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

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

SELECT IMPORTANT SAFETY INFORMATION

[1]

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.**

Because of the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS REMS.

INDICATION

ULTOMIRIS is indicated for the treatment of adult 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).

Subcutaneous Use in Adult Patients with aHUS
Subcutaneous administration of ULTOMIRIS is not approved for use 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.

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

"WHEN PATRICK GOT SICK, I DIDN'T KNOW WHAT TO DO."

— Patrick's dad

Case presented by:

Teri Mauch, MD, PhD

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

Based on an actual patient in the 312 study[1]

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[1,a]	
Hemoglobin (g/L) (reference range: 107-139 g/L)	79
LDH (U/L) (reference range: 155-345 U/L)	2228
Platelet count (x 10^9/L) (reference range: 217-497 x 10^9/L)	41
Creatinine (ranges μmol/L) (reference range: 18-62 μmol/L)	256
eGFR (mL/min/1.73 m^2)	15
Urine protein/creatinine (mg/mmol) (reference range: <20 mg/mmol)[2]	1252
ADAMTS13 activity (%)[3,b]	76
Albumin (g/L) (reference range: 32-47 g/L)	27

[a]Day 1 is relative to first dose of ULTOMIRIS administered intravenously.
[b]>5% ADAMTS activity=atypical-HUS. ≤5% ADAMTS13 activity=TTP (range found in published data is 5%-10%).

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.

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

Diagnosing atypical-HUS requires excluding other conditions[1,3-5]

- 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 test[1]
- 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 system[1,3,5]
- While not required for diagnosis, genetic analysis was performed, with the following results[3]
  - 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 unknown[6]
  - Het, silent variant (c.417A>G, p.Leu139Leu) in exon 4 of *MCP*[7]

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

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.

Differential diagnosis of TMA, including atypical-HUS[3,5,8,9]

Thrombocytopenia
Platelet count <150 x 10^9/L
or >25% decrease from baseline

AND

Microangiopathic hemolysis
Schistocytes and/or elevated LDH
and/or decreased haptoglobin
and/or decreased hemoglobin

Plus 1 or more of the following

Common symptoms

Neurological symptoms
Confusion and/or seizures and/or stroke and/or other cerebral abnormalities

Renal impairment
Elevated creatinine level and/or decreased eGFR and/or elevated blood pressure and/or abnormal urinalysis results

GI symptoms
Diarrhea ± blood and/or nausea/vomiting and/or abdominal pain and/or gastroenteritis/pancreatitis

Other symptoms

CV symptoms
MI and/or hypertension and/or arterial stenosis and/or peripheral gangrene

Pulmonary symptoms
Dyspnea and/or pulmonary hemorrhage and/or pulmonary edema

Visual symptoms
Pain and blurred vision and/or retinal vessel occlusion and/or ocular hemorrhage

Evaluate ADAMTS13 activity and Shiga toxin/EHEC test[a]

While ADAMTS13 results are awaited, **a platelet count >30 x 10^9/L and/or sCr >1.7 to 2.3 mg/dL[b] almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)**

≤5%[c] ADAMTS13 activity	>5% ADAMTS13 activity	Shiga toxin/EHEC positive
TTP	**Atypical-HUS**	**STEC-HUS[a]**

[a]Shiga toxin/EHEC test is warranted with history/presence of gastrointestinal symptoms.
[b]This is from a compilation of adult and pediatric studies.
[c]Range found in published data is 5%-10%.
CV=cardiovascular; EHEC=enterohemorrhagic *Escherichia coli*; GI=gastrointestinal; MI=myocardial infarction; sCr=serum creatinine; STEC=Shiga toxin-producing *Escherichia coli*; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

STUDY 312: ULTOMIRIS IN PEDIATRIC PATIENTS WITH ATYPICAL-HUS

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[10]
- Because of the high morbidity of atypical-HUS, parents were willing to start treatment immediately[2]

What is ULTOMIRIS?

- ULTOMIRIS, built on the foundation of eculizumab, is a C5 inhibitor that has an ~4X longer half-life 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[10-12,a,b]

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections

Life-threatening meningococcal infections have occurred in patients treated with ULTOMIRIS. The use of ULTOMIRIS increases a patient's susceptibility to serious meningococcal infections (septicemia 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. Patients who initiate ULTOMIRIS treatment less than 2 weeks after receiving meningococcal vaccine(s) must receive appropriate prophylactic antibiotics until 2 weeks after vaccination.

Pediatric study design

- The pediatric study was a 26-week, ongoing, multicenter, open-label, single-arm study of 16 pediatric patients, of which 14 eculizumab-naïve patients with documented diagnosis of atypical-HUS were enrolled and included in this interim analysis[10]
- Primary endpoint: complete TMA response, defined as normalization of hematological parameters (platelet count and LDH normalization)[c] 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[10]
- 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[1,10]

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[10]
- An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 60.50 x 10^9/L at baseline to 296.67 x 10^9/L at Day 8, and remained above 296 x 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) by 26 weeks[10]
- 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 pediatric patients included viral infection[10]

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

	TOTAL	RESPONDER	
		n	PROPORTION (95% CI)[d]
Complete TMA response	14	10	**71%** (42%-92%)
Components of complete TMA response			
Platelet count normalization	14	13	**93%** (66%-99%)
LDH normalization	14	12	**86%** (57%-98%)
≥25% improvement in serum creatinine from baseline	14	11	**79%** (49%-95%)
Hematologic normalization (platelet count and LDH normalization)	14	12	**86%** (57%-98%)

[a]The mean (%CV) terminal elimination half-life and clearance of ULTOMIRIS in patients with atypical-HUS are 51.8 (31.3) days and 0.08 (53.3) L/day, respectively. Half-life of eculizumab is 11.25 to 17.25 days.[10,11]

[b]Targeted engineering to incorporate 4 amino acid substitutions designed to reduce TMDD and enhance FcRn-mediated recycling into eculizumab has led to the generation of ULTOMIRIS, which exhibited an extended duration of action in preclinical models relative to eculizumab.[12]

[c]Includes ≥150 x 10^9/L for platelet count and a value less than the upper limit of normal for LDH.[1]

[d]95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.

