Arginase 1 Deficiency (ARG1-D)

FDA Patient-led Listening Session Report

Virtual Presentation by Individuals and Families Living with ARG1-D

June 10, 2021

PURPOSE AND PARTICIPANTS

On June 10, 2021, a group of patients and families affected by Arginase 1 Deficiency (ARG1-D) participated in a one-hour virtual listening session with officials from the Food and Drug Administration (FDA). The virtual listening session enabled those living with ARG1-D and their caregivers to share their experiences, perspectives, needs, and goals with officials from across the Agency.

During the Listening Session, the patients and caregivers shared:

- **Difficulties in getting a correct diagnosis**
- **Symptoms and experiences related to living with Arginase 1 Deficiency**
- **The impact of the condition on daily functioning and quality of life**
- **Experiences with existing treatments and the current state of disease management**
- **The need for more awareness, improved care guidelines, and better treatment options**

Representatives from several FDA divisions, including the Division of Rare Diseases and Medical Genetics, the Office of New Drugs, the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research, attended the virtual session, along with the following ARG1-D patients and caregivers:

- Christine – grandmother to Willow
- Vanessa – mother of B, a 6-year-old living with ARG1-D
- Angela – mother of Isaiah, a 5-year-old living with ARG1-D
- Jean – mother of Jackson, a 30-year-old living with ARG1-D
- Leafy – mother of Jackson, a 30-year-old living with ARG1-D
- Jackson – 30-year-old man living with ARG1-D
- Tanja – mother of Willow, a 9-year-old living with ARG1-D
- Alexandra – mother of Josh, a 23-year-old living with ARG1-D

The group of patients and caregivers at the Listening Session did not participate in affiliation with any non-profit patient or advocacy group. The group of families connected via Urea Cycle Disorders umbrella organizations and worked together on the presentation. At that time of this writing, there is no formally organized patient advocacy group specifically for ARG1-D in the United States.

Overview of Arginase 1 Deficiency (ARG1-D)

Arginase 1 Deficiency (ARG1-D) is a rare and debilitating metabolic disease that worsens over time. ARG1-D is caused by a fault in a gene that limits the body's ability to break down arginine, resulting in persistently high levels in the blood. Arginine is a vital amino acid that plays an important role in the body, but elevated and accumulated arginine levels can have a devastating and progressive impact on the patient's ability to function.

Arginase 1 deficiency has been estimated to occur in approximately 1 in 300,000-1,000,000 births, making it one of the least common of all the disorders of the urea cycle, which collectively occur in about one of 30,000 people. The urea cycle disorders (UCDs) affect a series of biochemical processes in which nitrogen is converted into urea and excreted from the body through the urine. Failure to break down nitrogen results in the abnormal accumulation of nitrogen, in the form of ammonia, in the blood. Unlike the other UCDs, in ARG1-D the predominant pathological abnormality is the accumulation of arginine, and not excess ammonia. This is important distinction when considering treatments for ARG1-D.

Historically, Arginase 1 Deficiency has been unrecognized and potentially under-diagnosed, making it difficult to determine the true frequency of the disorder in the general population. This is likely to change now that Arginase 1 Deficiency can be diagnosed by newborn screening. ARG1-D is inherited in an autosomal recessive pattern, meaning both parents of an individual with ARG1-D each carry a copy of the mutated gene, but they typically do not develop symptoms.

"To find family members or friends that know anything about Arginase 1 Deficiency is almost impossible. Support and guidance are desperately needed but severely lacking."

Christine opened the Listening Session by giving a broad overview of Arg1-D and some of the unique challenges that come from the rare diagnosis:

"*Arginase 1 Deficiency, also known as Arg1-D, is a rare metabolic disorder resulting from a deficiency of the Arginase 1 enzyme which leads to high arginine blood levels. While we are one of six Urea Cycle Disorders, Arginase 1 Deficiency is also very different. Being so different has led to a lot of confusion for all of us, especially when first diagnosed. Arginase 1 Deficiency is one of the rarest of the UCDs, creating even more issues due to the simple lack of knowledge and experience by medical providers. All UCDs are uncommon and relatively unheard of. To find family members or friends that know anything about Arginase 1 Deficiency is almost impossible. Support and guidance are desperately needed but severely lacking.*

Christine continued with more details of ARG1-D, describing how lack of awareness of the disease and late diagnosis can contribute to irreversible damage.

"The body needs a way to dispose of ammonia. This is carried out in the liver, by a continuous process called the urea cycle. As the cycle turns, the toxic ammonia is changed, step by step, into urea (a non-toxic component in the blood), which is later excreted through the urine.

The urea cycle is controlled by a series of enzymes. In urea cycle disorders, one of the six necessary enzymes is not working correctly, and the cycle is interrupted. With Arginase 1 Deficiency, the Arginase 1 enzyme is not working correctly. Since the arginine cannot be removed or excreted through the urine, there is a buildup of arginine and guanidino compounds which leads to toxicity and causes the symptoms and damage.

"By the time it becomes obvious that something is wrong, the damage is already done."

Babies affected by Arginase 1 Deficiency often appear to be normal and meeting developmental milestones until their 3rd birthday. The progression of damage is slow and not generally noticed at first. By the time it becomes obvious that something is wrong, the damage is already done."

Although ARG1- D has overlapping features with other UCDs, it has distinct characteristics and manifestations.

ARG1-D

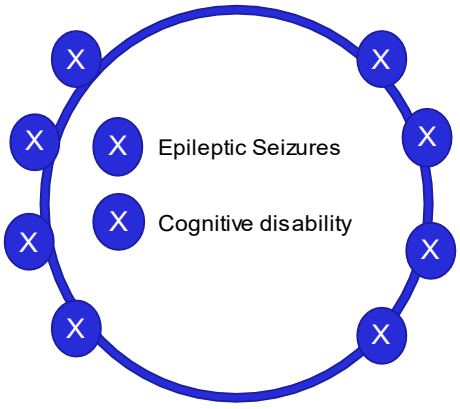
Mean age of symptom onset is 1.7 –2.3 years

Newborns appear healthy at birth

Hyperammonemia is triggered by physiologic stress e.g. illness, infections, food refusal

Spasticity is often present

Common Features



Other UCDs

Symptoms such as lethargy and seizures within the first few days of life

Neonatal hyperammonemia and encephalopathy are common

Episodic hyperammonemia may occur throughout life

Spasticity commonly not found

Patient and Family Experiences

Symptoms and Progression

The patients and caregivers shared experiences with the following symptoms, many of which began early in life and worsened as the patients got older.

- ***Vomiting*** – Several of the caregivers said frequent and profuse vomiting during infancy was one of the first symptoms that they noticed. When describing her son's early infancy, Alexandra said, "I breast fed Josh for 18 months and he always projectile vomited after nursing." Alexandra said Josh, now 23, still vomits frequently when he laughs or gets excited. Leafy recalled that her son Jackson's early childhood activities were severely restricted by the frequency of his vomiting, saying, "If we walked out the front door, we always had the pan and towels to catch his vomit. He vomited 6 to 12 times a day, throwing up what little he could eat and all of his formula." Wilson added, "Because he was unable to walk, run, or laugh without vomiting, his world was limited to riding in a stroller or a little red wagon, and no cartoons which he would laugh at."

- ***Spasticity*** – Three of the five families pointed out that muscle spasticity was one of the first signs that something was not right with their babies and toddlers. Vanessa said her daughter B struggles with progressive spasticity despite intensive physical therapy. B's physical and occupational therapists have said they fear she will have substantial joint issues as she gets older. Jackson, the only patient who spoke at the meeting and the oldest of the patients represented, first exhibited spasticity when he was an infant. Now 30 years old, he said spasticity, coupled with fatigue and osteoporosis, limits his ability to work. Jackson and Josh both toe walk and have endured painful Botox injections in their legs in an attempt to control the causative spasticity.

> ***"Josh, while more progressed and affected by ARG1-D than the families you have heard from… has experienced many of the similar affects, they have just worsened over time. "***

- ***Blood Clotting Difficulties*** – Two of the patients represented had blood clotting disorders: B was 18 months old when nosebleeds and easy bruising prompted a search for a diagnosis that ended up being ARG1-D. Josh has had blood clots and now has SVC syndrome and

takes blood thinners.

- ***Seizures*** – Seizures during infancy and early childhood were among the first symptoms for several of the families, including Isaiah, who was diagnosed through newborn screening and had his first gazing seizure when he was 6 months old. Josh and Jackson began having seizures when they were three and four years old.

