aHUS: Advances in Pathogenesis, Diagnosis and Treatment

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Speaker: Alexion Pharmaceuticals
Objectives

- Discuss the role of unregulated complement in complement mediated diseases
- Provide an overview in the advances of pathophysiology and disease severity in aHUS
- Discuss the challenges in the differential diagnosis of aHUS, STEC-HUS, and TTP
- Discuss the state of the art treatment in aHUS and benefits of early intervention
Thrombotic Microangiopathy (TMA)

- Endothelial cell injury with the subsequent release of platelet-aggregating substances resulting in the formation of thrombotic lesions in terminal arterioles and capillaries

- Microangiopathic hemolytic anemia with thrombocytopenia (nonimmune)

- Systemic organ involvement (kidney, central nervous system)
TMA: Platelet, Endothelial, and Leukocyte Activation Leading to Inflammation, Thrombosis, and Systemic Small Vessel Occlusion


Manifestations of TMA

Cardiovascular\(^2,3,4,6\)
- Myocardial infarction
- Thromboembolism
- Cardiomyopathy
- Diffuse vasculopathy

CNS\(^1,2,3,4,5\)
- Confusion
- Seizures
- Stroke
- Encephalopathy
- Diffuse cerebral dysfunction

Renal\(^7,8,9,11,12\)
- Elevated creatinine
- Edema
- Malignant hypertension
- Renal failure
- Dialysis
- Transplant

Gastrointestinal\(^2,3,5,10,11,12\)
- Liver necrosis
- Pancreatitis
- Diabetes Mellitus
- Colitis
- Diarrhea
- Nausea/vomiting
- Abdominal pain

Pulmonary\(^1,6,14\)
- Dyspnea
- Pulmonary hemorrhage
- Pulmonary edema

Blood\(^11\)
- Hemolysis
- Decreased platelets
- Fatigue
- Transfusions

Impaired Quality of Life\(^13\)
- Fatigue
- Pain/anxiety
- Reduced mobility

TTP - Dr. Eli Moschcowitz

- Attending Physician, The Mount Sinai Hospital
- An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries: An Undescribed Disease
- Archiv Intern Med 1925; 36(1):89-93
- Read before the NY Pathological Society, Feb. 7, 1924
HUS – Dr. Conrad von Gasser

- Swiss hematologist, in September 1955, described five children in whom he had noted: diarrhea, hemolytic uremia, thrombocytopenia, and acute renal failure.

- Biopsy/Autopsy noted: hemorrhagic colitis, thrombosis of capillaries and precapillary arterioles in the lungs, brain, heart, and kidneys as well as renal cortical necrosis.

Atypical HUS (~10%)


Thrombotic Microangiopathies

**Primary TMAs**
- Hemolytic Uremic Syndrome (HUS)
  - Typical and Atypical
- Thrombotic Thrombocytopenic Purpura (TTP)
  - Acquired and Inherited

**Secondary TMAs**
- Systemic sclerosis (CREST)
- Systemic Lupus Erythematosus (SLE)
- Malignant hypertension
- Sepsis (DIC)
- Bone marrow transplantation
- HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets): pregnancy-associated
- Drugs (quinine induced; tacrolimus, cyclosporine; bleomycin, mitomycin, cisplatin; bevacizumab; rifampicin; clopidopogrel/ticlopidine)
Classification of HUS

- **Atypical**
  - Formerly D-
  - May have diarrhea
  - Familial
  - Recurrent
  - Can be sporadic
  - Often insidious presentation
  - Inexorable progression

- **Typical**
  - Formerly D+
  - Diarrhea prodrome (usually bloody)
  - E. coli & Shigella
  - Generally explosive presentation
  - Can be epidemic, endemic or sporadic
aHUS: A Life-Threatening Disease

- Rare, genetic disease that affects both children and adults
- Permanent, uncontrolled complement activation causes platelet and endothelial cell activation and systemic TMA
- Systemic TMA causes progressive renal failure, as well as multiple-organ damage
- Despite plasma exchange/infusion, more than half of aHUS patients die or suffer from end-stage renal disease (ESRD) within 1 year of diagnosis

Early History of Complement

- Began with studies on bacterial killing “Pfeiffer phenomenon”¹
- Identification of thermolabile factor in normal serum that enhanced antibody activity (Nuttall, 1888, Bordet 1894, Ehrlich 1899)³,⁴,⁵
- Optimal reactions of immune destruction depend on 2 principles¹,²,³:
  - 1 present in immune serum (fresh or heated)
    - Called “amboceptor” or “antibody”
  - 1 present in fresh (unheated) nonimmune serum
    - Called “alexin” or “complement”
- Donath and Landsteiner in human disease (paroxysmal cold hemoglobinuria)⁵

Balance Between Regulation and Amplification

Lectin Pathway  Classical Pathway  Alternative Pathway

Immune Complex Clearance  Microbial Opsonization

C3 + H₂O - ALWAYS ACTIVE (chronic)

Amplification

Natural Inhibitors: Factor H, I, MCP, CD55

C5a
- Potent Anaphylatoxin
- Chemotaxis
- Proinflammatory
- Leukocyte Activation
- Endothelial Activation
- Prothrombotic

C5

C5b-9
Membrane Attack Complex
- Cell Lysis
- Proinflammatory
- Platelet Activation
- Leukocyte Activation
- Endothelial Activation
- Prothrombotic

Natural Inhibitor: CD59

Research on Complement Inhibitors

- A variety of genetic mutations in complement inhibitor genes have been described starting in the early 1970’s for both PNH and aHUS