CI=confidence interval; CKD=chronic kidney disease; FcRn=human neonatal Fc receptor; LDH=lactate dehydrogenase; TMA=thrombotic microangiopathy; TMDD=target-mediated drug disposition.

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®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

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

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[1,10]
  - 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[1,10]
  - 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[1,10]
- Starting 2 weeks after the initial loading dose, 600-mg maintenance doses were administered once every 4 weeks[1,10]
- Patient remained hospitalized for several weeks and required 3 packed red blood cell transfusions during the first week of treatment[1]
  - Patient exhibited complete TMA response[a] by Day 22 and maintained it through Day 351
  - His kidney function also showed improvement[b]
- 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[10]
- 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[10]
- 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[10]
  - 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. Interrupt infusion and institute supportive measures if signs of cardiovascular instability or respiratory compromise occur[10]

LAB VALUES	WEEK 1	WEEK 2	WEEK 4	WEEK 12	WEEK 26	WEEK 52
Hemoglobin (g/L) (reference range: 107-139 g/L)	83	87	117	121	115	128
LDH (U/L) (reference range: 155-345 U/L)	2480	808	310	302	244	271
Platelet count (x 10^9/L) (reference range: 217-497 x 10^9/L)	N/A	243	395	350	344	246
Creatinine (μmol/L) (reference range: 18-62 μmol/L)	62	53	35	27	35	35
eGFR (mL/min/1.73 m^2)	62	72	106	141	108	111
Urine protein/creatinine (mg/mmol) (reference range: <20 mg/mmol)[2]	N/A	269	15	11	8	9
Albumin (g/L) (reference range: 32-47 g/L)	28	35	41	42	39	40

[a]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.
[b]Secondary endpoint.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

ULTOMIRIS REMS

Due to the risk of meningococcal infections, ULTOMIRIS is available only through a restricted program under a REMS called ULTOMIRIS REMS.

Under the ULTOMIRIS REMS, prescribers must enroll in the program. 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.

Additional information on the REMS requirements is available at www.ultomirisrems.com or 1-888-765-4747.

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®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

Other Infections
Patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *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.

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
Intravenous or subcutaneous administration of ULTOMIRIS may result in systemic infusion-related reactions, including anaphylaxis and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures.

Injection Site Reactions- Subcutaneous administration
27% (23/84) of patients treated with subcutaneous administration of ULTOMIRIS experienced injection site reactions which included application site rash, device allergy, infusion site pain, infusion site reaction, injection site bruising, injection site erythema, injection site hematoma, injection site induration, injection site inflammation, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria, medical device site bruise, medical device site erythema, medical device site hematoma, medical device site induration, medical device site pruritus, medical device site rash, and medical device site reaction.

Allergies to Acrylic Adhesives
The on-body injector of ULTOMIRIS uses acrylic adhesive. For patients with a known allergy to acrylic adhesive, use of this product may result in an allergic reaction. Premedication can be considered, and supportive measures should be instituted if signs of allergy appear.

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 and in 3% of adult patients include infusion-related reactions.

Adverse Reactions for Subcutaneous Administration of ULTOMIRIS
Most common adverse reactions (≥10%) with ULTOMIRIS subcutaneous administration via On Body Injector in adult patients with PNH were local injection site reactions, diarrhea, and headache.

DRUG INTERACTIONS

Plasma Exchange, Plasmapheresis, and Intravenous Immunoglobulins
Concomitant use of ULTOMIRIS with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg) treatment can reduce serum ravulizumab concentrations and requires a supplemental dose of ULTOMIRIS.

Neonatal Fc Receptor Blockers
Concomitant use of ULTOMIRIS with neonatal Fc receptor (FcRn) blockers (e.g., efgartigimod) may lower systemic exposures and reduce effectiveness of ULTOMIRIS. Closely monitor for reduced effectiveness of 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.

References

1. Data on file [ALXN1210-aHUS-312 CSR]. **2.** Kamińska J, et al. *Crit Rev Clin Lab Sci.* 2020;57(5):345-364. **3.** Laurence J. *Clin Adv Hematol Oncol.* 2016;14:2-15. **4.** Berger BE. *Clin Kidney J.* 2019;12(3):338-347. **5.** Asif A, et al. *J Nephrol.* 2017;30:347-362. **6.** Stengaard-Pedersen K, et al. *N Engl J Med.* 2003;349(6):554-560. **7.** National Center for Biotechnology Information. Published 2004. Updated February 4, 2021. Accessed February 26, 2021. https://www.ncbi.nlm.nih.gov/gene/4179 **8.** Goodship THJ, et al. *Kidney Int.* 2017;91:539-551. **9.** Azoulay E, et al. *Chest.* 2017;152:424-434. **10.** ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc.; 2020. **11.** SOLIRIS. Prescribing information. Alexion Pharmaceuticals, Inc.; 2020. **12.** Sheridan D, et al. *PLoS One.* 2018;13(4):e0195909.

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial