PNH: Current Thinking on Disease, Diagnosis and Treatment

- PNH is underappreciated
- PNH affects 8,000 - 10,000 people in North America and Western Europe
- PNH can be diagnosed at all ages
  - Median age of diagnosis is in the early 30’s
- PNH can occur in men and women of all races
- PNH is a progressive disease
  - Uncontrolled complement activation underlies the morbidities and mortality

Paroxysmal Nocturnal Hemoglobinuria: A Chronic Disease of Uncontrolled Complement Activation
Common Misconceptions about PNH

- It's not paroxysmal\(^1\)
  - Even in the absence of symptoms, destructive progression of hemolysis is ongoing

- It's not nocturnal\(^1\)
  - Hemolysis in PNH is subtle and constant, 24 hours a day

- Hemoglobinuria is a less commonly seen complication
  - ¾ patients present without hemoglobinuria\(^2\)


Overview of Complement

The Defect in PNH

The Somatic Mutation of the PIG A gene prevents all GPI anchored proteins from binding to cell surface

CD55
• Prevents formation and augments instability of the C3 convertases, attenuating the complement cascade

CD59
• Forms a defensive shield for RBCs from complement-mediated lysis
• Inhibits the assembly of the membrane attack complex (MAC)

What does Membrane Attack Complex Formation on the Cell Surface Look Like?

Multimeric C9 Lesions on PNH Red Blood Cell
**What Activates Complement?**

- Complement “Tick-over”
  - Spontaneous activation of the alternative pathway
  - Designed to always be “on”, as a constant immuno-surveillance mechanism
- Exposure to endotoxin from GI tract can lead to increased risk of massive hemolysis
- Other infections, surgery, trauma, pregnancy

---

**What are the Consequences of Chronic Hemolysis and Release of Free Hemoglobin?**

Normal red blood cells are protected from complement attack by a shield of terminal complement inhibitors

Without this protective complement inhibitor shield, PNH red blood cells are destroyed

- Thrombosis
- Renal Failure
- Pulmonary Hypertension
- Abdominal Pain
- Dyspnea
- Dysphagia
- Fatigue
- Hemoglobinuria
- Erectile Dysfunction

---

What is the Relationship of PNH to AA and other BMFs?

- PNH cells are frequently found in patients with aplastic anemia (AA), myelodysplastic syndromes (MDS), and other forms of bone marrow failure (BMF).

- In patients with AA and MDS, red cells are not destroyed
  - AA and MDS cause the body to make fewer healthy ones

- The presence of PNH clones indicates higher likelihood of positive response to immunosuppressive therapy (IST)
  - 12-fold higher likelihood of response to IST with PNH clone

- Small populations of PNH cells can expand into hemolytic PNH in a short period of time.

How do PNH Clones Expand?

Step 1
Somatic Mutation of PIG-A

Step 2
Immunological Attack Selective Damage

Step 3
Growth Advantage

GPI deficient Cell
Selected Cells
Expanded Cells

Normal Hematopoietic Stem Cells
GPI-Anchor Deficiency
Immunological Selection
Benign Tumor Like Expansion

- Selection not enough
- Expansion of the clone size is necessary to result in clinical PNH
- Expansion may be due to another somatic mutation
- The need for both selection and expansion may explain the rarity of PNH

Adapted from Inoue N et al, Int J Hematol 2003;77 p107

What Happens to PNH Cells in AA Patients?

Patients with PNH Clones Present at the Start of Follow-Up (n=75)

- PNH Clone Expanded 17% (13/75)
- PNH Clone Disappeared 24% (18/75)
- PNH Clone Persisted 59% (44/75)

Patients with No PNH Clones at the Start of Follow-Up (n=114)

- Newly Developed PNH Clone 4% (5/114)

- In 13 patients whose PNH clone expanded, 62% (8/13) developed hemolytic PNH
- If you have a PNH clone it is important to have your doctor track it regularly over time, as clones can expand rapidly

Sugimori C et al. BJH 2009; 147: 102-12
Why is it Important to be Aware of the Risks of PNH?

If left unaddressed, PNH can lead to:

- Thrombosis
- Chronic Kidney Disease
- Fatigue/Impaired Quality of Life
- Pulmonary Hypertension

Thrombosis in PNH

- Occurs in both venous and arterial sites
  - Up to 44% of patients experience clinical thrombotic events
- Is not adequately managed with anticoagulation
- All patients with PNH are at risk for thrombosis

What Clinical Symptoms May Be Predictive of TE?

