2

• Bone marrow examination demonstrates a normal appearing marrow (normo cellular)
• Normal sized spleen
• The patient asks if it is OK to continue on the lovenox injections with a platelet count of 40 (normal is >130)
Case # 2

• Break for discussion
Case # 2

• Outcome: patient started cyclosporine, and the platelet count came back up to 80
• Several attempts to stop the cyclosporine resulted in lowering of the platelet count back down to the 50’s
• Patient has been on low dose cyclosporine for years
• Started Eculizumab (Soliris) when this became available
Case # 3
Case # 3

- 34 Year old woman comes to the Hematologist for a consultation
- During her first pregnancy, she was noted to have dark urine, an elevated LDH, and mild anemia (Hemoglobin of 8)
- Did not require transfusion
- Healthy baby delivered at 35 weeks
Case # 3

• After the delivery, a flow cytometry test is performed, confirming the diagnosis of PNH.
• 23% of red cells do not express CD59
• 87% of granulocytes do not express CD24 or FLAER
• Patient was started on coumadin after the delivery
Case 3

• At time of consultation: patient appears well

• white count is 4.0, 66% polys, 26% lymphs hemoglobin 13.4. The platelets 152. Total bilirubin is 3.5. LDH 500, [upper limit of normal being 200]. The INR is 2.44.
Case 3

At the time of the consultation, the patient has a healthy 4 year old son

She wants to have another child and asks if this is safe.

What would you recommend?
• Break for DISCUSSION
Literature reviewed with the patient
Women with *Aplastic Anemia* Effects on Pregnancy

Tichelli et al., Ann Intern Med 2002;137:164-172

Multicenter European Group for Blood and Marrow Transplantation (EBMT)

Retrospective analysis of pregnancy in women with aplastic anemia treated with immunosuppression

36 women, 4 with PNH arising from aplastic anemia

14 (39%) had complications, mostly low blood counts

All 4 with PNH had problems: aplastic anemia, transfusion dependency, eclampsia, and fatal cerebral thrombosis
Women with Aplastic Anemia
Effects on Infants

Tichelli et al., Ann Intern Med 2002;137:164-172

5 of 36 babies were born prematurely, with slightly low birth weight

One infant had neonatal thrombocytopenia

Aplastic anemia or PNH was never passed on to the offspring

Infants had normal growth and development
Women with PNH Effects on Pregnancy

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

Review of published papers from 1966 – 1999, plus unpublished data

33 pregnancies in 24 women with PNH

Five women died (3 thrombosis, 2 infection)
Women with PNH Effects on Infants

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

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
Pregnancy and PNH Therapy Recommendations

Thromboprophylaxis during pregnancy
- Twice daily heparin injections
- Single daily dose of LMWH
- First trimester until 6 weeks post-partum
- Monitor the Anti Xa level during pregnancy

Treatment of active thrombosis
- Aggressive anticoagulation
- Thromobolytics for major clotting
- Difficult if thrombocytopenia also present
PNH, Aplastic Anemia and Pregnancy

Pregnancy is possible for women with PNH, with or without aplastic anemia

Pregnancy frequently leads to complications in up to 50% of women: worse cytopenia, transfusion dependency, relapse of aplasia, thrombosis, and the need for anticoagulation or immunosuppressive therapy

Pregnancy for women with PNH is risky, and may also be problematic for the infants

Eculizumab may change this situation
Outcome

• Coumadin was stopped prior to planned conception
• Patient was switched to Lovenox 1 mg per kg of body weight every 12 hours
• An anti-factor Xa level was drawn 4 hours after lovenox injections every week to monitor the effect of the lovenox
• Lovenox doses adjusted accordingly
Outcome

- Hemoglobin dropped to 10. No transfusions
- Labor was induced at 35 weeks
- Vaginal delivery
- No epidural anesthesia used (because of lovenox)
- Baby and mother healthy
- Now back on Coumadin

Case # 3
Currently 59 year old man
-- 1984 Aplasic Anemia
-- 1985 Antithymocyte Globulin and Male Hormones
-Responded, off transfusions
-- 1987 Black Urine, PNH diagnosed
--Hemoglobinuria every 4 weeks lasting 3-7 days

Case # 4
• Dysphagia (difficulty swallowing) during attacks of hemoglobinuria
• Erectile Failure for 10 years
• (Viagara effective)
• Abdominal Pain During Bouts of Hemoglobinuria
• No thromboses
• Gurgling and “Wind” in Abdomen
• Severe Lethargy When hemoglobin less than 10
• Warfarin (Coumadin) Prophylaxis

• Transfusions 2 units every 4 weeks
Question

How do you treat anemia in this patient?
• Break for DISCUSSION
Eculizumab

- Anti C5 complement antibody
- Started 5/29/02
- No symptoms at time of infusion
- Urine clear since starting the drug
- No symptoms of PNH
- Erectile function improved
- Feels extremely well
Question: is it OK to stop Coumadin in this patient when he goes on The Eculizumab
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