PAROXYSMAL NOKTURNAL HEMOGLOBINURIA

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Paroxysmal Nocturnal Hemoglobinuria (PNH)

- PNH is an acquired, clonal, non malignant but life-threatening stem cell disorder.
- Affects 8,000 to 10,000 people in North America and Europe
- Can develop without warning in men and women of all races, backgrounds and ages
- Often strikes people in the prime of their lives, with an average age of onset is in the early thirties
- Intravascular hemolysis, thrombophilia and bone marrow failure are the major clinical findings

Mortality rates in patients with PNH

80 patients with PNH treated between 1940 and 1970

The Defect in PNH

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

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

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

GPI - Glycosylphosphatidylinositol; PIG A - phosphatidylinositol glycan anchor biosynthesis A

In PNH, somatic mutation lead to chronic uncontrolled complement activation

- Inflammation
- Thrombosis

**Lectin pathway**
- Immune complex clearance
- Microbial opsonisation

**Classical pathway**
- C3
- **Amplification**
- C3 + H₂O – Always active (chronic)

**Alternative pathway**
- C3 + H₂O – Always active (chronic)

**Natural inhibitors:**
- Factor H, I, MCP, CD55
- CD59

**Consequences**
- **C5a**
  - Potent anaphylatoxin
  - Chemotaxis
  - Pro-inflammatory
  - Leucocyte activation
  - Endothelial activation
  - Prothrombotic

- **C5b-9**
  - Membrane attack complex
  - Cell lysis
  - Pro-inflammatory
  - Platelet activation
  - Leucocyte activation
  - Endothelial activation
  - Prothrombotic

- Anaphylaxis
- Inflammation
- Thrombosis

- aHUS, atypical Haemolytic Uraemic Syndrome
- MCP, membrane cofactor protein
PNH is a Progressive Disease of Chronic Hemolysis

Normal RBC are protected from complement attack by a shield of terminal complement inhibitors.

Without this protective complement inhibitor shield, PNH red blood cells are destroyed, releasing free hemoglobin (Hb).

Complement Activation

Intact RBC

Hemolysis

Destroyed RBC

Free Hb

Anemia

Thrombosis

Renal Failure

Pulmonary Hypertension

Abdominal Pain

Dyspnea

Dysphagia

Fatigue

Hemoglobinuria

Erectile Dysfunction

Significant Impact on Survival

Significant Impact on Morbidity

PNH Can Be Challenging to Diagnose

Delays in diagnosis range from 1 to more than 10 years\(^1\)
Directly question patients for all potential symptoms

<table>
<thead>
<tr>
<th>Clinical Signs or Symptoms</th>
<th>Incidence Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>40%(^1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>66%(^2)</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>47%(^6)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>64%(^3)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>57%(^2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>88%(^4)</td>
</tr>
<tr>
<td>Fatigue, impaired QOL</td>
<td>96%(^2)</td>
</tr>
<tr>
<td><strong>Hemoglobinuria (at presentation)</strong></td>
<td><strong>26%(^5)</strong></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>41%(^2)</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>47%(^2)</td>
</tr>
</tbody>
</table>

Thrombosis in PNH

- Thrombosis is the leading cause of death in PNH\(^2\)
  - 40-67% mortality in PNH results from thrombosis\(^1\)
  - First TE increases risk for death 5- to 10-fold\(^1\)

- TE occur both at arterial and venous sites\(^1,4\)

- Anticoagulant therapy may not be adequate to control thrombosis in PNH\(^1,5\)

- Clinical thrombosis evident in all PNH patients
  - Minimal hemolysis\(^1\)
  - Minimal transfusion history\(^1\)
  - Smaller clone size\(^4\)

PNH Diagnosis can be Challenging - Who should be screened?