Chronic Uncontrolled Complement Activation Leads to Devastating Consequences

**Lectin Pathway**
- Immune Complex Clearance
- Microbial Opsonization

**Classical Pathway**
- **C3**
  - **C3 + H₂O - ALWAYS ACTIVE (chronic)**

**Alternative Pathway**
- **C3**
  - **C5**
    - **C5a**
      - Potent Anaphylatoxin
      - Chemotaxis
      - Proinflammatory
      - Leukocyte Activation
      - Endothelial Activation
      - Prothrombotic
    - **C5b-9**
      - Membrane Attack Complex
      - Cell Lysis
      - Proinflammatory
      - Platelet Activation
      - Leukocyte Activation
      - Endothelial Activation
      - Prothrombotic

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

**Consequences**
- Anaphylaxis
- Inflammation
- Thrombosis

Complement Involved in Many Diseases

- Paroxysmal nocturnal hemoglobinuria (PNH)
- Atypical Hemolytic Uremic Syndrome (aHUS)
- Cold agglutinin disease (CAD)
- Anti-phospholipid syndrome (APS) and Catastrophic APS
- MPGN Type II (Dense Deposit Disease; DDD)
- Antibody / Immune complex diseases
- Age-related macular degeneration
- Recurrent fetal loss
- Asthma
- Rheumatoid arthritis
- Lupus
- Ischemia and reperfusion injury (intestinal, hepatic)
Complement Activity Testing

- Most aHUS patients (including patients with identifiable mutations) have normal C3 and C4 levels, and complement regulatory protein levels are almost always normal.

- As a result, measurement of complement protein or complement regulatory protein levels are extremely insensitive and cannot rule out the presence of aHUS:
  - Serum C3 – normal in up to 80% \(^1,2,3\)
  - Serum C4 – normal in up to 93% \(^2\)
  - Factor H levels – normal in up to 87% of aHUS patients with identified CFH mutation \(^4\)

References:
Definition of aHUS

Signs and symptoms of complement-mediated TMA\(^1,2\)
- Decreased platelet count\(^1\)
- Evidence of microangiopathic hemolysis\(^1\)
- Evidence of organ impairment/damage (e.g. serum creatinine >ULN\(^2,3\))

Differentiate from other TMA diseases\(^1,2\)
- ADAMTS13 Activity >5% \(\rightarrow\) excludes severe ADAMTS13 deficiency (congenital or acquired TTP)\(^4,5,6,7\)
- Absence of positive STEC test \(\rightarrow\) excludes STEC as sole cause of TMA\(^8\)

No requirement for identified complement gene mutation
- Genetic mutation cannot be identified in 30%-50% of patients with aHUS\(^5\)

Atypical Hemolytic Uremic Syndrome (aHUS): A Genetic, Devastating and Life-Threatening Disease

- Sudden death and vital organ damage\(^1\)
- 33-40% of patients die or progress to End Stage Renal Disease (ESRD) with the first clinical manifestation\(^2,3\)
- Chronic progressive course with premature mortality\(^2,3,4\)
- 65% of all patients have died, require dialysis, or have permanent renal damage within the first year after diagnosis despite plasma exchange or plasma infusion (PE/PI)\(^2\)

Incidence of aHUS Complications by System

- aHUS can cause progressive and sudden damage across multiple organs through TMA manifestations
  - Evidence of TMA or progressive systemic involvement should prompt high suspicion of aHUS

<table>
<thead>
<tr>
<th>System</th>
<th>Signs/Symptoms</th>
<th>Number (%) of Patients with Complication</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>14 (47)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea, vomiting, pancreatitis, splenic vein occlusion</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Seizure, acute disseminated encephalomyelitis, stroke, transient ischemic attacks, facial paralysis, headache</td>
<td>6 (20)</td>
</tr>
<tr>
<td>aHUS complications in &gt;1 system</td>
<td></td>
<td>19 (63)</td>
</tr>
</tbody>
</table>

- 11 (37%) of the 30 aHUS patients experienced thrombi beyond the kidney

Plasma Therapy for aHUS


<table>
<thead>
<tr>
<th>Affected Protein</th>
<th>Response to Short-term Plasma Therapy (remission rate, %)</th>
<th>Long-term Outcome (rate of death or ESRD, %)</th>
<th>Recurrence After Kidney Transplantation (rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor H</td>
<td>60%</td>
<td>70%-80%</td>
<td>80%-90%</td>
</tr>
<tr>
<td>CFHR1, R3</td>
<td>70%-80%</td>
<td>30%-40%</td>
<td>20%</td>
</tr>
<tr>
<td>MCP</td>
<td>No definitive indication for therapy</td>
<td>&lt;20%</td>
<td>15%-20%</td>
</tr>
<tr>
<td>Factor I</td>
<td>30%-40%</td>
<td>60%-70%</td>
<td>70%-80%</td>
</tr>
<tr>
<td>Factor B</td>
<td>30%</td>
<td>70%</td>
<td>Recurrence in 1 case</td>
</tr>
<tr>
<td>C3</td>
<td>40%-50%</td>
<td>60%</td>
<td>40%-50%</td>
</tr>
<tr>
<td>THBD</td>
<td>60%</td>
<td>60%</td>
<td>Recurrence in 1 case</td>
</tr>
</tbody>
</table>

Atypical Hemolytic Uremic Syndrome in Children: Complement Mutations and Clinical Characteristics

