TREATMENT-NAÏVE PEDIATRIC PATIENT WITH ATYPICAL HEMOLYTIC UREMIC SYNDROME (ATYPICAL-HUS): A CASE STUDY

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS. 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 meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a meningococcal infection. See Warnings and Precautions for additional guidance on the management of the risk of meningococcal infection.
- Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program. Enrollment in the ULTOMIRIS REMS program and additional information are available by telephone: 1-888-765-4747 or at www.ultomirisrems.com.

INDICATION

ULTOMIRIS is indicated for the treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Limitation of Use: ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.
“WHEN PATRICK GOT SICK, I DIDN’T KNOW WHAT TO DO.”

— Patrick’s dad

This is Patrick. He is 4 years old and was just diagnosed with atypical-HUS.

Based on an actual patient in the 312 study

Patrick

Age: 4 years old
Height: 104.5 cm (3 ft 5 in)
Weight: 17.5 kg (38.6 lbs)
Diagnosed with atypical-HUS

Family history

- Family history of diabetes, kidney disease, and anatomical defects of kidneys

Select signs and symptoms at presentation

- Vital signs: BP: 123/81, Temp: 37°C (98.6°F), HR: 120, RR: 26
- Seizures, cough, and emesis
- Patient had a single functioning kidney
- Patient had evidence of cerebellar lesions (possibly pre-existing)
- Patient did not present with fever or diarrhea

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; BP=blood pressure; eGFR=estimated glomerular filtration rate; HR=heart rate; HUS=hemolytic uremic syndrome; LDH=lactate dehydrogenase; RR=respiratory rate; TTP=thrombotic thrombocytopenic purpura.

LAB VALUES AT DAY 1

<table>
<thead>
<tr>
<th>Measured Parameter</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/L)</td>
<td>79</td>
<td>107-139 g/L</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>2228</td>
<td>155-345 U/L</td>
</tr>
<tr>
<td>Platelet count (x 10^9/L)</td>
<td>41</td>
<td>217-497 x 10^9/L</td>
</tr>
<tr>
<td>Creatinine (ranges μmol/L)</td>
<td>256</td>
<td>18-62 μmol/L</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Urine protein/creatinine (mg/mmol)</td>
<td>1252</td>
<td>≤0.2 mg/mmol</td>
</tr>
<tr>
<td>ADAMTS13 activity (%)</td>
<td>76</td>
<td>&gt;5% ADAMTS activity=atypical-HUS, ≤5% ADAMTS13 activity=TTP (range found in published data is 5%-10%).</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>27</td>
<td>32-47 g/L</td>
</tr>
</tbody>
</table>

Case presented by:
Tori Mauch, MD, PhD

Dr. Mauch is a paid consultant of Alexion Pharmaceuticals, Inc., and was compensated for her time.

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.
Diagnosing atypical-HUS requires excluding other conditions1,3,5

- Patient showed evidence of TMA, including
  - Thrombocytopenia
  - Elevated LDH levels
  - Decreased hemoglobin levels
  - Evidence of microangiopathic hemolysis
  - Other symptoms:
    - Acute kidney injury, seizures, emesis, and new hypertension
- Patient had a negative stool test for Shiga toxin-producing E. coli and a negative Coombs test1
- Patient had a negative Shiga toxin panel and ADAMTS13 activity of 76%, which ruled out TTP and STEC-HUS, indicating atypical-HUS: a rare, life-threatening disease caused by dysregulation of the alternative pathway of the complement system1,3
- While not required for diagnosis, genetic analysis was performed, with the following results3
  - Het missense (c.359A>G, p.Asp120Gly) in exon 3 of MASP. This variant is associated with impairment of the Mannan-binding lectin pathway of the complement system. Its contribution to atypical-HUS is unknown5
  - Het, silent variant (c.417A>G, p.Leu139Leu) in exon 4 of MCP6
- Evaluate ADAMTS13 activity and Shiga toxin/EHEC test