- Aplastic anaemia, especially upon recovery
- Myelodysplastic syndromes: refractory anaemia variant
- Hemoglobinuria: positive urine test but no red blood cells
- Coombs’ negative acquired haemolytic anaemia
- Venous thrombosis at atypical sites
  - Budd-Chiari syndrome, Other intra-abdominal sites (eg, mesenteric or portal veins), Cerebral veins, Dermal veins
  - Arterial thrombosis observed in PNH, but less common than venous
- Episodic dysphagia or abdominal pain with abnormal LDH
Diagnosis of PNH

- Ham test and the sucrose lysis test (sugar water test)
- **Flow cytometric analysis using antibodies directed against GPI-AP** is the most sensitive and informative assay available for diagnosis of PNH
  - The proportion of abnormal granulocytes more accurately reflects the PNH clone size and is unaffected by red cell transfusion
- The FLAER (fluorescently labeled aerolysin) assay is useful for analyzing leukocytes for expression of GPI-AP but cannot be used for analysis of erythrocytes
- Documentation of the PIGA mutation(s)

The Defect in PNH

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CD55
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GPI - Glycosylphosphatidylinositol; PIG A - phosphatidylinositol glycan anchor biosynthesis A

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%
  - Minimal-Routine analysis: 1%
- Use more than one reagent against GPI-anchored proteins

Treatment and management options in PNH
Neither impact on progression nor on the risk for severe morbidities and mortality¹,²

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

- Anticoagulants
  - Ineffective in many patients³
  - Risk of hemorrhage

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

- Steroids/androgen hormones
  - No controlled clinical trials
  - Adverse event

- HSCT

Hematopoietic Stem Cell Transplantation (HSCT)

BMT is associated with significant morbidity and mortality

Hemolysis and thrombosis are risk factors for poor outcomes

• 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 transplant³,⁴

Treatment and management options in PNH

- Treatments of PNH aimed to manage the symptoms only and do not address the underlying cause, chronic hemolysis.

- Complement inhibitors:
  - Eculizumab is a recombinant humanised monoclonal IgG2/4k antibody that binds to the human C5 complement protein and inhibits the activation of terminal complement.

SOLIRIS® Blocks Terminal Complement

**Complement Cascade**

**Proximal**
- C3 → C3a
- C3b

**Terminal**
- C5 → C5a → C5b-9
  - Cause of Hemolysis in PNH

- **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

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3. SOLIRIS® (eculizumab) [package insert]. Alexion Pharmaceuticals; 2009.
Chronic Hemolysis is the Underlying Cause of Progressive Morbidities and Mortality in PNH
SOLIRIS® PNH Clinical Studies

Pilot Study – *NEJM*. 2004
N = 11
Primary endpoint: reduction of hemolysis

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

Broader patient population, including those receiving minimal transfusions or with thrombocytopenia, N = 97

Long-Term Extension Trial
Hillmen *Blood*. 2007
Evaluated long-term safety, efficacy and effect on thrombosis; Placebo patients switched to SOLIRIS®
N = 187
TRIUMPH and SHEPHERD:
Median LDH reduction by 86% in 100% of patients\textsuperscript{1, 2}

\begin{itemize}
  \item TRIUMPH – Placebo/Extension
  \item TRIUMPH – SOLIRIS®/Extension
  \item SHEPHERD – SOLIRIS®
\end{itemize}

→ TRIUMPH placebo patients switched to SOLIRIS® after week 26\textsuperscript{2}
All TRIUMPH patients entered the long-term extension study\textsuperscript{1}

\(P<0.001\) at all measured time points.
Sustained & Significant Reduction of Hemolysis in PNH Patients over 36 months

- Intravascular hemolysis was reduced rapidly in 100% of patients treated with eculizumab and was sustained over the entire course of the 36 month treatment period ($P<0.000001$)

![Graph showing mean LDH (U/L) over study months with a dashed line representing the upper limit of the normal range (103 – 223 U/L).](image)

**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

Mortality rates in patients with PNH

80 patients with PNH treated between 1940 and 1970

Age- and sex-matched controls

Patients with PNH

Years After Diagnosis

SOLIRIS has a Major Impact on Survival in PNH

Survival is comparable to age and sex matched control population

- There was no difference in mortality between patients on eculizumab and the normal population ($P=0.46$)
  - 96% (76/79) patient survival
  - 94% (74/79) remain on Soliris to date

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.
- Patient survival on eculizumab compares favorably to a predicted mortality rate in PNH patients of 35% at 5 years.