Thrombosis in PNH Conclusions

- DVT or PE most common clinical presentation\(^1\)
- Arterial thromboses are also common\(^1\)
- Anticoagulant therapy may not be adequate to control thrombosis in PNH\(^1\)
- Clinical thrombosis evident in PNH patients with:\(^1\)
  - Minimal hemolysis
  - No transfusion history
  - Smaller clone size\(^3\)

What Causes Kidney Damage in PNH?

- The kidneys can clean small amounts of free hemoglobin from the blood
- In PNH patients, chronic hemolysis releases large amounts of free hemoglobin
- Over time, hemoglobin damages the kidneys and can lead to chronic kidney disease (CKD)\(^1\)\(^-\)\(^4\)
  - Kidney damage may be evident by MRI even with no overt clinical symptoms\(^1\)\(^-\)\(^5\)
- Chronic kidney damage can also occur due to renal vein thrombosis\(^6\)
- If left untreated, chronic kidney damage can lead to kidney failure

Kidney Disease Conclusions

- Kidney disease in PNH is caused by chronic hemolysis\(^2\)
- 64% of patients with PNH exhibit CKD\(^3\)
  - Prevalence of renal insufficiency in PNH is 6.6 times higher than the general population\(^4\)
- Renal insufficiency increases the risk of thrombosis
- Kidney disease is underappreciated in PNH\(^3\)
What are Some Common Signs and Symptoms in Patients with PNH?

<table>
<thead>
<tr>
<th>Clinical Signs or Symptoms</th>
<th>Incidence Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>40%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>66%</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>47%</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>64%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>57%</td>
</tr>
<tr>
<td>Anemia</td>
<td>88%</td>
</tr>
<tr>
<td>Fatigue, impaired QOL</td>
<td>96%</td>
</tr>
<tr>
<td><strong>Hemoglobinuria (at presentation)</strong></td>
<td>26%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>41%</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>47%</td>
</tr>
</tbody>
</table>


Is the Fatigue in PNH Caused by Anemia?

- **Rosse (Hoffman-Hematology)**¹
  - “Many patients note a feeling of fatigue that may be disabling during periods of hemoglobinuria.”
  - This is not related to hemoglobin level (anemia), as it disappears when the hemoglobinuria stops.”

- **Brodsky (Hoffman-Hematology)**²
  - “PNH patients frequently complain of disabling fatigue that is often out of proportion to the degree of anemia.”

- **Multivariate analysis indicates hemolysis drives fatigue in PNH – not anemia**³

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How Does PNH Impact Quality of Life?

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

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

Fatigue and Quality of Life Conclusions

Common symptoms in PNH are predictive of TE

- 96% of patients report fatigue¹
  - Fatigue/QoL independent of anemia/transfusion requirements
- 76% of patients with PNH have disruptions in daily activities¹
  - 17% of patients were unemployed due to PNH
- Abdominal pain, dyspnea, chest pain and hemoglobinuria are linked by underlying hemolysis and the threat of thrombosis²
  - 66% of patients report shortness of breath
  - 57% of patients report abdominal pain
- PNH symptoms are independent of clone size³

² Lee JW et al. Hematologica 2010. 95 (s2): Abstract #506.
³ Urbano-Ispizua A et al. Hematologica 2010. 95 (s2): Abstract #1022.
What Causes Dyspnea and Pulmonary Hypertension in PNH?

- The release of free hemoglobin during chronic hemolysis leads to depletion of nitric oxide

- Nitric oxide depletion causes
  - Smooth muscles in the lungs to tighten, making it more difficult to breathe
  - Increased risk of thrombosis due to constricted blood vessels and activated platelets

- Microscopic thromboses can lead to organ damage, including lungs
  - This damage can lead to pulmonary hypertension, which increases the blood pressure in the lungs
  - Shortness of breath is a common symptom of lung damage

Dyspnea and Pulmonary Hypertension in PNH Conclusions

- Hemolysis results in cell-free hemoglobin and NO consumption leading to pulmonary hypertension\(^1,2\)

- 47% of PNH patients have pulmonary hypertension\(^3\)
  - PNH patients with pulmonary hypertension have cardiac dysfunction\(^3\)

- 66% of PNH patients report dyspnea\(^4\)

- Improvement in dyspnea is associated with
  - A reduction in LDH and nitric oxide consumption\(^2\)
  - No change in hemoglobin\(^2\)

- Dyspnea and chest pain increase risk of thrombosis

---

Common Symptoms of Hemolysis

- Dyspnea
- Impaired QoL
- Fatigue
- Anemia
- Dysphagia
- Hemoglobinuria
- Abdominal Pain
- Erectile Dysfunction

How is PNH Diagnosed?
PNH Diagnosis Can Be Challenging

- Delays in diagnosis can range from 1 to more than 10 years
- Signs and symptoms vary between patients, and are often similar to other diseases

What are Some of the Common Tests Used to Diagnose and Monitor PNH?