- ***Fatigue*** – Beginning in infancy, fatigue is a hallmark of ARG1-D. This commonly reported symptom was discussed at the meeting, including in remarks by Jean, who said Jackson slept 12 hours a night as a baby and took 3–4-hour naps. In his remarks, Jackson said fatigue presents daily limitations for him as an adult. Fatigue was cited as an issue for all of the patients represented.

- ***Osteoporosis, Muscle Weakness, Falls, and Fractures*** – These symptoms taken together were experienced by all of the patients and were cited as presenting some of the biggest challenges in living with ARG1-D. Just three months after being diagnosed and still under three years of age, B was hospitalized after suddenly losing the ability to walk. As Isaiah developed into a toddler, his clumsiness and falls became a pronounced symptom. Willow, who was diagnosed shortly before her fifth birthday, struggles emotionally because of muscle weakness and frequent falls. She has developed a fear of heights due to falling, including once down a steep flight of stairs at home. Josh and Jackson, the oldest of the patients represented at the meeting, have contractures, hip dysplasia, and frequent falls due to muscle weakness. Jackson has severe osteoporosis and falls have resulted in fractures of both hands. Many ARG1-D patients, including some of those at the meeting, require wheelchairs, orthoses, and other mobility devices at least part of the time.

- ***Behavioral Issues*** – Several of the caregivers talked about short attention span, hyperactivity, high distractibility, poor impulse control, cognitive impairment, outbursts, fear, and anger. Alexandra linked her son Josh's arginine and ammonia levels directly to behavioral disruptions, saying, "Depending on his levels and his neurological state, we have sleepless nights, constant whining or yelling and behavioral issues that can lead to aggressive behaviors."

- Other long-term effects of ARG1-D mentioned by the caregivers and patients include ***glaucoma***, ***weakened immunity***, ***neurological dysfunction*** due to arginine buildup in the brain, and ***liver dysfunction*** which can become serious enough to require a liver transplant.

- ***Hyperammonemia*** – All of the families said they most feared this symptom, which occurs when arginine levels get too high and interfere with the body's ability to process nitrogen, resulting in the accumulation of ammonia in the blood. Hyperammonemia can escalate quickly and requires hospitalization. If left untreated for too long, it can be fatal.

"A cold isn't just a cold with these kids. It could potentially spin into a life and death situation, and we are constantly worried about this."

Impact on Quality of Life

In addition to the burden of ARG1-D's symptoms and progression, the patients and caregivers said common diagnostic odysseys, care and treatment routines, and financial and emotional burdens also negatively affected their lives.

- ***Side Effects of Medications*** – There is no medication or treatment for ARG1-D specifically, but many medications, supplements, and medical foods are used to help control symptoms of the disease. The families discussed a wide array of these, including ammonia scavenging drugs, anti-seizure and anti-nausea medications, muscle relaxants, medications to control acid reflux and constipation, mood disorder drugs, sleep aids, and protein-free and essential amino acids-free medical foods. The side effects of some of these include vomiting, blisters in the esophagus, throat, mouth, and tongue, and scar tissue buildup and infections around ports and sites of frequent IV placements. Willow's mother Tanja said Willow gets her medications at the hospital every two weeks via transfusion. She said, "For the past 2 years, they are getting very difficult due to the amount of scar tissue she is building."

> ***"I just want my child to be happy and healthy, but I look at Willow... I can see in her face that she isn't."***

- ***Inconvenience of medications*** – In addition to the side effects of current treatments for ARG1-D, several of the families said that many of the measures are significantly inconvenient and have a negative impact on quality of life for the entire family. Tanja described her 9-year-old daughter's typical day: "She has to drink a formula twice a day, every day, that takes us 2-3 hours per drink to get her to finish and she only achieves this by us telling her, 'Drink your juice, Willow' about every minute." Tanja said she believes that the flavoring that they add to the formula to make it more palatable may be responsible for the blisters that Willow has developed in her throat. Jackson and Josh also have had episodes of such blisters.

- ***Diet Restrictions*** – The first recommended course of action to control symptoms of ARG1-D is usually diet-related, specifically severe restrictions on protein intake. Vanessa and Angela described very low allowances of protein for their children,

> ***"The hardest thing for me to deal with is his diet and he does not understand the restrictions. I feel and he feels like he is deprived of foods that he likes."***

with Angela saying this diet restriction was one of the more difficult aspects of the condition for her family. Jackson and his parents said his unusual diet has caused social difficulties for Jackson throughout his life.