Summary of Clinical Efficacy

SOLIRIS® significantly reduced hemolysis, the underlying cause of morbidity and mortality in PNH¹

- 86% sustained reduction in hemolysis as measured by LDH²
- 92% reduction in thrombotic events across all patient types³
- 94% reduction in thrombotic events in patients treated with anticoagulants³
- Patients treated with SOLIRIS experienced clinically significant improvement in CKD and pulmonary hypertension⁴,⁵
- 78% clinically meaningful improvement in fatigue
  - Fatigue in PNH impacted by hemolysis
  - Significant improvement noted in pain and dyspnea along with a broad range of QoL measures⁶
- 73% reduction in need for transfusions across all patient populations⁷

SOLIRIS has a major impact on survival²

Survival is comparable to age and sex matched control population

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1. SOLIRIS® (eculizumab) [package insert]. Alexion Pharmaceuticals; 2009.
Contraindications

- Do not initiate SOLIRIS® in patients:
  - With unresolved serious *Neisseria meningitidis* infection
  - Who are not currently vaccinated against *Neisseria meningitidis*
  - Who have known or suspected hereditary complement deficiencies

ATYPICAL HEMOLYTIC UREMIC SYNDROME
aHUS is a form of TMA\(^1,2\)

- Systemic TMA is a process of widespread thrombi and inflammation in the small blood vessels of vital organs throughout the body
- The multiple thrombi and inflammation occur throughout the body, affecting the brain, kidneys, heart, organs of the gastrointestinal system and lungs
- The clinical presentation of aHUS can have significant clinical overlap (signs and symptoms) with other diseases, some of which are caused by systemic TMA such as TTP and STEC-HUS

Clinical measure of TMA

Microangiopathic haemolysis
- In many cases, patients will present with microangiopathic haemolysis (also historically called MAHA)
- Coombs test negative
- Decreased haemoglobin
- LDH greater than ULN
- Low / undetectable haptoglobin concentrations
- Schistocytes

Decreased platelet count
- Thrombus formation consumes platelets
- Patient can present with thrombocytopenia
  - Platelet counts less than normal <150,000 per mm$^3$
- Patients can also present with declining platelet counts suggesting ongoing platelet consumption
- Giant platelets may be observed in the peripheral smear


MAHA, microangiopathic haemolytic anaemia; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy; ULN, upper limit of normal
TMA: thrombosis, inflammation and occlusion of small blood vessels throughout the body; characterised by decreased platelets / thrombocytopenia and haemolysis.

- TTP / HUS (typical and atypical)
- Malignant hypertension
- Systemic lupus erythematosus
- Antiphospholipid antibody syndrome
- Scleroderma
- Cobalamin C disease
- Pre-eclampsia
- HIV
- Drug-associated

HUS, haemolytic uraemic syndrome; HIV, human immunodeficiency virus; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

Typical and atypical HUS

- HUS is a systemic TMA characterised by:\(^1\)
  - Microangiopathic haemolytic anaemia
  - Thrombocytopenia
  - Renal failure

- Typical HUS is caused by infection with Shiga toxin-producing *Escherichia coli* or streptococci

- aHUS is a lifelong chronic disease caused by genetic defects in complement regulation that lead to uncontrolled and excessive complement activation\(^2,3\)

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1. Loirat C, Frémeaux-Bacchi V. Orphanet J Rare Dis 2011;6:60;
In aHUS, genetic defects lead to chronic uncontrolled complement activation¹-³

- **Lectin pathway**
- **Classical pathway**
- **Alternative pathway**

**Proximal**
- Immune complex clearance
- Microbial opsonisation

**C3**
- C3 + H₂O – Always active (chronic)
- Amplification

**Natural inhibitors:**
- factor H, I, MCP, CD55
- CD59

**Terminal**
- **C5a**
  - Potent anaphylatoxin
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- **C5b-9**
  - Membrane attack complex
  - Cell lysis
  - Pro-inflammatory
  - Platelet activation
  - Leucocyte activation
  - Endothelial activation
  - Prothrombotic

**Consequences**
- Anaphylaxis
- Inflammation
- Thrombosis

**Cell destruction**
- Inflammation
- Thrombosis

**References**

**aHUS**, atypical Haemolytic Uraemic Syndrome;
MCP, membrane cofactor protein
Diagnosis of TTP cannot be made on clinical symptoms alone

<table>
<thead>
<tr>
<th>aHUS</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well-recognised aHUS signs:</strong></td>
<td><strong>Well-recognised TTP signs:</strong></td>
</tr>
<tr>
<td>Decrease platelet count</td>
<td>Decrease platelet count</td>
</tr>
<tr>
<td>Microangiopathic haemolysis</td>
<td>Microangiopathic haemolysis</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Neurological dysfunction</td>
</tr>
<tr>
<td><strong>Under-recognised aHUS signs:</strong></td>
<td><strong>Under-recognised TTP signs:</strong></td>
</tr>
<tr>
<td>Neurological dysfunction</td>
<td>Renal pathology (96%)</td>
</tr>
<tr>
<td>(up to 48%)</td>
<td>Renal insufficiency (47%)</td>
</tr>
<tr>
<td>Cardiac symptoms (up to 43%)</td>
<td></td>
</tr>
</tbody>
</table>

