Transcript Details

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Managing the Severe Consequences of PNH With Targeted Therapy

Announcer:
Welcome to ReachMD. This medical industry feature, titled “Managing the Severe Consequences of PNH With Targeted Therapy”, is sponsored by Alexion, AstraZeneca Rare Disease. And now, here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I’m your host Dr. Jennifer Caudle. Joining me today to discuss targeted complement inhibition with the treatment option ULTOMIRIS® (ravulizumab-cwvz) for paroxysmal nocturnal hemoglobinuria, or PNH for short, is Dr. Rondeep Brar.

He’s a Clinical Professor of Medicine and Hematology at the Stanford Medicine Cancer Center in Palo Alto, California. Dr. Brar, welcome to the program.

Dr. Brar:
Thanks for having me.

Dr. Caudle:
Of Course, now before we dive in, let’s take a moment to hear the indication and select important safety information on ULTOMIRIS.

Announcer:

INDICATION
ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

ULTOMIRIS, a complement inhibitor, increases the risk of serious infections caused by *Neisseria meningitidis* [*see Warnings and Precautions (5.1)*] Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.**
- **Patients receiving ULTOMIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious 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 and SOLIRIS REMS [*see Warnings and Precautions (5.2)*].

Dr. Caudle:
With that important safety information in mind, let's begin our discussion with some background. Now Dr. Brar, what is PNH, and why does it carry such significant risk for patients?

Dr. Brar:
So PNH is a rare, chronic, and life-threatening hematopoietic stem cell disorder that affects the red blood cells, white blood cells, and platelets due to a somatic mutation in the *PIGA* gene. It manifests with hemolysis, bone marrow failure, and thrombosis.[1-4]

It's important to note that while a high percentage of patients with PNH experience anemia and fatigue as symptoms, PNH is much more than just a disease of anemia.[1-3] In fact, PNH can be life-threatening, with a five-year mortality risk of up to 35% despite historical supportive care. The leading causes of death are[4]:

- Thrombosis, which accounts for 16 to 46 percent of all deaths in patients with PNH,[5-7]
- And chronic kidney disease, which occurs in 33 percent of patients with PNH and is the second leading cause of death.[6,8]

Other signs and symptoms of PNH include anemia, fatigue, hemoglobinuria, dyspnea, pulmonary hypertension, chest pain, abdominal pain, dysphagia, and erectile dysfunction.[3,9,10]

Now, if we look at the mechanism behind the disease, the complement system, which plays an important role in the immune response, must be carefully regulated to prevent the formation of the membrane attack complex, or MAC.[1,2] In PNH, CD55 and CD59 can be partially or completely absent, resulting in uncontrolled C3b opsonization and uncontrolled terminal complement activation resulting in MAC formation.[1-4] Now, C3b opsonization may lead to extravascular hemolysis and anemia, which have no known impacts on survival.[5,6] But uncontrolled terminal complement activity and MAC formation leads to intravascular hemolysis, which is the predominant cause of life-threatening PNH consequences such as thrombosis, organ damage, and premature mortality.[2-4,7]

Dr. Caudle:
And could you elaborate on how leaving terminal complement activity uncontrolled can impact patients with PNH?

Dr. Brar:
Sure. So it's important to understand that the prothrombotic mechanism in PNH is multifactorial.

An important consequence of intravascular hemolysis caused by the C5b-9 MAC is the release of hemoglobin from PNH red blood cells. This leads to nitric oxide depletion and results in smooth muscle contraction, vasoconstriction, inflammation, platelet activation and aggregation, hypercoagulation, and leukocyte and endothelial cell activation.[1,2] Also, C5a may result in proinflammatory and prothrombotic processes by generating inflammatory cytokines.[3] These consequences are ultimately responsible for the morbidities and premature mortality associated with PNH, including thrombosis.[1-3] And in these patients, even the first thrombotic event can be fatal.[4] Now after that first event occurs, patients with PNH have a greater risk of recurrent thrombosis, and a increased risk of premature mortality.[4-6] So trying to control terminal complement activation is critical.

Dr. Caudle:
So then how can we control terminal complement activity in PNH and manage the risks associated with it?

Dr. Brar:
Well this is where ULTOMIRIS can help[1] Terminal complement can be activated downstream, including at C5, even if the proximal complement pathway is blocked, potentially leading to serious PNH consequences such as intravascular hemolysis or thromboembolism.[2-8] So ULTOMIRIS is designed to target terminal complement activation in PNH by binding C5 with complete and sustained inhibition, which prevents the MAC generation that leads to intravascular hemolysis in these patients.[1]

Dr. Caudle:
You're listening to ReachMD. I'm your host Dr. Jennifer Caudle, and today I'm speaking with Dr. Rondeep Brar about the role of ULTOMIRIS in treating patients with paroxysmal nocturnal hemoglobinuria.