- ***Medical Complexity*** – Alexandra used this term when describing her son's health condition, citing multiple hospitalizations due to hyperammonemia, 31 different medications, 24-hour care requirements including home health care, and the placement of a g-tube in order to meet his required amounts of daily medical foods and medications. She also stated that Josh's medical team has recently expressed concern that Josh has reached his maximum threshold of medications. Eaton said this a tremendous worry because they have always increased medication amounts to meet Josh's disease progression, and this new reality may prompt consideration of a liver transplant that would bring another set of issues. Josh was the most medically complex case presented at the listening session, but all the families talked about the issue to some degree.

- ***Loss of Childhood*** -- The medical requirements and lifestyle limitations of ARG1-D negatively impacted the childhoods of all of the patients presented, according to their parents. Angela said her 5-year-old son is often angry about not being able eat what his friends eat and physically do what his friends do. She said, "It's very heartbreaking every day to feel like you're depriving your child from just having a normal life. Vanessa said her 3-year-old daughter B went from running and jumping around to being unable to walk just 3 months after diagnosis. B has regained the ability to walk but now needs 5 hours of physical, occupational and speech therapy a week and takes several medications daily.

- ***Quality of Life for Affected Adults*** – Jackson said his disease and all the measures that he must take to control it severely limit his ability to work and support himself. Now 30, Jackson worked part-time at Amazon before the 2020 Coronavirus pandemic and hopes to return, although he cannot work long hours due to fatigue, osteoporosis, and spasticity. He also cited concerns that his required medical foods cannot be made and stored in advance, further limiting his ability to work.

"My biggest concern is the present and the future due to worry about how I can support myself. I will be dependent on government aid for the rest of my life."

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- ***Insurance Coverage and Financial Hardship*** – Leafy, the parent of Jackson, spoke at length about the hardships her family has encountered in trying to get insurance coverage for Jackson's medical needs. She said, "Battling the health insurance companies was a constant, daily struggle and still exists today." Because there are no approved therapies specifically for Arginase 1 Deficiency, she said many of the insurance denials stated "experimental" use of medication as a reason. In addition, she said they could not get coverage for many of Jackson's medical foods, because insurers considered them to be "body-building protein drinks." Coupled with the insurance burden was the financial hardship brought on by Jackson's caregiving needs and the resulting loss of income due to reduced work hours. The family eventually lost their business and home and declared bankruptcy.

"They did not want to pay for any of the drugs that were recommended because they were not approved, or they were classified as experimental for his

Wilson, citing rising insurance costs and out of pocket expenses, said the financial worries brought on by ARG1-D have only grown, as she and Jean are now well into their 70s. "We go to sleep and wake up in the morning, worrying about his ongoing illness, how that will affect his future health, happiness and life," she said.

- ***Importance of Early Diagnosis –*** The group of families presented an array of diagnostic scenarios. Alexandra recalled that a routine heel prick test performed shortly after Josh's birth in 1997 was positive for PKU, although repeat follow-on testing was negative. "That was a red flag," said Alexandra. While it was clear that something was not right with Josh as a baby, it would be three years before he was diagnosed with ARG1-D after the onset of seizures and elevated liver enzymes. Jackson's mother Jean also spoke of "red flags" in infancy, but Jackson was 4 years old before a diagnosis was made despite him having persistent jaundice in early infancy, breast milk and formula intolerance, and sleeping excessively. He also developed spasticity, had seizures, and fell frequently in early childhood before being diagnosed with ARG1-D.

Newborn screening for ARG1-D became available as early as 1999, but not every U.S. state conducts the necessary tests. Only one patient represented at the listening session, California-born Isaiah, was diagnosed through newborn screening. The other patients, B and

"Newborn screenings didn't test for Arginase 1 Deficiency back in 1997 in Massachusetts."

Willow, both underwent diagnostic odysseys, enduring grueling testing and symptomatic episodes before being accurately diagnosed with ARG1-D.

Goals of Patients and Families

The families were thankful for the opportunity to tell officials at the listening session about their lives with Arginase 1 Deficiency. They also took the opportunity to suggest ways in which their lives and the lives of all affected by the disorder could be improved.