Distinguishing between aHUS and TTP

Despite their apparent clinical similarities, the cause of TTP (severe ADAMTS13 deficiency) is quite different from that of aHUS (genetic deficiency of complement)

- TTP can be ruled-in on the basis of ADAMTS13 activity
- A severe deficiency in ADAMTS13 activity with plasma ADAMTS13 ≤5% of normal activity is required for diagnosis of TTP
- Higher levels of ADAMTS13 activity are not sufficient to effect clot activity and are, therefore, not diagnostic of TTP

aHUS, atypical Haemolytic Uraemic Syndrome; TTP, thrombotic thrombocytopenic purpura

aHUS is a genetic, devastating and life-threatening disease

- aHUS causes vital organ damage\(^1\) and sudden death\(^2\)
- Chronic progressive course with premature mortality\(^1,3,4\)
- 33–40% of patients die or progress to end-stage renal disease with the first clinical manifestation\(^1,3\)
- 65% of all patients die, require dialysis or have permanent renal damage within the first year after diagnosis despite plasma exchange or plasma infusion\(^3\)

Modified from Caprioli J et al. Blood 2006. *CFH* mutations only depicted

Chronic uncontrolled complement activation underlies the pathology of aHUS\textsuperscript{1-3}

- Endothelial swelling and disruption
- Platelet consumption
- Mechanical haemolysis
  (Schistocytes)
- Blood clots
- Inflammation
- Occlusion
- Ischaemia
- Hypoxia


aHUS, atypical Haemolytic Uraemic Syndrome
Complement-mediated TMA leads to the morbidities and mortality in aHUS

CNS\textsuperscript{1-5} \hspace{1cm} Cardiovascular\textsuperscript{2-4,6}
- Confusion
- Seizures
- Stroke
- Encephalopathy
- Diffuse cerebral dysfunction
- Myocardial infarction
- Thromboembolism
- Cardiomyopathy
- Diffuse vasculopathy

Renal\textsuperscript{4,7-9,11,12,14} \hspace{1cm} Gastrointestinal\textsuperscript{1-3,5,10-12}
- Elevated creatinine
- Oedema
- Malignant hypertension
- Renal failure
- Dialysis
- Transplant
- Liver necrosis
- Pancreatitis
- Diabetes mellitus
- Colitis
- Diarrhoea
- Nausea and vomiting
- Abdominal pain

Pulmonary\textsuperscript{1,3,6,14} \hspace{1cm} Blood\textsuperscript{1,11}
- Dyspnoea
- Pulmonary haemorrhage
- Pulmonary oedema
- Haemolysis
- Decreased platelets
- Fatigue
- Transfusions

Blood\textsuperscript{1,11} \hspace{1cm} Impaired quality of life\textsuperscript{13}
- Fatigue
- Pain and anxiety
- Reduced mobility

Impaired quality of life\textsuperscript{13}
- Fatigue
- Pain and anxiety
- Reduced mobility


aHUS, atypical Haemolytic Uraemic Syndrome;
CNS, central nervous system;
TMA, thrombotic microangiopathy
Chronic complement-mediated TMA results in renal damage

- Kidney damage can manifest as either acute or chronic renal insufficiency, or proteinuria\(^1\)\(^-\)\(^7\)

- End-stage renal disease occurs in the majority of patients, regardless of initial manifestation\(^8\)

- Kidney damage may not be the predominant manifestation in all aHUS patients\(^1\)
  - 17% of patients reported to present with haematuria and proteinuria only, not renal failure\(^1\)

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**References**


aHUS, atypical Haemolytic Uraemic Syndrome;
TMA, thrombotic microangiopathy
Extrarenal complications are common in patients with aHUS

- Retrospective observations in a clinical setting (study C09-001) (n=30)¹
  - 100% evidence of kidney impairment
  - 63% of patients had extrarenal, systemic organ complications
  - 37% of patients had extrarenal thrombosis