### Treatment of First Episode

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (no.)</th>
<th>No genetic defect (no.)</th>
<th>Genetic defect (no.)</th>
<th>CFH (no.)</th>
<th>CFI (no.)</th>
<th>MCP (no.)</th>
<th>CFB (no.)</th>
<th>C3 (no.)</th>
<th>ΔCFHR1/3 (no.)</th>
<th>αFIH (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma therapy</strong></td>
<td>27 (45)</td>
<td>15 (25)</td>
<td>12 (20)</td>
<td>3 (5)</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td>1 (4)</td>
<td>3 (5)</td>
<td>4 (6)</td>
</tr>
<tr>
<td><strong>Dialysis</strong></td>
<td>20 (45)</td>
<td>12 (25)</td>
<td>8 (20)</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>1 (5)</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>PT and dialysis</strong></td>
<td>11 (45)</td>
<td>8 (25)</td>
<td>3 (20)</td>
<td>0 (5)</td>
<td>0 (3)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>0 (4)</td>
<td>0 (5)</td>
<td>0 (6)</td>
</tr>
<tr>
<td><strong>No PT or dialysis</strong></td>
<td>9 (45)</td>
<td>6 (25)</td>
<td>3 (20)</td>
<td>2 (5)</td>
<td>0 (3)</td>
<td>1 (4)</td>
<td>0 (2)</td>
<td>1 (4)</td>
<td>1 (5)</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td>12 (45)</td>
<td>9 (25)</td>
<td>3 (20)</td>
<td>2 (5)</td>
<td>0 (3)</td>
<td>1 (4)</td>
<td>0 (2)</td>
<td>0 (4)</td>
<td>0 (5)</td>
<td>0 (6)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>31 (45)</td>
<td>14 (25)</td>
<td>17 (20)</td>
<td>3 (5)</td>
<td>3 (3)</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>5 (5)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Chronic PT</td>
<td>12 (44)</td>
<td>6 (25)</td>
<td>6 (20)</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>0 (2)</td>
<td>0 (4)</td>
<td>3 (5)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>7 (45)</td>
<td>3 (25)</td>
<td>4 (20)</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>0 (4)</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0 (5)</td>
<td>0 (6)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (45)</td>
<td>1 (25)</td>
<td>0 (20)</td>
<td>0 (5)</td>
<td>0 (3)</td>
<td>0 (4)</td>
<td>0 (2)</td>
<td>0 (4)</td>
<td>0 (5)</td>
<td>0 (6)</td>
</tr>
</tbody>
</table>

### Long-term Outcome – 10 years (mean 7.5)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (no.)</th>
<th>No genetic defect (no.)</th>
<th>Genetic defect (no.)</th>
<th>CFH (no.)</th>
<th>CFI (no.)</th>
<th>MCP (no.)</th>
<th>CFB (no.)</th>
<th>C3 (no.)</th>
<th>ΔCFHR1/3 (no.)</th>
<th>αFIH (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapses</strong></td>
<td>21 (43)</td>
<td>9 (23)</td>
<td>12 (20)</td>
<td>3 (5)</td>
<td>1 (3)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>3 (4)</td>
<td>3 (5)</td>
<td>3 (6)</td>
</tr>
<tr>
<td><strong>No. of relapses</strong></td>
<td>43 (21)</td>
<td>14 (9)</td>
<td>29 (20)</td>
<td>8 (3)</td>
<td>4 (1)</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>8 (3)</td>
<td>9 (3)</td>
<td>9 (3)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>23 (43)</td>
<td>12 (23)</td>
<td>11 (19)</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td>2 (4)</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>3 (5)</td>
<td>4 (6)</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>18 (38)</td>
<td>9 (21)</td>
<td>9 (17)</td>
<td>0 (2)</td>
<td>1 (3)</td>
<td>1 (2)</td>
<td>2 (2)</td>
<td>2 (4)</td>
<td>2 (5)</td>
<td>2 (6)</td>
</tr>
<tr>
<td><strong>Renal Tx</strong></td>
<td>7 (44)</td>
<td>3 (24)</td>
<td>4 (20)</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>0 (2)</td>
<td>1 (4)</td>
<td>0 (5)</td>
<td>0 (6)</td>
</tr>
<tr>
<td><strong>No. of Tx</strong></td>
<td>13 (7)</td>
<td>5 (3)</td>
<td>8 (4)</td>
<td>4 (2)</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>3 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>No. of relapses in renal graft</strong></td>
<td>10 (13)</td>
<td>4 (5)</td>
<td>6 (8)</td>
<td>5 (4)</td>
<td>2 (3)</td>
<td>0 (1)</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>4 (45)</td>
<td>2 (25)</td>
<td>2 (20)</td>
<td>0 (5)</td>
<td>0 (3)</td>
<td>1 (4)</td>
<td>0 (2)</td>
<td>0 (4)</td>
<td>1 (5)</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

Time to first relapse, from 1 month to 8.5 years

aHUS is Frequently Diagnosed in Patients With Comorbid Diseases

- 25% (47/191) of patients with aHUS and no known affected family member have coexisting diseases
- Complement mutations identifiable in only 27% of aHUS patients
  - Similar to rate in all aHUS patients with no known affected family member (41%)

<table>
<thead>
<tr>
<th>Comorbid Diseases</th>
<th>aHUS Patients With Comorbid Disease, n (%)</th>
<th>aHUS Patient With No Identified Mutation and Comorbid Disease, n</th>
<th>aHUS Patient With Identified Mutation and Comorbid Disease, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy and Chemotherapy</td>
<td>1 (2%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Malignant Hypertension</td>
<td>14 (30%)</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Post Transplant HUS* and Calcineurin Inhibitors</td>
<td>11 (23%)</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Pregnancy-related HUS</td>
<td>10 (21%)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Systemic disease -Scleroderma</td>
<td>3 (6%)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>-SLE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulopathy†</td>
<td>8 (17%)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>47 (100%)</td>
<td>34</td>
<td>13</td>
</tr>
</tbody>
</table>