- Flow cytometry of red blood cells and granulocytes: Identifies the type and percentage of PNH cells
- Lactate dehydrogenase (LDH): Measures the level of hemolysis
- Red blood cells (RBCs): Deliver oxygen and remove waste from your body; tests measure the amount in the blood
- Creatinine (CRT): Indicates how well the kidneys are working
What are Some of the Common Tests Used to Diagnose and Monitor PNH?

- **Complete blood count (CBC):**
  - **Hematocrit (HCT):** Measures the volume of RBCs; given as a percentage of how much of the blood is made up of RBCs
  - **Hemoglobin (Hgb):** Measures the amount of hgb in the blood and its ability to carry oxygen throughout the body
  - **Platelets (thrombocyte) count:** Used for clotting and play an important role in healing; measures the amount of platelets in the blood
  - **White blood cells (WBCs):** Protect the body against infection; measures the amount of white blood cells in the blood

Flow Cytometry is the Standard Diagnostic Test for PNH

- **Flow cytometry performed on peripheral blood**
- **Granulocytes and at least one additional cell line should be evaluated**
  - Red blood cells (RBCs)
  - Monocytes
- **Quantitative results**
  - Optimal-High sensitivity analysis: ≥0.01%
  - Routine analysis: ≥1%
- **Easy to understand PNH reports**
- **Use more than one reagent against GPI-anchored proteins**

Why is it Important to Test RBCs for PNH?

- Normal RBC’s with normal CD59 expression (Type I cells)
- PNH clone with complete CD59 deficiency (Type III cells)
- PNH clone with complete CD59 deficiency (Type III cells) and partial CD59 deficiency (Type II cells)

Gating on GPA+ RBC’s

GPA = glycophorin A.
Data Source - Dahl Chase Diagnostic Services.

Your Physician Should Look Beyond RBCs for PNH

- Granulocytes provide more accurate representation of PNH clone size
- Percentages of PNH RBCs may be affected by
  - Hemolysis
  - Blood transfusion

Who Should Be Tested for PNH?

Two Independent International Groups Recommend Testing High Risk Patients for PNH

Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry


Suggestions for PNH Testing by ICCS PNH Guidelines

Clinical indications for PNH testing

**Intravascular hemolysis as evidenced by hemoglobinuria or elevated plasma hemoglobin**
- Evidence of unexplained hemolysis with accompanying:
  - Iron-deficiency, or
  - Abdominal pain or esophageal spasm, or
  - Thrombosis (see below), or
  - Granulocytopenia and/or thrombocytopenia
- Other acquired Coombs-negative, non-schistocytic, non-infectious hemolytic anemia

**Thrombosis with unusual features**
- Unusual sites
  - Hepatic veins (Budd-Chiari syndrome)
  - Other intra-abdominal veins (portal, splenic, splanchnic)
  - Cerebral sinuses
  - Dermal veins
- With signs of accompanying hemolytic anemia (see above)
- With unexplained cytopenia

**Evidence of bone marrow failure**
- Suspected or proven aplastic or hypoplastic anemia
- Refractory cytopenia with unilineage dysplasia
- Other cytopenias of unknown etiology after adequate workup


What are the Treatment Options for PNH?
Historical Management of PNH

Supportive Care Options Do Not Impact Disease Progression and Risk for Severe Consequences

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

- Anticoagulants
  - Risk of hemorrhage
  - Ineffective in many patients

- Red cell supplements
  - ESAs may expand clones and elevate hemolysis
  - Folic acid, iron, erythropoiesis-stimulating agents

- Steroids/androgen hormones
  - No controlled clinical trials
  - AE’s

Supportive Care Options Do Not Impact Disease Progression and Risk for Severe Consequences

ESA = erythropoietin stimulating agents.