<table>
<thead>
<tr>
<th>System</th>
<th>Signs and symptoms</th>
<th>Patients with complication, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Kidney impairment</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Thrombi (various locations), cardiac arrest, cardiomyopathy</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhoea, vomiting, pancreatitis, splenic vein occlusion</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Neurological</td>
<td>Seizure, acute disseminated encephalomyelitis, stroke, transient ischaemic attacks, facial paralysis, headache</td>
<td>5 (17)</td>
</tr>
<tr>
<td>aHUS complications in &gt;1 system</td>
<td></td>
<td>19 (63)</td>
</tr>
</tbody>
</table>

aHUS, atypical Haemolytic Uraemic Syndrome

1. Langman CB. 17th EHA Congress 2012, abstract 0490
aHUS can cause numerous gastrointestinal symptoms, including diarrhoea

- Gastrointestinal signs and symptoms reported in aHUS patients:
  - Abdominal pain,¹,² nausea and vomiting,¹ gastroenteritis,³ ischaemic colitis,⁴ pancolitis⁴,⁵
  - Pancreatitis,⁴ diabetes mellitus¹
  - Liver necrosis,¹ hepatitis, hepatic insufficiency¹,⁴

- Diarrhoea +/- blood reported as presenting symptom in ~30% of aHUS patients³


aHUS, atypical Haemolytic Uraemic Syndrome
## Genetic mutations in aHUS

<table>
<thead>
<tr>
<th>Mutated gene</th>
<th>Protein affected</th>
<th>Consequence</th>
<th>Frequency (%)</th>
<th>Death / ESRD 5–10 years after onset (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>Factor H</td>
<td>No binding to epithelium</td>
<td>20–30</td>
<td>70–80</td>
</tr>
<tr>
<td>CFHR1/3</td>
<td>CFHR1, R3</td>
<td>Anti-CFH antibodies</td>
<td>6</td>
<td>30–40</td>
</tr>
<tr>
<td>MCP</td>
<td>Membrane cofactor protein (CD46)</td>
<td>No surface expression</td>
<td>10–15</td>
<td>&lt;20</td>
</tr>
<tr>
<td>CFI</td>
<td>Factor I</td>
<td>Low level</td>
<td>4–10</td>
<td>60–70</td>
</tr>
<tr>
<td>CFB</td>
<td>Factor B</td>
<td>C3 convertase stabilisation</td>
<td>1–2</td>
<td>70</td>
</tr>
<tr>
<td>C3</td>
<td>C3</td>
<td>Resistance to C3b inactivation</td>
<td>5–10</td>
<td>60</td>
</tr>
<tr>
<td>THBD</td>
<td>Thrombomodulin</td>
<td>Reduced C3b inactivation</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>None identified</td>
<td>?</td>
<td>-</td>
<td>25–30</td>
<td>50&lt;sup&gt;a2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Rate of death or ESRD 3 years after aHUS onset, %

aHUS, atypical Haemolytic Uraemic Syndrome; CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; ESRD, end-stage renal disease; MCP, membrane cofactor protein; THBD, thrombomodulin

Pathophysiology of aHUS: summary

- aHUS is a life-threatening, catastrophic disease of chronic progressive TMA
- Chronic uncontrolled complement activation underlies the pathology of aHUS
- aHUS can occur at any age
- aHUS affects multiple organ systems
- Development of aHUS requires the presence of a combination of an endothelial insult and genetic factors
  - Common triggers of vascular injury include infection and pregnancy
  - 50–70% of aHUS patients have mutations in genes encoding components of the complement system
  - The presence of a complement mutation is not required for diagnosis
PE / PI does not reliably treat aHUS patients effectively and safely

- PE / PI does not target the cause of aHUS¹
  - Uncontrolled complement activation and resulting platelet activation persist during PE / PI²,³
  - Patients who initially improve on PE / PI may still develop anaemia, hypertension, renal impairment, neurological involvement or digital ischaemia⁴

- Despite PE / PI:
  - 33–40% of patients die or progress to ESRD with the first clinical manifestation¹,⁵
  - 65% of all patients die, require dialysis or have permanent renal damage within the first year after diagnosis⁵

- No controlled clinical trials have been conducted to show PE / PI to be either safe or effective as aHUS therapy⁶

- PE / PI has frequent and severe complications in both adults and children⁶–⁸

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Dialysis in aHUS

- Most patients with aHUS present with renal insufficiency and many require dialysis at admission\(^1\)