*Primary cause nephropathy unknown - 6/11 pts (3 w/mutations), 2 IgA nephrop., 1 DM nephrop., 1 MPGN, 1 reflux nephropathy.
†Glomerulopathy: MPGN, nephrotic syndrome, mesangioproliferative glomerulonephritis, membranous glomerulonephritis.

aHUS Patients Generally are Not Effectively and Safely Treated With Plasma Exchange/Infusion

- 33-40% of patients die or progress to ESRD with the first clinical manifestation\(^1,2\)

- 65% of all patients have died, require dialysis, or have permanent renal damage within the first year after diagnosis despite PE/PI \(^1\)

- No well-controlled clinical trials showing plasma exchange/infusion to be either safe or effective as aHUS therapy\(^3,4\)

- Frequent and severe complications in adults and in children\(^5,6\)

- Plasma exchange/infusion does not target the cause of aHUS: uncontrolled, excessive complement activation\(^2\)
  - Uncontrolled complement activation and resulting platelet activation demonstrated to persist during PE/PI\(^7,8\)

### Challenges in Diagnosing aHUS

- Clinical presentation can be similar to other systemic TMAs\(^1-3\)
- Historical treatment did not require differential diagnosis between aHUS, TTP and STEC-HUS – historically grouped as TTP/HUS\(^4,5\)
- aHUS is a rare disease leading to lack of clinical suspicion
- Rarity of aHUS may impact accurate and rapid diagnosis
  - Perception that genetic mutation needs to be identified\(^6\)
  - Perception that aHUS is only a pediatric disease\(^6\)
  - Perception that aHUS is only a renal disease\(^6\)

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Genetic mutation cannot be identified in 30%-50% of patients with aHUS\(^1\)

Absence of identifiable genetic mutations does not rule out aHUS\(^1\)

Results generally takes weeks to months – therefore does not impact initial clinical management\(^2\)

Differential Diagnosis for TMAs: aHUS, TTP and STEC-HUS

**Thrombocytopenia**
- Platelet count <150,000 Or
- >25% Decrease from baseline

**AND**

**Microangiopathic Hemolysis**
- Schistocytes and/or
- Elevated LDH and/or
- Decreased Haptoglobin and/or
- Decreased Hemoglobin

**Plus One or More of the Following:**

**Neurological Symptoms**
- Confusion and/or
- Seizures and/or
- Other Cerebral Abnormalities

**Renal Impairment**
- Elevated Creatinine and/or
- Decreased eGFR and/or
- Elevated Blood Pressure and/or
- Abnormal Urinalysis

**Gastrointestinal Symptoms**
- Diarrhea +/- Blood and/or
- Nausea/Vomiting and/or
- Abdominal Pain and/or
- Gastroenteritis

Evaluate ADAMTS13 Activity and Shiga-toxin/EHEC* Test

- ≤5% ADAMTS13 Activity
- >5% ADAMTS13 Activity
- Shiga-toxin/EHEC Positive

**TTP**
**aHUS**
**STEC-HUS**

* Shiga-toxin/EHEC test is warranted with history/presence of GI symptoms.

Novel Strategies for the Treatment of aHUS
Eculizumab (Soliris) First in Class Humanized Anti-C5 Monoclonal Antibody

Eculizumab Blocks Terminal Complement \(^1,^2\)

- Eculizumab binds with high affinity to C5 \(^1,^2\)
- Terminal complement - C5a and C5b-9 activity blocked \(^1,^2\)
- Proximal functions of complement remain intact \(^1,^2\)
  - Weak anaphylatoxin \(^2,^4\)
  - Immune complex clearance \(^2\)
  - Microbial opsonization \(^2\)

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Eculizumab for Congenital Atypical Hemolytic-Uremic Syndrome

18 m.o. boy; 4th relapse; normal ADAMTS13; no identifiable mutations

Figure 1. Response to Eculizumab Therapy in a Patient with Congenital Atypical Hemolytic-Uremic Syndrome.
Eculizumab Multinational, Multi-Center Clinical Program in aHUS (N=67)

Clinical Diagnosis of aHUS With¹
- TMA (measured by platelet count, hemolysis)
- Organ Damage (serum creatinine ≥ULN)
- ADAMTS13 >5%; no positive STEC test
- No requirement for identified genetic mutation

Prospective (26 weeks)¹
- Patients with long duration of aHUS (C08-003) (N=20)
  Adult/adolescent
- aHUS patients with progressing TMA (C08-002) (N=17)
  Adult/adolescent

Long-term Extension Studies²,³
86% (32/37) of patients continued chronic Eculizumab treatment in extension studies

Retrospective¹
- Medical Practice Setting (C09-001) (N=30)
  19 Patients <18 years old

### Eculizumab Multinational Clinical Program
Includes Broad aHUS Patient Population

<table>
<thead>
<tr>
<th>Age</th>
<th>2 month&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Adults&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration from aHUS Diagnosis to Study</td>
<td>&lt;1 month&lt;sup&gt;1&lt;/sup&gt;</td>
<td>286 months&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Identified Genetic Complement Mutations</td>
<td>None identified&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Multiple per patient&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>TMA in Patients With</td>
<td>Normal platelet count&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Reduced platelet count&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Degree of Organ Damage</td>
<td>CKD Stage 1&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CKD Stage 5&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dialysis</td>
<td>None&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3/week&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>PE/PI</td>
<td>No intervention&lt;sup&gt;1*&lt;/sup&gt;</td>
<td>230 interventions&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Renal Transplant</td>
<td>None&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3 prior kidney grafts lost&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Based on study definition.

