aTYPICAL HEMOLYTIC UREMIC SYNDROME (aHUS)

Report on a Patient Led Food and Drug Administration (FDA) Patient Listening Session.

(Held virtually on 21st September 2023)

Introduction

A Patient Listen Session (PLS) can help the FDA understand what is important to patients, caregivers, and advocates when medical products are being developed. The session can educate the FDA review staff about health-related experiences, perspectives, and needs that are most important to patients, caregivers, advocates, and community representatives. A patient led PLS on atypical Hemolytic Uremic Syndrome (aHUS) was held on 21 September 2023. The audience included representatives from FDA Centers/Divisions as listed in Appendix A.

A US aHUS Patient Advisory Partnership (USaHUSPAP) was formed specifically to undertake this aHUS PLS. The USaHUSPAP was made up of representatives of the Atypical HUS Foundation, aHUS Action Network, atypical HUS Families Facebook Group, and aHUS alliance Global Action organisations which have an aHUS advocacy reach in the USA. The USaHUSPAP consisted of six speakers who were patients or parents/carers of patients nominated by the partner organisations. See the list of speakers at Appendix B.

The Patient Listening Session

The Session began with introductory comments by The FDA's Patient Affairs representative.

USaHUSPAP leader, LW, a parent/carer of a patient from the UK, stated that the objectives of the PLS were to give the FDA a greater understanding of:

- aHUS
- the challenges of having and the difficulties of living with aHUS
- the challenges and opportunities for the wider aHUS community in the remainder of this decade.

He explained that aHUS is a thrombotic microangiopathy (TMA), a clotting condition in capillaries. It is triggered by the patient's own immune system. Specifically, an innate part of the immune system called complement which when it becomes uncontrolled, begins to damage endothelial cells in a form of friendly fire which then needs repairing by the coagulation system.

The micro clots narrow the path of blood through the capillaries which ultimately leads to red blood cell fragmentation. The functions of all organs, but particularly the kidneys, can be impaired and they can fail completely. Signs and symptoms of anaemia and toxins build up appear in patients manifesting with aHUS, along with low levels of platelets because of their excessive consumption by the TMA.

aHUS can occur at any age, though typically there are more adults than children in the prevalent patient population as well as more females than males particularly during and after puberty. Most patients are found to have pathogenic variants in one or more of the components of their complement system. A minority of patients have inherited these variants from parents who are carriers of the aHUS predisposing variants but for most patients they are the first in the family to experience aHUS.

Although there is no accurate record of the number of aHUS patients in the USA, estimates suggest a prevalent patient population of between 2000 and 3000, with a much better chance of survival since the advent of complement inhibitor treatment more than a decade ago. Each year between 150 and 200 people may onset with aHUS in the USA.

People at risk of having aHUS because of predisposing complement genetic variants still require a triggering hit for uncontrolled complement over-activation. In families with the same variant and triggering hits, penetrance may be incomplete because of more common "at risk" or "protective" genetic factors.

LW went on to describe and illustrate the complexities of the term aHUS in the context of all TMAs. Thrombotic Thrombocytopenic Purpura, (TTP), and Hemolytic Uremic Syndromes, (HUSs), are the primary TMAs and each has a different, but occasionally overlapping, cause of a TMA.
The HUSs consist of two distinct versions, Shiga-like Toxin producing E. coli causing HUS, (STEC-HUS), and aHUS. aHUS also consists of two versions, primary aHUS, described earlier in this overview, and secondary aHUS which consists of many conditions which can also result in a TMA. Such conditions include pregnancy, solid organ transplants, malignant hypertension, auto-immune diseases, infections, hematopoietic stem cell transplants, malignancy, cobalamin C deficiency, and this list is not exhaustive.

A novel infection recently added to the list of infections would be Coronavirus disease (COVID-19) which has been reported as either triggering an Infection TMA, or in those predisposed, a primary aHUS. A vaccination for COVID-19 can also be a trigger of primary aHUS.