- Dialysis fails to suppress uncontrolled complement activation or to impact on ongoing TMA

- Patients on long-term dialysis have high morbidity and mortality\(^2-4\)
  - In patients on dialysis for ESRD by any cause, 1-year survival rate after TMA diagnosis is 58\(^%\)\(^5\)
  - 5-year survival rate for all dialysis patients is only 35\(^%\)\(^6\)

- Patients with ESRD on dialysis should be considered for chronic treatment with eculizumab:
  - to potentially improve renal function
  - to prevent progressive systemic TMA and its extrarenal complications

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aHUS, atypical Haemolytic Uraemic Syndrome; CKD, chronic kidney disease; ESRD, end-stage renal disease; TMA, thrombotic microangiopathy

1. Loirat C, Frémeaux-Bacchi V. Orphanet J Rare Dis 2011;6:60;
Kidney transplantation in aHUS patients

- Up to 80% of patients who develop aHUS progress to ESRD\(^1\)
- aHUS patients with ESRD awaiting transplant have high mortality risk\(^2\) and poor quality of life due to:
  - cumulative complications of plasma therapy\(^3\) including development of
    - immune / anaphylactic reactions\(^4\)
    - treatment resistance\(^5-7\)
  - infectious and thrombotic complications of vascular access\(^3,4\)
  - complications related to prolonged renal insufficiency\(^3\)
  - complications related to chronic dialysis\(^3\)
- High risk of graft failure\(^1\) may discourage use of transplantation\(^2\)

\(^{1}\) Noris M, Remuzzi G. N Engl J Med 2009;361:1676-87;
\(^{2}\) aHUS Action 2012;
\(^{4}\) Loirat C, Frémeaux-Bacchi V. Orphanet J Rare Dis 2011;6:60;
\(^{5}\) Davin JC et al. Pediatr Nephrol 2009;24:1757-60;

aHUS, atypical Haemolytic Uraemic Syndrome;
ESRD, end-stage renal disease
aHUS patients have a high risk of renal graft failure

- aHUS patients undergoing renal transplantation have a high risk of graft rejection
  - Ongoing TMA in ~50% of patients who undergo transplantation\(^1\)
  - Graft failure occurs in 80–90% of those with chronic TMA of aHUS\(^2\)
- Patients with aHUS may require multiple renal transplants\(^3,4\)

<table>
<thead>
<tr>
<th>1-year graft survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients(^5)</td>
</tr>
<tr>
<td>All aHUS patients(^6)</td>
</tr>
<tr>
<td>aHUS patients with CFH mutation(^6)</td>
</tr>
<tr>
<td>aHUS patients with no CFH mutation(^6)</td>
</tr>
<tr>
<td>aHUS patients with isolated MCP mutation(^5,6)</td>
</tr>
</tbody>
</table>


aHUS, atypical Haemolytic Uraemic Syndrome;
CFH, complement factor H; MCP, membrane cofactor protein;
TMA, thrombotic microangiopathy
Liver or combined liver and kidney transplantation in aHUS patients

- **Rationale**¹
  - Liver transplantation provides a source of functional complement proteins in patients with defects of complement factors originating from the liver
  - Combined liver–kidney transplantation restores renal function and provides functional complement

- **Early experience disappointing**²
  - 3 transplant recipients died

- **Modified transplant procedure**¹,²
  - Intensive PE + PI pre- and intra-operatively + low molecular weight heparin + aspirin

- **Transplant procedure remains high risk**¹
  - Of 14 combined transplantations performed with PE ± PI, 2 children have died from operative vascular difficulties

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aHUS, atypical Haemolytic Uraemic Syndrome; PE, plasma exchange; PI, plasma infusion
Eculizumab is indicated for the treatment of all paediatric and adult patients with aHUS

- **Mechanism of action in aHUS**
  - In aHUS patients, uncontrolled terminal complement activation and the resulting complement-mediated TMA are blocked with eculizumab treatment
  - In aHUS, chronic administration of eculizumab resulted in a rapid and sustained reduction in complement-mediated TMA

- **Treatment monitoring**
  - aHUS patients should be monitored for signs and symptoms of TMA
  - Eculizumab treatment is recommended to continue for a patient’s lifetime, unless the discontinuation of eculizumab is clinically indicated

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aHUS, atypical Haemolytic Uraemic Syndrome; TMA, thrombotic microangiopathy