**Prospective Studies: Eculizumab 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>1</td>
<td>2</td>
</tr>
<tr>
<td>Neisseria meningitidis vaccination</td>
<td>Eculizumab dose, mg</td>
<td>900</td>
</tr>
</tbody>
</table>

- **Administration**: IV infusion over 35 min every 7 d during induction and every 14 d during maintenance
  - Dose adjustment to every 12 days may be necessary

- **Meningococcal prophylaxis**: patients received meningococcal vaccination prior to receipt of Eculizumab or received prophylactic treatment with antibiotics until 2 weeks after vaccination

- **Severe TMA complications** observed in aHUS patients deviating from recommended dosing schedule
  - 5/18 patients experienced TMA complications following missed dose
  - Eculizumab was reinitiated in 4/5 patients

*For patients <18 years of age, administration of Eculizumab is based on body weight.

### Eculizumab Prospective Trials: Key Clinical Trial Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Patients with long duration of aHUS (C08-003) (N=20)</th>
<th>aHUS patients with progressing TMA (C08-002) (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in TMA (Change in platelet count)</td>
<td>✓ Primary</td>
<td></td>
</tr>
<tr>
<td>TMA event-free status</td>
<td>Primary</td>
<td>✓</td>
</tr>
<tr>
<td>Hematologic normalization</td>
<td>Coprimary</td>
<td>Coprimary</td>
</tr>
<tr>
<td>Reduction in PE/PI or new dialysis (TMA intervention rate)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Change in renal function (eGFR, CKD stage)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HRQoL measures</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**TMA event-free status:** For 12 consecutive weeks, no decrease in platelet count >25% from baseline, and no plasma exchange/infusion, and no new dialysis

**Hematologic normalization:** Normalization of both platelet count and LDH sustained for at least 2 consecutive measurements that span a period of at least 4 weeks

**TMA intervention rate:** Number of plasma exchange or plasma infusion interventions or dialyses required per patient per day

HRQoL = health-related quality of life. *Primary endpoint requested by the regulatory authorities.*

Long Duration of aHUS Clinical Trial Patient Population

- Long duration of aHUS and substantial renal damage despite prior long-term PE/PI
  - Median duration from aHUS diagnosis to screening: 48 months (range 0.66-286)
  - 50% of patients with eGFR <30 mL/min/1.73M², including 2 patients on chronic dialysis
  - PE/PI for a median duration of 10 months (range 2.4-47) prior to eculizumab

Licht C et al. ESPN Annual Meeting 2011 (Poster PS2-FRI-272); Licht C et al. ASN Annual Meeting 2011 (Poster TH-PO366).
Eculizumab Led to TMA Event-Free Status in 85% of Patients At Median of 62 Weeks Treatment

- No decrease in platelet count >25% from baseline AND
- No plasma exchange/infusion AND
- No new dialysis

*For at least 12 consecutive weeks*

- In 20/20 patients:
  - Elimination of PE/PI AND
  - No new dialysis
- The benefit was sustained through the entire study period (median eculizumab 62 weeks)

Licht C et al. ASH Annual Meeting 2011 (Poster 3033).
Eculizumab Eliminated PE/PI in 100% of Patients and No Patient Required New Dialysis

- In every patient:
  - Elimination of PE/PI AND
  - No new dialysis

- Reduction from:
  - Approximately median (range) of 1.5 (0.4-7.6) interventions per patient per week prior to eculizumab treatment
  - 0 interventions in all 20 patients during the entire study period

- The benefit was sustained through the entire study period (median eculizumab 62 weeks)

TMA intervention rate: Number of plasma exchange or plasma infusion interventions and number of new dialyses required per patient per day.
Licht C et al. ASH Annual Meeting 2011 (Poster 3033).
Chronic Eculizumab Improved Renal Function During Median of 62 Weeks

- Eculizumab treatment was associated with a significant and continuous, time-dependent improvement in eGFR through a median duration of 62 weeks ($P<0.0001$).
- Mean increase from baseline of 6.1 mL/min/1.73 m$^2$ at week 26 (95% CI: 3.3, 8.8; 21% increase) 8.3 mL/min/1.73 m$^2$ at week 60 (95% CI: 4.8, 11.7; 27% increase).

Eculizumab was associated with a significant, continuous increase in eGFR, from day 0 through day 28 (positive rate of change, $P=0.022$), and a sustained increase in eGFR over time from day 28 through a median duration of 62 weeks (positive rate of change, $P=0.048$).