While ADAMTS13 results are awaited, a platelet count > 30 x 10⁹/L and/or sCr > 1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)

- ≤5% ADAMTS13 activity
- >5% ADAMTS13 activity
- Shiga toxin/EHEC positive
- TTP
- Atypical-HUS
- STEC-HUS

*aHUS Case Study: Naïve to ULTOMIRIS*

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.
Because of the high morbidity of atypical-HUS, parents were willing to start treatment immediately for patients with complement deficiencies. Immunize patients without history of meningococcal vaccination. Vaccinate or revaccinate for meningococcal disease according to the most current ACIP recommendations (meningitis). Meningococcal disease due to any serogroup may occur.

ULTOMIRIS increases a patient’s susceptibility to serious meningococcal infections (septicemia and/or life-threatening meningococcal infections/sepsis). Life-threatening meningococcal infections have occurred in patients treated with ULTOMIRIS. The use of drug prophylaxis. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

**Pediatric study design**

- The pediatric study was a 26-week, ongoing, multicenter, open-label, single-arm study of 15 pediatric patients, of which 14 eculizumab-naive patients with documented diagnosis of atypical-HUS were enrolled and included in this interim analysis.
- Primary endpoint: complete TMA response, defined as normalization of hematological parameters (platelet count and LDH normalization) and ≥25% improvement in serum creatinine from baseline during the 26-week initial evaluation period. Patients had to meet all complete TMA response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart and any measurement in between.
- Select secondary endpoints: time to complete TMA response and complete TMA response status over time, dialysis requirement and CKD stage as evaluated by eGFR, hemoglobin response, and change from baseline in quality of life.

**Pediatric study results**

- Complete TMA response during the initial evaluation period was achieved at a median time of 30 days (range: 15 to 88 days). The median duration of complete TMA response was 5.08 months (range: 3.08 to 5.54 months). All responses were maintained through all available follow-up.
- An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 60.50 × 10^9/L at baseline to 296.67 × 10^9/L at Day 8, and remained above 296 × 10^9/L at all subsequent visits in the initial evaluation period (26 weeks). The mean eGFR (+/- SD) increased from 28.4 (23.11) at baseline to 108.0 (63.21) at 26 weeks.
- The most frequent adverse reactions reported in ≥20% of pediatric patients treated with ULTOMIRIS were upper respiratory tract infection, diarrhea, constipation, vomiting, headache, hypertension, and pyrexia. Clinically relevant adverse reactions in <10% of eculizumab-naive pediatric patients included viral infection.

**Efficacy results in aHUS during the 26-week initial evaluation period (ALXN1210-aHUS-312)**

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>TOTAL</th>
<th>RESPONDER: PROPORTION (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response</td>
<td>14</td>
<td>10 71% (42%-92%)</td>
</tr>
<tr>
<td>Components of complete TMA response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count normalization</td>
<td>14</td>
<td>13 93% (66%-99%)</td>
</tr>
<tr>
<td>LDH normalization</td>
<td>14</td>
<td>12 86% (57%-98%)</td>
</tr>
<tr>
<td>≥25% improvement in serum creatinine</td>
<td>14</td>
<td>11 79% (49%-95%)</td>
</tr>
<tr>
<td>from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic normalization</td>
<td>14</td>
<td>12 86% (57%-98%)</td>
</tr>
</tbody>
</table>

**Treatment discussion**

- Discussed treatment options, including ULTOMIRIS risks and benefits. Parents felt ULTOMIRIS was the preferred option due to its long half-life, weight-based dosing for pediatric patients, safety profile and benefits, and every 4-week dosing interval.
- Because of the high morbidity of atypical-HUS, parents were willing to start treatment immediately.