For earlier complement inhibitor technologies, approval was limited to primary aHUS patients because of the inclusion and exclusion criteria used in trials. Specifically, the TMA caused by uncontrolled complement whether dysfunction was caused by identifiable genetic factors in the complement system or not; or even in non-complement systems which can hamper complement's control.

Science is increasingly finding that complement can be implicated to a greater or lesser extent in secondary aHUS TMAs, or even in the cause of those conditions themselves. Thus, new complement inhibitor drug technologies are being trialed on secondary aHUS conditions including "copans", "limabs"and repurposed "lizumabs". At the same time there is a revision to TMA categorisations taking place and a new nomenclature is to be introduced. This includes removing the term aHUS which will impact FDA's historic approvals and future treatment approvals which may put patients care at risk. The disease name changes could be so significant that FDA might wish to call its own PLS for renamed TMAs at some point.

Patient and Carer Presentations

Patient on dialysis after failed transplant and continuous TMA requiring complement inhibition, no genetic test result.

HY's encounter with aHUS began in 2012 after a tooth extraction operation. Over several months she experienced ill health and became critically ill requiring an air lift to a specialist hospital. She was found to have unexplained kidney failure resulting in a need for dialysis. After some time, a paired kidney transplant followed, and she was diagnosed with aHUS and began complement inhibitor treatment which controlled her TMA. However, periods off inhibitor treatment because of insurance funding protocols impacted on her graft kidney function resulting in a decision to return to dialysis because she was in end stage kidney failure again.

She continued to receive complement Inhibitor treatment because of recurring aHUS. Despite the length of time of living with aHUS she has only recently had any genetic tests of her complement system to help explain the cause of her aHUS and advise on her prognosis with continuous aHUS. The test results are still awaited. She explained that her medical team are unfamiliar with the disease and frequently need her to explain it to them. She is now seeking a return to the transplant list waiting for another transplant which could take years. Meanwhile her focus is to return to a normal family life.

Patient with a successful kidney transplant and on complement inhibitor treatment, genetic variants in Complement Factor H, Complement Factor I, and Thrombomodulin.

AD was a healthy and active 21-year-old when her aHUS illness happened overnight and, one morning, she woke up feeling very ill. As her condition worsened her family decided to see an adult doctor as she had been seeing her paediatrician who had not drawn a blood sample. Once the blood results came back, she was rapidly admitted to hospital and put on dialysis as she had quickly reached acute kidney failure. She entered intensive care and was put into an induced coma with a potentially terminal prognosis. A specialist who had only recently seen a case of aHUS diagnosed her with aHUS. She recovered but her kidneys had failed. After a period of stability on continuous ambulatory peritoneal dialysis which allowed her some freedom, she was able to have a kidney transplant with a close family member as a donor. A kidney transplant could trigger aHUS again but at that time a complement inhibitor was being trialed and although patients on dialysis were excluded from the trial, her doctors sought and obtained compassionate use to perform the transplant surgery. The operation was a success and she soon recovered with improved health and a return to a more active life. She worked, travelled, and got married and looked forward to a family life. AD is now a patient advocate.

Patient with postpartum pregnancy onset and on complement inhibitor treatment, no genetic mutation found.

TC had a very active life and an uneventful pregnancy when very quickly after giving birth by Cesarean-section (C-section) she became very ill. Post-partum bleeding required several operations to stop the blood flow. It became apparent she was thrombocytopenic and needed platelet transfusions. It also was evident she was suffering from multi micro clotting impacting all organs including her kidneys which were failing. At the same time, she acquired a sepsis pneumonia infection which contra indicated the use of a complement inhibitor treatment for her now suspected aHUS diagnosis. In this perfect storm of conditions, she became critically ill and was put into an induced coma.