Historical Management of PNH

Bone Marrow Transplant

Although BMT is the only potential curative therapy for PNH, BMT is associated with significant risks

Hemolysis and thrombosis are risk factors for poor outcomes

- In a recent retrospective study in France examining PNH patients²
  - 54% had GVHD

- In another study examining PNH patients (n=23)¹
  - 50% chronic GVHD; 42% acute GVHD

- BMT has a significant impact on quality of life post transplant³,⁴

- Allogeneic BMT recommended for PNH patients with life-threatening cytopenias or possibly the rare patient with disabling hemolysis or thrombosis not controlled with existing therapy⁵

**SOLIRIS® (eculizumab) for the Treatment of PNH**

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

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**SOLIRIS® Blocks Terminal Complement**

**Complement Cascade**

- **Proximal**
  - C3 \(\rightarrow\) C3a
  - C3b

- **Terminal**
  - C5 \(\rightarrow\) C5a
  - C5b \(\rightarrow\) C5b-9

**SOLIRIS®**

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

---

Summary of Clinical Efficacy in PNH

In clinical trials, SOLIRIS® significantly reduced hemolysis, the underlying cause of morbidity and mortality in PNH

- 86% sustained reduction in hemolysis as measured by LDH
- Fewer thrombotic events were observed with SOLIRIS treatment
  - The majority of patients (63%) received concomitant anticoagulant therapy
  - The effect of anticoagulant withdrawal during SOLIRIS treatment has not been studied
- Fatigue in PNH impacted by hemolysis
  - With SOLIRIS, significant improvements noted in pain and dyspnea along with a broad range of QoL measures
- 73% reduction in need for transfusions across all patient populations


What Can I do to Manage PNH?

- It is important to address PNH early and aggressively
- The serious consequences of PNH are caused by ongoing hemolysis
  - Lowering hemolysis is the primary goal of managing PNH
- It is important to track
  - Your symptoms: Stomach pain, difficulty swallowing, shortness of breath, fatigue, and erectile dysfunction
  - Your lab results: LDH, hemoglobin, RBCs and WBCs, creatinine
In clinical trials all patients received a meningococcal vaccination.

SOLIRIS® should be administered via IV infusion over 35 minutes every 7 days during induction and every 14 days during maintenance.

SOLIRIS® dose adjustment to every 12 days may be necessary for some patients to maintain LDH reduction.

Concomitant medications allowed:
- Steroids, immunosuppressant drugs, anti-clotting agents and hematinics


Recent ASH Abstracts

Long-Term Clinical Outcomes With Sustained Eculizumab Therapy in Paroxysmal Nocturnal Hemoglobinuria (PNH)

Jeffrey Szer, BMedSc, MBBS, FRACP1, Peter Hillmen, MBChB, FRCP, FRCPath, PhD2, Antonio M. Ristano, MD, PhD3, Hubert Schrezenmeier, MD, Professor4, Joerg Schubert, MD5, Jaroslaw P. Maciejewski, MD, PhD, FACP6, Ulrich Dührsen, MD7, Petra Muus, MD, PhD8, Carlos de Castro III, MD9, Gérard Socié, MD, PhD10, and Robert A. Brodsky, MD11

1Clinical Haematology & BMT Service, The Royal Melbourne Hospital, Parkville, Australia; 2Department of Haematology, St. James’s University Hospital, Leeds, United Kingdom; 3Department of Biochemistry and Medical Biotechnologies, University of Naples, Naples, Italy; 4University of Ulm Transfusion Medicine, Inst for Clin. Transfusion Med. & Immunogen., Ulm, Germany; 5Hematology, Oncology, Stem Cell Transplantation, Hemostaseology, Evangelisches Krankenhaus Hamm, Hamm, Germany; 6Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; 7Hematology, University Hospital Essen, Essen, Germany; 8Dept. of Hematology, Radboud University Nijmegen, Medical Centre, Nijmegen, Netherlands; 9Medicine - Division of Medical Oncology, Duke University Medical Center, Durham, NC; 10Hematology-Bone Marrow Transplantation, Saint-Louis Hospital, Paris, France; 11Division of Hematology, Department of Medicine, Johns Hopkins University, Baltimore, MD.