So, Dr. Brar, now that we understand the mechanism of action behind ULTOMIRIS, what can you tell us about its efficacy data?

Dr. Brar:
ULTOMIRIS is the critical backbone for the management of PNH.[1] ULTOMIRIS was assessed in a phase 3, open-label, randomized, noninferiority, active-comparator controlled trial in complement-inhibitor naïve adult patients—also known as study 301. Study 301

consisted of a 4-week screening period and a 26-week randomized open-label treatment period to evaluate the efficacy and safety of ULTOMIRIS versus eculizumab, followed by an extension period of up through 5 years during which all patients received ULTOMIRIS.[1-3]

- Coprimary endpoints were transfusion avoidance and LDH normalization.[2]
- Secondary endpoints included[2]:
  - Percentage change from baseline in LDH levels
  - Change in FACIT-Fatigue
  - Proportion of patients with breakthrough IVH
  - Major adverse vascular events
  - And proportion of patients with stabilized hemoglobin.

ULTOMIRIS resulted in complete and sustained free C5 reduction throughout the treatment period in clinical trials, with no free C5 excursions ≥0.5 µg/mL compared to eculizumab.[3]

The study found that ULTOMIRIS was noninferior to eculizumab across all endpoints during the randomized treatment period in complement inhibitor-naïve patients.[1,2] Through the 26-week RCP, 53.6 percent of patients treated with ULTOMIRIS achieved LDH normalization versus 49.4 percent of patients treated with eculizumab.[1,2] Additionally, a rapid LDH reduction was observed with LDH less than one point five times the upper limit of normal by week 2 and normalized by week 4.[2-4] These normalized LDH levels were maintained through 5.6 years. We also saw that 73.6 percent of these complement inhibitor-naïve patients receiving ULTOMIRIS avoided transfusions through 26 weeks, which was maintained in 53.9 percent through the five-year extension.[1-4]

And lastly, efficacy was maintained through the 5-year extension period of the complement inhibitor-naïve study, during which all patients received ULTOMIRIS.[3]

Dr. Caudle:
And what do the data tell us about the risk of intravascular hemolysis and thrombosis in patients receiving ULTOMIRIS?

Dr. Brar:
In the study, we saw that:

1. 96 percent of patients did not experience major adverse vascular events—including thrombosis—for over five years[1]
2. 86 percent of patients did not experience breakthrough intravascular hemolysis through the five-year extension period[1]
3. From week 27 through the 5-year extension, 45 percent or (110/243) patients treated with ULTOMIRIS achieved hemoglobin stabilization[1]

Additionally, ULTOMIRIS provided a greater than 7.07-point mean change in FACIT-Fatigue score at the end of the randomized period versus eculizumab in complement inhibitor–naïve patients, and the improvement in FACIT-Fatigue was maintained through 5.6 years.[1,3,4] At 5.6 years, mean FACIT-Fatigue with ULTOMIRIS was 42.8, compared with 43.5 in the general population.[1,4,5]

Dr. Caudle:
And what should we know about the safety profile?

Dr. Brar:
In the 26-week randomized period of the adult PNH treatment-naïve study, the most frequent adverse reactions with ULTOMIRIS were upper respiratory tract infection and headache.[1,2] Serious adverse reactions were reported in 8.8 percent of patients receiving ULTOMIRIS and 7.4 percent of patients receiving eculizumab.[2] No patients reported meningococcal or *Aspergillus* infections or sepsis.[2]

Throughout the entire 5.6-year period of the adult PNH treatment-naïve study, the most frequent adverse reactions with ULTOMIRIS were headache, upper respiratory tract infection, pyrexia, nasopharyngitis, COVID-19, and arthralgia.[3] Serious adverse events resulting in drug discontinuation were reported in 3.4 percent of patients receiving ULTOMIRIS.[3]

Dr. Caudle:
Now, as we approach the end of our program today, Dr. Brar, what key takeaways would you like to share with our audience?