Licht C et al. Presented at ASH; December 10–12, 2011; San Diego, CA. 3033.
Earlier Intervention with Eculizumab Led to Greater Improvement in eGFR

- Earlier eculizumab treatment was a significant predictor of improved eGFR through week 62, (ANOVA with clinical disease manifestation as covariate, $P=0.008$)

Correlation = -0.60; $P=0.0066$

Progressing TMA Clinical Trial Patient Population

- aHUS patients with progressing TMA
  - Shorter duration of disease compared with Study C08-003
  - 10 months median duration (range 0.26-236) from aHUS diagnosis

Greenbaum L et al. ASN Annual Meeting 2011 (Poster TH-PO367).
Chronic Eculizumab Inhibited Complement-Mediated TMA as Measured by a Significant Increase in Platelet Count

- Mean platelet increase between baseline and 52 weeks: $90 \times 10^9/L$ ($P<0.0001$)
- Significant increase in platelet count as early as Day 7 ($P=0.027$)
- Platelet increase sustained through a median duration of 64 weeks

Greenbaum L et al. ASH Annual Meeting 2011 (Oral Presentation 193).
Complement Activity, the Cause of Symptoms and Clinical Manifestations of aHUS, Was Reduced in All Patients During Eculizumab Treatment

Change From Baseline to End of Study Period

- Reduction observed in all patients after commencement of Eculizumab
- Reduction sustained through end of study

*Based on a pharmacodynamic assay that quantified the complement activity in patient’s serum by measuring the degree of hemolysis; the measure of hemolysis is the amount of hemoglobin release as determined via spectrophotometer.
Chronic Eculizumab Inhibited Complement-Mediated TMA: 88% of Patients Achieved TMA Event-Free Status

- No decrease in platelet count >25% from baseline AND
- No plasma exchange/infusion AND
- No new dialysis
  
  For at least 12 consecutive weeks

- Benefit sustained through a median duration of 64 weeks

*Two patients discontinued Eculizumab treatment after 1 and 4 doses and did not achieve TMA event-free status.

Greenbaum L et al. ASH Annual Meeting 2011 (Oral Presentation 193).
Chronic Eculizumab Treatment Significantly Improved eGFR

- Sustained eculizumab treatment showed a statistically significant, time-dependent increase in eGFR
  - 31 mL/min/1.73m² (95% CI, 17-45) through Week 26 ($P=0.0001$)
  - 31 mL/min/1.73m² (95% CI, 14-44) through a median duration of 64 weeks ($P=0.0003$)

Greenbaum L et al. ASH Annual Meeting 2011 (Oral Presentation 193).
Eculizumab Eliminated Dialysis in 4/5 Patients (80%)

- Patients remained dialysis-free at a median duration of 64 weeks eculizumab treatment
- One patient developed a new dialysis requirement during eculizumab treatment; this patient discontinued eculizumab due to an adverse event unrelated to eculizumab treatment (worsening of pancytopenia)
- Patients eliminated dialysis within 14 days following initiation of eculizumab

Greenbaum L et al. ASH Annual Meeting 2011 (Oral Presentation 193).
Earlier Intervention with Eculizumab Leads to Greater Improvement in Renal Function

- Earlier eculizumab treatment resulted in greater eGFR improvement through median duration of 64 weeks (duration of current clinical TMA manifestation as covariate, p=0.005)

Median duration of aHUS current clinical manifestation to study was 0.75 months (range 0.2–4.0).
Medical Practice Patient Population (age <18 years)

- Children (2 months to 11 years, n=15), adolescents (12 to 18 years, n=4)\(^1\)
- Median (range) duration of eculizumab treatment: 28 (1-70) weeks\(^2\)
- 47% with no identified genetic mutation\(^1\)
- Medical practice setting:\(^2\)
  - No requirement for PE/PI
  - No requirement for platelet count, ADAMTS13 activity, complement mutation, or LDH/creatinine values
  - Median duration since aHUS diagnosis was 19 months (range: <1-177 months)

---

Key Outcomes from the Retrospective Trial

**Eculizumab Inhibited Complement-Mediated TMA:**
- **68% of Patients Achieved TMA Event-Free Status**

**Patients Achieving TMA Event-Free Status, % (n/N)**
- All Patients (n=19): 68% (13/19)

**Eculizumab Reduced Burden of Disease as Measured by Reduction in PE/PI and New Dialysis**

**Patients with Normalized Platelet Count, % (n/N)**
- All Patients (n=19): 89% (17/19)
- Patients with abnormal platelet count at baseline (n=8): 88% (7/8)

**Eculizumab Markedly Improved Renal Function**

**eGFR improvement ≥15 mL/min/1.73 m², n (%)**
- **Pediatrics N=19**: 9 (47*)

**Note:** For all parameters, improvement in at least 2 consecutive measurements over 4 weeks.
*One patient obtained eGFR improvement after renal transplantation.

---

### Patient History and Outcomes Across Eculizumab Clinical Program in aHUS

<table>
<thead>
<tr>
<th></th>
<th>Patients With Long Duration of aHUS (C08-003) Adolescent/Adult Prospective Study(^1) ((N=20))</th>
<th>aHUS Patients With Progressing TMA (C08-002) Adolescent/Adult Prospective Study(^2) ((N=17))</th>
<th>Medical Practice Setting (C09-001) Retrospective Pediatric Study(^3,4) ((N=19))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (range) Duration Since aHUS Diagnosis</strong></td>
<td>48 months ((0.66-286 \text{ mo}))</td>
<td>10 months ((0.26-236 \text{ mo}))</td>
<td>19 months ((0.39-177 \text{ mo}))</td>
</tr>
<tr>
<td><strong>Uncontrolled Complement Activation Inhibited</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Complement-mediated TMA Inhibited</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Burden of Interventions Reduced</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Renal Function</strong></td>
<td>Maintained or Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td><strong>Requirement for Dialysis</strong></td>
<td>No New Dialysis</td>
<td>Eliminated in 80%</td>
<td>Eliminated in 50%, no new dialysis</td>
</tr>
<tr>
<td><strong>Safety During Study Period</strong></td>
<td>Well tolerated(^*)</td>
<td>Well tolerated(^*)</td>
<td>Well tolerated(^\ddagger)</td>
</tr>
<tr>
<td><strong>Complement mutation</strong></td>
<td></td>
<td></td>
<td>Similar outcomes with or without identified mutation</td>
</tr>
</tbody>
</table>

\(^*\)All patients alive; no meningococcal infections.  
\(^\ddagger\)1 patient died (not drug related); 1 meningococcal infection (post-study follow-up period).