ASH 2010
Eculizumab PNH Clinical Program

Pilot Study – NEJM. 2004
N=11

TRIUMPH – NEJM. 2006
Pivotal Phase III, Double-Blind, Placebo-Controlled Trial, N=87

SHEPHERD – Blood. 2008
Broader patient population, including those receiving minimal transfusions or with thrombocytopenia, N=97

Long-Term Extension Trial Evaluated long-term safety, efficacy and effect on thrombosis; Placebo patients switched to SOLIRIS®
N=187

Hillmen et al. Long Term Safety and Efficacy (N=195). To be submitted, BJH

Baseline Patient Demographics

- All patients (N=195) enrolled in the PNH eculizumab clinical trials (Pilot study (N=11), TRIUMPH (N=87) and SHEPHERD (N=97) and subsequent Extension studies were assessed for long term safety and sustained efficacy

**Baseline Patient Demographics**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (years)</td>
<td>40 (18-85)</td>
</tr>
<tr>
<td>Median Treatment Duration (months)</td>
<td>29 (1-66)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>54%</td>
</tr>
<tr>
<td>Male</td>
<td>46%</td>
</tr>
<tr>
<td>History of Aplastic Anemia</td>
<td>29%</td>
</tr>
<tr>
<td>History of MDS</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Eculizumab Significantly Reduced Intravascular Hemolysis in 100% of Patients

- Mean LDH was reduced rapidly and significantly from a baseline of 2,293 U/L (~10x ULN) to 310 U/L at 1 month treatment, and was sustained through 36 months.

Study Month | Baseline | .25 | 1 | 6 | 12 | 18 | 24 | 30 | 36
---|---|---|---|---|---|---|---|---|---
Patients (n) | 195 | 168 | 195 | 192 | 188 | 189 | 181 | 132 | 87

*P<0.0000001

Dashed line represents the upper limit of the normal range (103 – 223 U/L).

Continued Patient Survival with Sustained Eculizumab Therapy

- 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.
  - Overall survival rate confirms the recently reported 5-year survival rate of 95.5% for PNH 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.

90% of Patients Completed Parent and Extension Trials

- 20 of the 195 patients did not complete the trial
- 9 patients discontinued due to an adverse event (AE)
  - In a 16 week follow-up of these 20 patients, TE was reported in 3 patients, including 1 death due to TE
- No patients experienced serious hemolysis at the time of study discontinuation

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Meningococcal Sepsis</td>
<td>1</td>
</tr>
<tr>
<td>Worsening of PNH</td>
<td>1</td>
</tr>
</tbody>
</table>

Sustained Eculizumab Therapy Was Well Tolerated

- The majority of adverse events (91.3%) were mild to moderate in severity
- Over the course of up to 5 years eculizumab treatment, the most common AEs were:
  - Headache (55%)
  - Nasopharyngitis (50%)
  - Upper respiratory tract infection (41%)
  - Diarrhea (35%)
  - Nausea (32%)
- 71 patients (36.4%) experienced at least 1 infusion-related AEs
  - The most common infusion-related AEs were peripheral edema, pruritus, and rash, each occurring in 10.3% of patients (20/195)
The Clinical Benefit of Eculizumab is Significant and Sustained

- Long-term eculizumab therapy provides significant and sustained clinical benefit in a broad population of PNH patients
  - Overall survival on treatment was 97.6% at 3 years and was maintained through 5.5 years
  - Significant reduction in intravascular hemolysis was sustained in 100% of patients
  - Mean units transfused were significantly reduced at all time points
  - Hemoglobin levels were significantly increased compared to baseline
- Significant reductions in thrombosis and improvements in CKD were maintained over 36 months when compared to baseline and previously published data

The Clinical Benefit of Eculizumab is Significant and Sustained

- Long-term eculizumab therapy is well tolerated by patients with PNH
  - No TE events were reported in PNH patients who discontinued anticoagulant treatment while on eculizumab therapy. However, TE was observed within 16 weeks of discontinuation of Eculizumab
- Collectively, the results presented here confirm data published earlier this year from a single center study¹
  - Kelly et al. (2011) demonstrated that long-term treatment with Eculizumab is associated with normalization of survival compared to an age- and sex-matched control population
  - Patient survival on eculizumab from both studies compares favorably to the 5-year survival rate of 66.8% observed in those patients treated with supportive care

¹ Kelly et al. Prepublished online April 1, 2011; doi:10.1182/blood-2011-02-330937.
Effects of Eculizumab Therapy in Patients with PNH Receiving Concurrent Immunosuppressive Therapy (IST) for Bone Marrow Insufficiency