At some point with return to complement inhibitor treatment her condition improved, and she was finally able to hold her daughter. Only temporarily because her kidney failure caused mental confusion when her urea levels built up requiring yet another induced coma. Eventually after recovery from the coma she stabilised but was now dependent on maintenance hemodialysis. She was able to go home and return to a family life. After a few months on dialysis and complement inhibitor treatment there was evidence of returning kidney function and eventually she became dialysis free. She had lost some kidney function and felt that her cognitive levels had not returned to her pre illness levels but was able to both enjoy her daughter and return to full time working. TC continues to have her complement inhibitor treatment at home. She is a writer about aHUS.

Patient and Parent/Carer of Patient both on complement inhibitor treatment, genetic variant in Membrane Cofactor Protein (MCP)/ CD46

JS explained that his daughter first showed symptoms back in 2014. She started with a cold and was not being able to keep food down. She also had abdominal bruising. JS and his wife took her to the children's Emergency Room, and she was given blood transfusions. The medical staff thought his daughter could have leukaemia. Her bone marrow was tested, and doctors continued to monitor her. However, her nephrologist had some experience with aHUS and was able to diagnose it relatively quickly. JS was advised not to Google it as the information was not current since treatment had become available and the information out there would scare them.

Complement inhibitor treatment was started on Day 6 and by Day 15 she was released from the hospital. Her kidneys bounced back to 100 percent. She had home infusions and genetic testing which showed an MCP/CD46 mutation. This mutation was also found in JS's genetic test results and in JS's mother. It was feared that JS' predisposition would lead to an aHUS episode.

In 2017 JS spiked a fever and two days later lost his appetite and by the third day he was yellow in colour. He drove himself to the ER. When he told doctors about his predisposing variant and about the aHUS diagnosis for his daughter, they said they had never heard of it but since he was all too familiar with it, they investigated it. He was officially diagnosed with aHUS and complement inhibitor treatment started one day later. His genetic tests were already available so that was helpful. He left hospital after 6 days.

He and his daughter now have complement inhibitor infusions together at home. He emphasised that his and his daughter's positive outcomes were due to early diagnosis and treatment. JS is a patient advocate.

Parent/Carer of Patient AD, genetically predisposed.

DD observed that when his daughter became ill, she deteriorated rapidly and alarmingly. He saw that it needed immediate attention but a visit to her health care professional yielded no diagnosis. So, he insisted on consulting his family doctor who advised an immediate visit to hospital. His family realised that this was beyond normal, and life was about to change when told "she may not make it through the night".

He saw his daughter go into intensive care but was no longer able to visit which added considerably to his anxiety because of a "communication blackout". After four days she left ICU and was on plasmapheresis and dialysis with a suspected TTP diagnosis. For the duration of her stay either he or his wife were by her bed side being vigilant about her treatment and normal life was set aside. After 16 days his daughter left hospital under the care of her parents but needing dialysis as an outpatient. Seeing the conditions of her dialysis treatment room he became very distressed about what his daughter had to endure. Life had changed and things were to get worse. His daughter's blood pressure was extremely high and not able to be controlled resulting in encephalitis leading to seizures. She returned to the ER where after multi-disciplinary attention she was put into an induced coma. Again, he had to deal with the advice that this could be terminal. It was at this point a diagnosis of aHUS was made and DD and his wife were told all about it. Having a diagnosis was a relief but for the next 16 days his daughter was in and out of intensive care where others in the room were dying.

She was eventually allowed to leave the hospital and his family cared for her, taking her back and

fore to hospital when needed became his routine over months as their new normal life. DD became very anxious over setbacks like blood pressure spikes.

When his daughter moved to continuous ambulatory peritoneal dialysis, he could see a difference in her with the freedom it gave her despite the daily burden of treatment at home. He noted that on that mode of dialysis the family could holiday again, and they visited Disney World. His daughter's newfound freedom gave him and his wife more freedom from her care.
Life continued that way until the following year when his daughter had a kidney transplant from a living donor relative. A transplant, which was known to trigger aHUS, was now possible because of a complement inhibitor treatment, which although still in trial, was available for compassionate use. It changed everything. Soon after she moved into her own apartment. She is now married.

He said there were many ongoing worries, graft rejection, insurance, facing other triggers, legislative changes of funding for pre-existing conditions. He said that complement inhibitors are not a cure but offered a remission from aHUS with a lifelong treatment for his daughter and a return to a regular life for him and his wife and the rest of the family.

Matters Important to aHUS Patients and Takeaway Messages.

LW rounded off the patient presentations by firstly highlighting some matters of importance to aHUS patients which relate to the work of the FDA and then listing the USaHUSPAP's key take away messages for the FDA.

He began by making clear that aHUS patients agree that on the balance of benefits and non-mitigable risks, complement inhibitors, when needed for as long as they are needed, are the magic bullet treatment for aHUS. If anything, patients believe that the net benefits would be greater with mitigation of more of the risks they face.

A serious risk of complement inhibitor treatment is meningococcal infection. The Centre for Disease Control has listed complement inhibitor users as the people most at-risk of infection in the USA. A handful of patient infections are reported each year, including aHUS patients. Patient guidance leaflets included in drug packages highlighting this serious side effect are not only rarely seen by patients but lack clarity about booster vaccinations necessity, monitoring, and scheduling.

Patients are uncertain whether the more common side effects of treatment are distinguishable from the latent co morbidities of having had aHUS and any resultant kidney disease. As is now more commonplace since the COVID-19 pandemic and its "long COVID", aHUS patients are describing a long version of their disease and calling for better information particularly from the FDA's post approval adverse events reporting process. Although manufacturers comply on a drug treatment basis there is little disease related information of the real-world patient experience for the disease. The manufacture's review of reported adverse events by patients could provide important information about what is deemed a non-drug related event, but the data is not disclosed.

Furthermore, the number of adverse events reported for eculizumab dropped by nearly two thirds in 2020 compared with 2019 and remained at around that level in subsequent years. It is unclear whether this is just a compromising of the adverse event reporting process because of COVID-19 or the result of the increasing transition from eculizumab to ravulizumab treatments because there are a diminishing number of adverse events in or around the infusion process. Ravulizumab adverse events reported are much lower and remain relatively low as usage increases. Either way, these are answers needed by patients.

Earlier versions of complement inhibitors for aHUS were indicated as a lifelong treatment. Real world evidence since has shown that treatment can be stopped safely for many patients. However, that early indicative advice in patient guidance and other leaflets about a lifelong complement inhibitor treatment has left a legacy of anxiety and reluctance about stopping treatment. Guidance on withdrawal from treatment needs updating to reflect the more flexible use of this technology according to patient's individual circumstances.

Greater flexibility of options for patients may also be possible if current trials for alternative complement inhibitors are successful. Different modes of treatment administration, e.g., pill and sub cutaneous injection at daily or four weekly intervals will provide alternatives to infusions depending on patients' preferences. It is likely that aHUS treatment could be increasingly personalised in the remainder of the 2020s.

Takeaway messages for the FDA

- aHUS can be a spectrum of incidences within a spectrum of TMAs.
- Living with aHUS becomes harder with less or no retained kidney function.
- Complement Inhibitors are magic bullet treatments for those with uncontrolled complement.
- Patients see the benefits of Complement inhibitor outweighing any non-mitigable risks from their use.
- More treatment options with more precise applications could be available to aHUS patients during this decade and patients' health outcomes could be improved further as a result.
- The name aHUS will be disappearing amid all TMAs reclassifications.

Discussion and questions by FDA

An FDA representative asked what effects of the treatment for aHUS were most bothersome.