SOLIRIS® (eculizumab) Indication for aHUS

Soliris is a complement inhibitor indicated for:

- 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)
Severe TMA Complications Observed After Eculizumab Discontinuation
Definition of Severe TMA Complication

Severe TMA complication identified by either:

1. Any 2, or repeated measurement of 1 of the following:
   - Decrease in platelet count of ≥25%, compared to baseline or peak during Soliris treatment

   OR

   - Increase in serum creatinine of ≥25%, compared to baseline or lowest during Soliris treatment

   OR

   - Increase in serum LDH of ≥25%, compared to baseline or peak during Soliris treatment

2. Any of the following:
   - Change in mental status
   - Seizures
   - Angina
   - Dyspnea
   - Thrombosis
Eculizumab Discontinuation from aHUS Clinical Trials - Outcome

- 18 aHUS clinical trial patients discontinued Soliris at least once during their respective study
  - 5 patients in prospective aHUS clinical trials:
    • 4 in C08-002 and 1 in C08-003
  - 13 patients in retrospective aHUS clinical trial (C09-001)
    • Medical practice patient population – variability in Soliris use
- 5/18 Patients (28%) experienced a severe TMA complication following missed* dose(s) of Soliris
  - 4/5 Patients subsequently re-initiated Soliris treatment
- Morbidities were observed in some of the remaining 13 patients following Soliris discontinuation
- Median follow-up time 27 days (range 0-347 days)
- Only 3 patients with >8 weeks follow-up
Eculizimab Discontinuation from aHUS Clinical Trials - Outcomes

Of 18 patients discontinuing Soliris

- 5 (28%) - Severe TMA complication
  - 4/5 Patients subsequently re-initiated Soliris treatment
- 4 (22%) - No follow-up
  - 2 deaths, 1 lost to follow up, 1 excluded from study
- 5 (28%) - On dialysis before and after Soliris treatment
  - Maximum follow-up 24 days
  - Occurrence of TMA and extra-renal symptoms not known
- 4 (22%) - No complication reported by end of data collection
  - Median follow-up 50 days, range 42-241
Patients Who Discontinue Eculizumab are at Early and Ongoing Risk of Severe TMA Complications

Duration of Time Between Soliris Discontinuation and Severe TMA Complication

Patient 1*
(1 dose)
347 days

Patient 2†
(28 weeks)
80 days

Patient 3*
(1 dose)
33 days

Patient 4§
(1 dose)
30 days

Patient 5§
(1 dose)
8 days

Number of Days

Patient discontinued due to:
* Normalized renal and/or hematologic function.
† Declining participation in extension study, or lack of improvement in renal function.
§ Data on file. Alexion Pharmaceuticals, Inc.
Important Safety Information
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).
Warnings and Precautions

- 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.
- Infusion reactions may occur, as with all protein products.
  - 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.
## Treatment Emergent Adverse Events Occurring in >10% of Adult and Adolescent Patients Enrolled in aHUS Study 1 and Study 2

<table>
<thead>
<tr>
<th>MedDRA ver. 11.0; patients, n (%)</th>
<th>Study 1 (n=17)</th>
<th>Study 2 (n=20)</th>
<th>Total (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (47)</td>
<td>5 (25)</td>
<td>13 (35)</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5 (29)</td>
<td>8 (40)</td>
<td>13 (35)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (24)</td>
<td>2 (10)</td>
<td>6 (16)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (35)</td>
<td>6 (30)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (29)</td>
<td>3 (15)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (24)</td>
<td>3 (15)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>4 (20)</td>
<td>4 (11)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7 (41)</td>
<td>4 (20)</td>
<td>11 (30)</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (35)</td>
<td>3 (15)</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4 (24)</td>
<td>2 (10)</td>
<td>6 (16)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MedDRA ver. 11.0; patients, n (%)</th>
<th>Study 1 (n=17)</th>
<th>Study 2 (n=20)</th>
<th>Total (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (24)</td>
<td>1 (5)</td>
<td>5 (14)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>2 (12)</td>
<td>3 (15)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Pharyngolaryngeal Pain</td>
<td>1 (6)</td>
<td>4 (20)</td>
<td>5 (14)</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (18)</td>
<td>1 (5)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3 (18)</td>
<td>1 (5)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (18)</td>
<td>1 (5)</td>
<td>4 (11)</td>
</tr>
<tr>
<td><strong>Ear and Labyrinth Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 (6)</td>
<td>3 (15)</td>
<td>4 (11)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (6)</td>
<td>3 (15)</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes the preferred terms hypertension, accelerated hypertension, and malignant hypertension.