Hubert Schrezenmeier¹, Joerg Schubert, MD², Lucio Luzzatto, MD³, Petra Muus, MD, PhD⁴, Gerard Socie, MD, PhD⁴, Antonio M. Risitano, MD, PhD⁵, Anita Hill, MBCHB, (Hons), PhD⁷ and Peter Hillmen, MB, CHB, PhD⁸

¹Institute of Clinical Transfusion Medicine and Immunogenetics, German Red Cross Blood Service Baden-Württemberg - Hessen, University of Ulm, Institute of Transfusion Medicine, Ulm, Germany; ²Internal Medicine I, Saarland University Medical School, Homburg/Saar, Germany; ³Istituto Toscano Tumori, Florence; ⁴Radboud University, Nijmegen, Netherlands; ⁵Bone Marrow Transplantation, Saint-Louis Hospital, Paris, France; ⁶Hematology, Department of Biochemistry and Medical Biotechnologies, Federico II, Naples, Italy; ⁷Department of Haematology, Bradford Royal Infirmary, Bradford, United Kingdom; ⁸St. James’s University Hospital, Leeds, United Kingdom

ASH 2009

SOLIRIS® Reduces Hemolysis and Improves Fatigue in IST-Treated Patients

- AA/PNH patients on IST (prior to eculizumab):
  - Significant transfusion requirement
  - Significant fatigue with low FACIT scores

- With SOLIRIS treatment:
  - Significant improvement in fatigue
  - Significant and sustained reduction in hemolysis
    • Demonstrates that hemolysis contributes to fatigue despite IST treatment
  - Significant reduction in transfusion requirements
    • Transfusion reduction apparent after 6 months of treatment with continued improvement
    • Hemoglobin remains stable despite reduced transfusions requirements

Conclusions

PNH and AA
- Two distinct, life-threatening diseases
- Different mechanisms and different complications
- Each requires specific treatment

Treatment
- SOLIRIS® and IST together appear to be well tolerated
  - AE event rate consistent with overall trial data
- SOLIRIS treatment inhibits hemolysis and complications in PNH
- IST treatment improves aplastic production complications in AA

Concomitant treatment with SOLIRIS and IST associated with improvement in both diseases

Case Study
PNH Case Study
57-Year Old with AA, hepatic vein thrombosis, and low levels of hemolysis

PNH Diagnostic Timeline
- 1997: AA treated and resolved
- 1998: Presented with thrombocytopenia after hepatitis vaccine
- 1999: Referred to hem/onc for continued thrombocytopenia
- 2000: Diagnosed with PNH

Key Takeaways
- AA and continued thrombocytopenia are triggers for PNH testing
- LDH alone does not indicate PNH
- Severity, frequency, and location of thrombotic events in PNH are unpredictable

Test results:
- LDH: 430 IU/L (ULN=200)
- Hemoglobin: 10.5 g/dL
- Granulocyte clone: 92.44%
- RBC type II clone: 0.00%
- RBC type III clone: 52.0%

PNH is NOT a mild disease
- PNH has far-reaching implications, involving essential organs:
  - Risk of Thromboembolism
  - Risk of Pulmonary Hypertension
  - Risk of Chronic Kidney Disease
  - Risk of Erectile Dysfunction
  - Poor Quality of Life

These symptoms are linked to poor outcomes

There is a targeted treatment approach for PNH patients with chronic hemolysis:
- SOLIRIS® is indicated for treatment of hemolysis associated with PNH
- SOLIRIS has improved survival for patients with PNH
- SOLIRIS has been put through the rigors of nearly a half-dozen clinical trials for complement-mediated diseases

Other treatment options:
- Bone Marrow Transplant
- Palliative Care
Important Safety Information For SOLIRIS®

All Patients Should Receive a Medication Guide and SOLIRIS® Patient Safety Information Card Before Starting SOLIRIS® Treatment

Please See Full Prescribing Information for SOLIRIS®

Warning

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.

- Immunize patients with a meningococcal vaccine at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. (See Serious Meningococcal Infections for additional guidance on the management of the risk of meningococcal infection.)

- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program (5.2). Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).

Please see full prescribing information for SOLIRIS® (eculizumab).

**Indications and Usage**

SOLIRIS® is a complement inhibitor indicated for:

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

The effectiveness of SOLIRIS in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function.

Prospective clinical trials in additional patients are ongoing to confirm the benefit of SOLIRIS in patients with aHUS.

**Limitation of Use:**

SOLIRIS is not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).