LW indicated that many patients reported loss of memory and mental incapacity and anxiety as most bothersome.
AD stated that she has memory loss issues and mentioned migraines, ocular migraines and PTSD from the initial onset and hospitalization and all that has happened with a constant fear of it happening again.
TC said that brain fog was her concern and that during the week of infusion she has a cold and is lethargic and has headaches and fatigue. She said she could not truly tell if what she was experiencing was the aHUS or an adverse effect of the drug. Patients do talk to each other about it brain fog is a thing and joint pain is something she experiences, and it is a side effect of what it is like to have an infusion. Most side effects happen in the week of infusion. Fatigue is so all encompassing, the level of fatigue she felt now compared to before her diagnosis is stark.
HY said that insurance and pharmacy never seem to be able to get together on coverage and complained of fatigue and headaches and she also mentioned clumsiness. HY indicated she is never feeling hungry. TC also agreed that insurance is a stressor and that hers had been denied three times before coverage, but she expressed her gratitude that a treatment is available for this disease.
LW added that fatigue and headaches were the most common complaints from patients but also that meningococcal infection was of great concern and even though affecting a small number of patients it was still a very serious risk. He referred to some research undertaken about adverse events by aHUS alliance Global Action using data from its Rare DiseaseDay 2023 Awareness Video,

full details at https://www.ahusallianceaction.org/rdd23-video-results-report/

The research concluded that it is adult aHUS patients that report most adverse events and not all patients experience all events. aHUS patients attribute the adverse events experienced in almost equal measure between latent aHUS impact and any side effects of complement inhibitors. More research is needed.

Appendix A - FDA Attendees

FDA staff from 14 different offices/divisions from 3 different Centers attended the aHUS Patient Listening Session.
Office of the Commissioner (OC) – 3 offices

- OC/OCPP/PAS – Office of Clinical Policy and Programs/Patient Affairs Staff (organizer)
- OC/OCPP/OOPD – Office of Clinical Policy and Programs/Office of Orphan Products Development
- OC/OCPP/OPT – Office of Clinical Policy and Programs/Office of Pediatric Therapeutics

Center for Biologics Evaluation and Research (CBER) – 4 offices/divisions

- CBER/OD – Office of the Center Director
- CBER/OCD/PS - Office of the Center Director/Policy Staff
- CBER/OTP/OCE/DCEH/BHB – Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation Hematology/Benign Hematology Branch
- CBER/OTP/ORMRR/DRMRR2 – Office of Therapeutic Products/Office of Review Management and Regulatory Review/Division of Review Management and Regulatory Review 2

Center for Drug Evaluation and Research (CDER) – 6 offices/divisions

- CDER/OCD – Office of the Center Director
- CDER/OND/ORDPURM/DRDMG
- CDER/OTS/OB/DBII - Office of Translational Sciences/Office of Biostatistics/Division of Biometrics II
- CDER/OTS/OB/DBIX - Office of Translational Sciences/Office of Biostatistics/Division of Biometrics IX

Center for Devices and Radiological Health (CDRH) – 1 office/division

- CDRH/OSPTI/DAHRSSP – Office of Strategic Partnerships and Technology Innovation/ Division of All Hazards Response, Science and Strategic Partnerships

Non-FDA Attendees

- Reagan Udall Foundation
- NIH/NCATS/DRDRI – National Center for Advancing Translational Sciences/ Division of Rare Diseases Research Innovation

Appendix B -USaHUSPAP Attendees

Speakers: -

TC - Taylor Coffman****
AD - Alyssa Deffenbaugh*
DD - Dave Deffenbaugh*
JS - James Shadinger**
LW - Len Woodward ****
HY - Heather Young***

Notetaker: -

Debbie Deffenbaugh*

*The Atypical HUS Foundation
https://www.ahus.org

**AHUS Action Network
https://ahusaction.net

*** Global aHUS Families Group
Facebook

**** aHUS alliance Global Action
Home - aHUS Alliance Action

Declaration of Financial Interest

The US aHUS Patient Advisory Partnership does not have any financial interests to disclose for this Patient Listening Session. None of the participants today are receiving compensation for attendance. LW and DD, have received support for consultancy from a variety of sponsors.

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and non-binding on FDA and all other participants. This report reflects the US aHUS Patient Advisory Partnership account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of atypical Hemolytic Uremic Syndrome (aHUS), health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire aHUS patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.