Eculizumab dosing schedule in aHUS¹

For patients ≥18 years of age:

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion (mg)</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>1200</td>
<td>—</td>
<td>1200</td>
<td>—</td>
<td>1200</td>
</tr>
</tbody>
</table>

For patients <18 years of age:

<table>
<thead>
<tr>
<th>Body weight</th>
<th>40 kg and over</th>
<th>30 kg to &lt;40 kg</th>
<th>20 kg to &lt;30 kg</th>
<th>10 kg to &lt;20 kg</th>
<th>5 kg to &lt;10 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion (mg)</td>
<td>900 900 900 900</td>
<td>600 600 900</td>
<td>600 600 600</td>
<td>600 300</td>
<td>300</td>
</tr>
</tbody>
</table>

- Eculizumab should be administered at the recommended dosing interval or within 2 days before or after these time points. In all aHUS patients, an eculizumab serum concentration of ~50–100 μg/mL is required to provide complete inhibition of terminal complement activity¹

¹. Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012

aHUS, atypical Haemolytic Uraemic Syndrome; q14d, every 14 days
What to expect with eculizumab therapy of aHUS

- Significantly reduced or eliminated need for PE / PI and new dialysis
- Improved renal function and eliminated dialysis in most patients
- Increased likelihood of improved kidney function when treatment initiated early in disease progress
- Clinically meaningful improvements in health-related quality of life
- Similar effectiveness in patients with and without identified genetic mutation
- Efficacy and safety in paediatric patients consistent with that in adolescent and adult patients
Earlier treatment with eculizumab achieves better outcomes in aHUS patients

- Earlier treatment of aHUS provides more effective renal protection\(^1\)

- In aHUS patients post-renal transplant, those treated sooner had better improvement of renal graft function\(^2\)

- In aHUS patients with a poor response to standard therapy, early treatment with eculizumab may avoid irreversible renal damage\(^3\)
  - Eculizumab is unable to impact on irreversible renal damage that has already occurred\(^1,3\)

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Eculizumab in aHUS patients receiving kidney transplant

In prospective clinical studies in aHUS:¹,²
- 15/37 (41%) aHUS patients enrolled had received ≥1 prior kidney transplant
- Eculizumab inhibited TMA, normalised haematological parameters and improved quality of life and mortality risk
- A continuous improvement in kidney graft function was seen, even in patients with a history of prior transplant
- There were no new cases of graft rejection

In 22 renal transplant patients with aHUS who received eculizumab therapy:³
- 8/9 treated with prophylactic eculizumab were TMA-free
- Eculizumab treatment in 13 patients reversed post-transplant TMA in all cases

aHUS, atypical Haemolytic Uraemic Syndrome;
TMA, thrombotic microangiopathy

1. Alexion. Data on file; C08-003;
2. Alexion. Data on file; C08-002;
Patients with aHUS should be monitored during eculizumab treatment¹

- Clinical evidence of TMA complications
  - Neurological and / or cardiovascular signs and symptoms

- Laboratory signs of TMA
  - Decreased platelets
  - Increased LDH
  - Increased creatinine

- aHUS patients may require eculizumab dose adjustment

- Treat bacterial infections early with antibiotics

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aHUS, atypical Haemolytic Uraemic Syndrome;
LDH, lactate dehydrogenase;
TMA, thrombotic microangiopathy

Severe TMA complications observed in patients after eculizumab discontinuation

- Eculizumab treatment is recommended to continue for a patient’s lifetime, unless discontinuation is clinically indicated

- After treatment discontinuation
  - Monitor patients with aHUS for signs and symptoms of severe TMA complications for at least 12 weeks

- Severe TMA complications have been observed in aHUS patients after eculizumab discontinuation
  - 5/18 patients experienced TMA complications following a missed dose
  - Eculizumab was reinitiated in 4/5 patients

aHUS, atypical Haemolytic Uraemic Syndrome; TMA, thrombotic microangiopathy

Precautions against infection

- Patients receiving eculizumab may have increased susceptibility to infections, especially with encapsulated bacteria.

- All patients must be vaccinated against meningococci >2 weeks prior to receiving eculizumab.
  - For patients <2 years of age treated with eculizumab <2 weeks after receiving a meningococcal vaccine, treat with appropriate prophylactic antibiotics until 2 weeks after vaccination.

- Patients <18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections.

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

THANK YOU