**What is ULTOMIRIS?**

- ULTOMIRIS, built on the foundation of eculizumab, is a CS inhibitor that has an ~4X longer half-life, starting 2 weeks after an initial loading dose, and a dosing schedule of maintenance doses every 4 or 8 weeks for pediatric patients (depending on body weight), starting 2 weeks after an initial loading dose.
- The most frequent adverse reactions reported in ≥20% of pediatric patients treated with ULTOMIRIS were upper respiratory tract infection, diarrhea, constipation, vomiting, headache, hypertension, and pyrexia. Clinically relevant adverse reactions in <10% of eculizumab-naive pediatric patients included viral infection.

**SELECT IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Serious Meningococcal Infections**

**Risk and Prevention**

Life-threatening meningococcal infections have occurred in patients treated with ULTOMIRIS. The use of ULTOMIRIS increases a patient’s susceptibility to serious meningococcal infectious (sepsisemia and/or meningitis). Meningococcal disease due to any serogroup may occur.

Vaccinate or revaccinate for meningococcal disease according to the most current ACIP recommendations for patients with complement deficiencies. Immunize patients without history of meningococcal vaccination at least 2 weeks prior to the first dose of ULTOMIRIS. If ULTOMIRIS must be initiated immediately in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide 2 weeks of antibacterial drug prophylaxis. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

**Please see additional Important Safety Information throughout and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.**
ULTOMIRIS treatment

• Based on patient’s weight of 17.5 kg, he was placed on a 600-mg initial loading dose of ULTOMIRIS within 12 hours post-diagnosis of atypical-HUS. Within a day of receiving the first dose of ULTOMIRIS, patient was vaccinated with pneumococcal vaccine, meningococcal vaccine B, and meningococcal vaccine A/C/Y/W according to current Advisory Committee on Immunization Practices (ACIP) guidelines to reduce the risk of serious infection.

– Patient was also prescribed 2 weeks of antibacterial drug prophylaxis, since ULTOMIRIS was initiated immediately and vaccines were administered less than 2 weeks before starting ULTOMIRIS.

• Starting 2 weeks after the initial loading dose, 600-mg maintenance doses were administered once every 4 weeks.

• Patient remained hospitalized for several weeks and required 3 packed red blood cell transfusions during the first week of treatment.

– Patient exhibited complete TMA response by Day 22 and maintained it through Day 35.

– His kidney function also showed improvement.

• Parents were advised that patient’s ULTOMIRIS dose would be adjusted and dosing schedule increased to every 8 weeks as his weight increased to 20 kg and over.

• No adverse events were reported.

– The most frequent adverse reactions reported in ≥20% of adult and pediatric patients treated with ULTOMIRIS were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia.

– No signs or symptoms of infusion-related reactions were reported.

– Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion-related reaction.

– Administration of ULTOMIRIS may result in infusion-related reactions. In clinical trials, 5 out of 296 patients treated with ULTOMIRIS experienced infusion-related reactions (lower back pain, drop in blood pressure, infusion-related pain, elevation in blood pressure and limbs discomfort) during ULTOMIRIS administration which did not require discontinuation. Intermittent infusion and institute supportive measures if signs of cardiovascular instability or respiratory compromise occur.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

REMS

Under the ULTOMIRIS REMS, prescribers must enroll in the program due to the risk of meningococcal infections. Prescribers must counsel patients about the risk of meningococcal infection/sepsis, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines.

Other Infections

Patients may have increased susceptibility to encapsulated bacteria infections, especially infections caused by Neisseria gonorrhoeae. Children treated with ULTOMIRIS may be at increased risk of developing serious infections due to Streptococcus pneumoniae and Haemophilus influenzae type b (Hib). Administer vaccinations for the prevention of Streptococcus pneumoniae and Haemophilus influenzae type b (Hib) infections according to ACIP guidelines. If ULTOMIRIS is administered to patients with active systemic infections, monitor closely for worsening infection.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

Patrick’s parents were concerned about his diagnosis. Yet they were happy that ULTOMIRIS provided a path forward in managing his atypical-HUS.