Please see full prescribing information for SOLIRIS® (eculizumab).  

---

**Contraindications**

SOLIRIS® is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying SOLIRIS treatment outweigh the risks of developing a meningococcal infection.

Please see full prescribing information for SOLIRIS® (eculizumab).  
**Warnings and Precautions**

- SOLIRIS® therapy increases a patient's susceptibility to serious meningococcal infections. Life-threatening and fatal meningococcal infections have occurred in patients treated with SOLIRIS.

- All patients must be vaccinated against *Neisseria meningitidis* ≥ 2 weeks prior to receiving SOLIRIS.

- Vaccination reduces, but does not eliminate, the risk of meningococcal infections.

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**Warnings & Precautions (cont.)**

- SOLIRIS® blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria.

- Children treated with SOLIRIS may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib)
  - Administer vaccinations for prevention of *S. pneumoniae* and Hib according to ACIP guidelines.

- Use caution when administering SOLIRIS to patients with any systemic infection.

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Please see full prescribing information for SOLIRIS® (eculizumab).
Safety: Warnings and Precautions (cont)

- The effect of withdrawal of anticoagulant therapy during SOLIRIS® treatment has not been established. Therefore, treatment with SOLIRIS should not alter anticoagulant management.

- Treatment Discontinuation for PNH
  - Monitor patients after discontinuing SOLIRIS for at least 8 weeks to detect hemolysis.

- Treatment Discontinuation for aHUS
  - Monitor patients with aHUS for signs and symptoms of thrombotic microangiopathy (TMA) complications for at least 12 weeks.

Please see full prescribing information for SOLIRIS® (eculizumab).

Warnings and Precautions (cont)

- LDH levels may be used to monitor hemolysis
  - SOLIRIS® dose adjustment to every 12 days may be necessary for some patients to maintain LDH reduction.

- Infusion reactions may occur
  - In clinical trials, no patients experienced infusion reactions that required discontinuation.
  - SOLIRIS treatment should be interrupted in all patients experiencing severe infusion reactions and appropriate medical therapy administered.

Please see full prescribing information for SOLIRIS® (eculizumab).
Meningococcal Infection Events: Clinical Trial Experience

- Meningococcal infections are the most important adverse events that may be experienced by patients receiving SOLIRIS®.
- In PNH clinical studies, 2 out of 196 patients developed serious meningococcal infections while receiving treatment with SOLIRIS.
  - Both patients had been vaccinated.
- In clinical studies among patients without PNH, meningococcal meningitis occurred in one patient, who was unvaccinated.
- Meningococcal sepsis occurred in one previously vaccination patient enrolled in the retrospective aHUS study during the post-study follow-up period.
- In post-marketing experience, cases of serious or fatal meningococcal infections have been reported.

Adverse Reactions

- The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea.
- The most frequently reported adverse reactions in aHUS single arm prospective trials (≥15% combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.
Patient Counseling

See FDA-approved patient labeling (Medication Guide)

Prior to treatment, patients should fully understand:

- The risks and benefits of SOLIRIS®, in particular the risk of meningococcal infection; Ensure that patients receive the Medication Guide
- Patients are required to receive a meningococcal vaccination at least 2 weeks prior to receiving the first dose of SOLIRIS, if they have not previously been vaccinated
  - Vaccination may not prevent meningococcal infection
- Patients should be educated about any of the signs and symptoms of meningococcal infection
- Patients should be informed that there may be an increased risk of other infections
- There is a potential for serious hemolysis when SOLIRIS is discontinued in patients with PNH and potential for TMA complications due to aHUS when SOLIRIS is discontinued.

Please see full prescribing information for SOLIRIS® (eculizumab).

Patient Safety Information Card

- You are provided with Patient Safety Information Cards to give to your patients. You should discuss the importance and the proper use of this card with every patient.
- Patients should carry this card at all times to show to any healthcare professional involved in their care.
- The Patient Safety Information Card contains safety guidance for SOLIRIS® patients and their healthcare providers.
- Prescribers should advise patients to seek medical attention immediately if they develop headache with nausea or vomiting, or headache and fever, even if they don’t have their Patient Safety Information Card with them.

Soliris can lower the ability of your immune system to fight infections, especially meningococcal infection, which requires immediate medical attention. If you experience any of the following symptoms, you should immediately call your doctor or seek emergency medical care, preferably in a major emergency medical center.

Please see full prescribing information for SOLIRIS® (eculizumab).