Dr. Brar:
Well as I mentioned, ULTOMIRIS is designed to control terminal complement–mediated IVH and reduce the risk of thrombotic events in

PNH.[1] Through over five years of study, rapid and sustained control of LDH was observed with ULTOMIRIS, resulting in low rates of breakthrough intravascular hemolysis and major adverse vascular events.[2] ULTOMIRIS demonstrated improvement in transfusion burden and hemoglobin stabilization. And fatigue improved to a level comparable with the general population for more than 5 years.[2-4] And importantly, ULTOMIRIS has an established safety profile.[2,5]

Lastly, I'd like to highlight OneSource™, which is a free, personalized support program dedicated to helping patients with PNH understand more about their treatment, navigate financial assistance programs, and make community connections.

Dr. Caudle:
That's a great way to round out our discussion on this topic. And I want to thank my guest, Dr. Rondeep Brar, for helping us better understand how ULTOMIRIS may help manage the severe consequences of PNH. Dr. Brar, it was great speaking with you today.

Dr. Brar:
Thank you. It was a pleasure to be here.

Dr. Caudle:
For ReachMD, I'm your host Dr. Jennifer Caudle. Before we close, let's take a moment to review some important safety information.

Announcer:

CONTRAINDICATIONS

- Initiation in patients with unresolved serious Neisseria meningitidis infection.

WARNINGS AND PRECAUTIONS
Serious Meningococcal Infections
ULTOMIRIS, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by meningococcal bacteria (septicemia and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.

Revaccinate patients in accordance with ACIP recommendations considering the duration of ULTOMIRIS therapy. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent ULTOMIRIS therapy is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, provide antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including ULTOMIRIS. The benefits and risks of treatment with ULTOMIRIS, as well as those associated with antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by Neisseria meningitidis.

Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection depending on the risks of interrupting treatment in the disease being treated.

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

Prescribers must enroll in the REMS, counsel patients about the risk of serious meningococcal infection, provide patients with the REMS educational materials, assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y, and B) and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of ULTOMIRIS. Antibacterial drug prophylaxis must be prescribed if treatment must be started urgently, and the patient is not up to date with both meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of ULTOMIRIS. Patients must receive counseling about the need to receive meningococcal vaccines and to take antibiotics as directed, signs and symptoms of meningococcal infection, and be instructed to carry the Patient Safety Card at all times during and for 8 months following ULTOMIRIS treatment.

Further information is available at www.UltSolREMS.com or 1-888-765-4747.

Other Infections
Serious infections with Neisseria species (other than Neisseria meningitidis), including disseminated gonococcal infections, have been reported.

ULTOMIRIS blocks terminal complement activation; therefore, 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 recommendations. Patients receiving ULTOMIRIS are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation
After discontinuing treatment with ULTOMIRIS, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH along with sudden decrease in PNH clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues ULTOMIRIS for at least 16 weeks to detect hemolysis and other reactions. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

WARNINGS AND PRECAUTIONS (CONT'D)

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 systemic infusion-related reactions, including anaphylaxis and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1 to 7% of patients, including lower back pain, abdominal pain, muscle spasms, drop or elevation in blood pressure, rigors, limb discomfort, drug hypersensitivity (allergic reaction), and dysgeusia (bad taste). These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS and institute appropriate supportive measures.

ADVERSE REACTIONS
Adverse reactions reported in ≥10% or more of patients with PNH were upper respiratory tract infection and headache. Serious adverse reactions were reported in 15 (6.8%) patients receiving ULTOMIRIS. The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse reaction was reported in more than 1 patient treated with ULTOMIRIS. One fatal case of sepsis was identified in a patient treated with ULTOMIRIS. In clinical studies, clinically relevant adverse reactions in 1% of adult patients include infusion-related reactions.

Adverse reactions reported in ≥10% of pediatric patients treated with ULTOMIRIS who were treatment-naïve vs. Eculizumab-experienced were anemia (20% vs. 25%), abdominal pain (0% vs. 38%), constipation (0% vs. 25%), pyrexia (20% vs. 13%), upper respiratory tract infection (20% vs. 75%), pain in extremity (0% vs. 25%), and headache (20% vs. 25%).

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.

USE IN SPECIFIC POPULATIONS
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ULTOMIRIS during pregnancy. Healthcare providers and patients may call 1-833-793-0563 or go to www.UltomirisPregnancyStudy.com to enroll in or to obtain information about the registry.

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Dr. Caudle:
Thank you for joining our discussion about targeted terminal complement inhibition therapy with ULTOMIRIS to manage the severe consequences of PNH. I'm your host Dr. Jennifer Caudle, and I hope you found this session valuable.

Announcer:
This program was brought to you by Alexion, AstraZeneca Rare Disease. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

The full Prescribing Information and Important Safety Information can be accessed on the ULTOMIRIS website or via the links below.

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