LAB VALUES

<table>
<thead>
<tr>
<th></th>
<th>WEEK 1</th>
<th>WEEK 2</th>
<th>WEEK 4</th>
<th>WEEK 12</th>
<th>WEEK 26</th>
<th>WEEK 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/L) (reference range: 107-139 g/L)</td>
<td>83</td>
<td>87</td>
<td>117</td>
<td>121</td>
<td>115</td>
<td>128</td>
</tr>
<tr>
<td>LDH (U/L) (reference range: 155-345 U/L)</td>
<td>2480</td>
<td>808</td>
<td>310</td>
<td>302</td>
<td>244</td>
<td>271</td>
</tr>
<tr>
<td>Platelet count (x 10^9/L) (reference range: 217-487 x 10^9/L)</td>
<td>N/A</td>
<td>243</td>
<td>395</td>
<td>350</td>
<td>344</td>
<td>246</td>
</tr>
<tr>
<td>Creatinine (μmol/L) (reference range: 88-126 μmol/L)</td>
<td>62</td>
<td>53</td>
<td>35</td>
<td>27</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>62</td>
<td>72</td>
<td>106</td>
<td>141</td>
<td>108</td>
<td>111</td>
</tr>
<tr>
<td>Urine protein/creatinine (mg/mmol) (reference range: &lt;20 mg/mmol)²</td>
<td>N/A</td>
<td>269</td>
<td>15</td>
<td>11</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Albumin (g/L) (reference range: 32-47 g/L)</td>
<td>28</td>
<td>35</td>
<td>41</td>
<td>42</td>
<td>39</td>
<td>40</td>
</tr>
</tbody>
</table>

*Complete TMA response was defined as normalization of hematological parameters (platelet count and LDH) and ≥25% improvement in serum creatinine from baseline during the 26-week initial evaluation period. Patients had to meet all criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart and any measurement in between.

*Secondary endpoint.
Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

ULTOMIRIS treatment of aHUS should be a minimum duration of 6 months. Due to heterogeneous nature of aHUS events and patient-specific risk factors, treatment duration beyond the initial 6 months should be individualized. There are no specific data on ULTOMIRIS discontinuation. After discontinuing treatment with ULTOMIRIS, patients should be monitored for clinical symptoms and laboratory signs of TMA complications for at least 12 months.

TMA complications post-discontinuation can be identified if any of the following is observed: Clinical symptoms of TMA include changes in mental status, seizures, angina, dyspnea, thrombosis or increasing blood pressure. In addition, at least two of the following laboratory signs observed concurrently and results should be confirmed by a second measurement 28 days apart with no interruption: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment. If TMA complications occur after discontinuation, consider reinitiation of ULTOMIRIS treatment or appropriate organ-specific supportive measures.

Thromboembolic Event Management

The effect of withdrawal of anticoagulant therapy during treatment with ULTOMIRIS has not been established. Treatment should not alter anticoagulant management.

Infusion-Related Reactions

Administration of ULTOMIRIS may result in infusion-related reactions. In clinical trials, 5 out of 296 patients treated with ULTOMIRIS experienced infusion-related reactions (lower back pain, drop in blood pressure, infusion-related pain, elevation in blood pressure and limbs discomfort) during ULTOMIRIS administration which did not require discontinuation. Intermittent infusion and institute supportive measures if signs of cardiovascular instability or respiratory compromise occur.

ADVERSE REACTIONS

Most common adverse reactions in patients with aHUS (incidence ≥20%) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Serious adverse reactions were reported in 42 (57%) patients with aHUS receiving ULTOMIRIS. The most frequent serious adverse reactions reported in more than 2 patients (2.7%) treated with ULTOMIRIS were hypertension, pneumonia and abdominal pain. In clinical studies, clinically relevant adverse reactions in <10% of patients include viral tonsillitis in adults and viral infection in pediatric patients.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

References

1. Data on file [ALXN1210-aHUS-312 CSR].