<sup>b</sup> Includes the preferred terms upper respiratory tract infection and nasopharyngitis.
### Treatment-Emergent Adverse Events Occurring in >15% of Patients <18 Years of Age Enrolled in aHUS Study 3

<table>
<thead>
<tr>
<th>MedDRA ver. 11.0; patients, n (%)</th>
<th>&lt;2 Years (n=5)</th>
<th>2 to &lt;12 Years (n=10)</th>
<th>12 to &lt;18 Years (n=4)</th>
<th>Total (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (80)</td>
<td>4 (60)</td>
<td>1 (25)</td>
<td>9 (47)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (20)</td>
<td>4 (40)</td>
<td>1 (25)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (40)</td>
<td>1 (10)</td>
<td>1 (25)</td>
<td>4 (21)</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infectiona</td>
<td>2 (40)</td>
<td>3 (30)</td>
<td>1 (25)</td>
<td>6 (32)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>3 (60)</td>
<td>2 (20)</td>
<td>0</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>2 (40)</td>
<td>2 (20)</td>
<td>0</td>
<td>4 (21)</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2 (40)</td>
<td>2 (20)</td>
<td>0</td>
<td>4 (21)</td>
</tr>
</tbody>
</table>

a Includes the preferred terms upper respiratory tract infection and nasopharyngitis.
Patient Safety Information Card

- Healthcare professionals (HCP) are provided with the Patient Safety Information Card to give to their patients. HCPs 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 HCP involved in their care.
- The Patient Safety Information Card contains safety guidance for Soliris patients and their HCPs.
- Prescribers should advise patients to seek medical attention immediately if they develop any symptoms listed on the card, even if they don’t have their Patient Safety Information Card with them.

**PATIENT SAFETY INFORMATION CARD**

**Important Safety Information for Patients Taking Soliris**

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 care center:

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever of 103°F (39.4°C) or higher
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Get emergency medical care right away if you have any of these signs or symptoms and show this card.
Eculizumab Treatment Expectations
In aHUS Clinical Trials, Many Eculizumab Benefits Occurred Rapidly, While Others Occurred Over Time

1 to 2 Weeks*
- Increase or normalization in platelet count in patients with progressing TMA\(^1,2\)
- Reduction or elimination of PE/PI and no new dialysis\(^1,2\)

4 Weeks*
- Maintenance or improvement in renal function
  - Increase in eGFR\(^1,2\)
- Decrease or normalization in hemolysis (as measured by LDH)\(^2\)

26 Weeks*
- Maintenance or greater improvement in renal function\(^1\)
- Hematologic normalization\(^1\)

Ongoing Eculizumab Treatment Inhibits Complement-mediated TMA\(^1,2\)

The majority of patients in prospective studies continued in extension studies\(^1\)

*Benefits at these time intervals were experienced by many patients but do not indicate that every patient will achieve the same results.

Eculizumab Prospective Clinical Trial

Conclusions

- Eculizumab treatment results in a rapid and sustained inhibition of the TMA process

- In patients with eculizumab initiation 10 months after aHUS diagnosis, eculizumab resulted in sustained improvement in renal function and 80% of patients eliminated dialysis

- In patients receiving long-term PE/PI with a median 48 month since aHUS diagnosis and severe renal impairment, eculizumab eliminated PE/PI in all patients and no new dialysis sessions were required

- Eculizumab treatment leads to significant and sustained, time-dependent improvement in renal function through 26 weeks and median duration >60 weeks

- In all three trials, earlier intervention with eculizumab is associated with greater improvement in renal function

Licht C et al. ESPN Annual Meeting 2011 (Poster PS2-FRI-272); Licht C et al. ASN Annual Meeting 2011 (Poster TH-PO366); Loirat C et al. ESPN Annual Meeting 2011 (Poster PS2-FRI-273); Greenbaum L et al. ASN Annual Meeting 2011 (Poster TH-PO367).
Mayo Medical Laboratories

ADAMTS13 Test
- ADAMTS13: Will be offered in-house the first week of August
- Test run 7 days a week with 24 hour TAT (first week of Aug.)
- ADAMTS13 activity: price to be finalized on August 6
- ADAMTS13 inhibitor: price to be finalized on August 6
- Critical call back for all results <10% activity

Shiga-Toxin Test
- Stool culture: List price $82.80
- *E. Coli* Rapid culture (EIA): List price $126.30
- *E. Coli* PCR: List price $327.90 – 100% specific/100% accurate
- 24 hour TAT for PCR real-time

Flow Cytometry for PNH
- High sensitivity flow cytometry for PNH
- 24 hour TAT
- Flow for PNH: List price $377.40
- Interpretation: List price additional $117.40
- Interpretation will be provided by Mayo on all abnormal results

TAT=Turn-around time; EIA=Electrophoresis immunoassay
Genetics Testing Labs

- **MORL (Molecular Otolaryngology & Renal Research Laboratories) at The University of Iowa**
  - [http://www.healthcare.uiowa.edu/labs/morl/index.htm](http://www.healthcare.uiowa.edu/labs/morl/index.htm)
  - Phone: 319-335-6623

- **The Mario Negri Institute for Pharmacological Research**
  - Phone: +39.02.39014.1

- **Institute of Genetic Medicine at Newcastle University (Goodship Lab)**
  - [http://www.ncl.ac.uk/igm/services/ngs/](http://www.ncl.ac.uk/igm/services/ngs/)
  - Phone ++ (0)191 241 8616
aHUS Registry

An Observational, Non-interventional, Multi-center, Multi-national Study of Patients With Atypical Hemolytic-Uremic Syndrome

Registry

- Patients with a diagnosis of aHUS, regardless of treatment, will be eligible for enrollment after signing an informed consent.

Inclusion Criteria

- Male or female patients of any age, including minors, who have been diagnosed with aHUS
- Diagnosis of aHUS includes:
  - Clinical diagnosis of aHUS
  - Patients with or without an identified complement regulatory factor genetic abnormality or anti-complement factor antibody
  - ADAMTS13 >5% (if performed)

Exclusion Criteria

- Patients with Hemolytic Uremic Syndrome (HUS) only due to Shiga Toxin are excluded.