- ***Standardized Guidance on Dietary Protein Amounts and Medication Administration*** – All of the families had different experiences in learning how to handle diet and medication management of the disease. Angela's son was diagnosed through newborn screening, but she did not receive any education about the disorder beyond a generic pamphlet of information and a list of foods that her child could and could not have. She said, "When your child is diagnosed with a rare disease, it's really difficult to understand and accept. No one told us what to do." During a three-month period of waiting for confirmation of an ARG1-D diagnosis, Vanessa said they were told to limit her daughter Briana's protein but were given no guidance about amounts. Leafy said they were told a list of likely symptoms, many of which were devastating, but not much about how they could best manage their toddler's new diagnosis.

> ***"We made sure to give her portions of food and watched what she ate, but still had no clue that what we were giving her was still too much protein."***

> ***"There was no support or recommendation on how to move forward on the worst day of our lives."***

- ***An Instrument to Monitor Daily Ammonia and Arginine Levels –*** Throughout the listening session, the caregivers spoke of anxiety caused by never knowing when their children would have a health crisis brought on by rising arginine and ammonia levels and other symptoms of ARG1-D. Tanja described the fear that runs through her mind when Willow becomes ill, saying, "We get everything ready for the hospital just in case she starts acting lethargic or the vomiting continues, and we think there might be a hyperammonemic state." Alex said a nurse visits her home weekly to monitor Josh's plasma amino acid levels in order to avoid hospitalizations. Tanja said her family would love a solution that would allow them to check ammonia and arginine levels daily at home. She said that would help enable them to administer medications more easily at home and in a less invasive manner than required in the event of a health crisis and hospitalization.

- ***More Disease Awareness*** – Arginase 1 Deficiency is not known or understood by many people, including some with direct involvement in the lives of patients, including teachers, doctors, and government and commercial insurers. This lack of awareness causes social, emotional, and financial hardships for patients and their families. Jean spoke about Jackson's school years, saying it was hard for him to participate in school functions, field trips, and parties in part because of his dietary limits and potential for falls, but also because school staff did not understand his limitations. She said, "Middle school and high school were always a problem because, even with doctor letters excusing him from Physical Education, they (teachers) would embarrass him by asking him if he wanted to 'just try,' circumventing ours and his doctors wishes." Tanja said Willow also endures social hardships brought on by lack of awareness about her health condition. "Willow is constantly putting on a brave face but internally struggles with issues in regard to being different," said Tanja.

  "A low protein diet and an amino acid formula isn't managing her symptoms to a healthy point. We need more."

- ***Drug Development*** -- In concluding their remarks, the patients and families said better options for ARG1-D are needed. As pointed out numerous times in the listening session, the only medications and medical foods in the battle against ARG1-D are being used off label, and there are no treatments specifically aimed at ARG1-D, despite the disorder having its own unique genetic cause and disease course. Jackson concluded by saying that living with ARG1-D is challenging, adding, "I especially hope that Arginase 1 Deficiency will not be a thing in the future." Alexandra finished her remarks by drawing comparisons between B, Isaiah, Willow, and Jackson with her son Josh, the most progressed patient represented at the meeting. "I am very concerned for these families," said Alexandra. Vanessa said she hoped her participation at the meeting helped pave the way for other families to share their stories.

  "Please get your brains around this. We need something. We are at a dead end and I don't know what to do anymore."

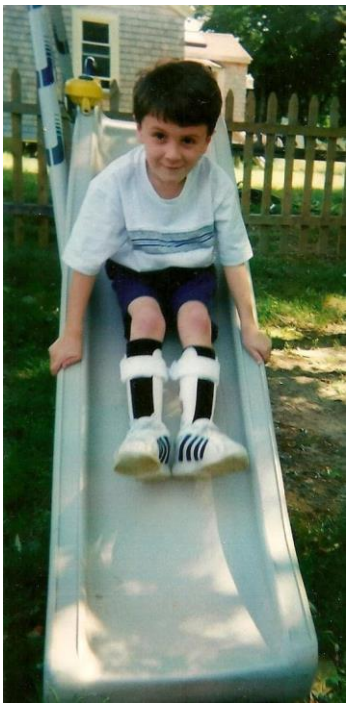
Before taking questions from FDA staff, Christine ended her remarks with the following:

"There is no cure. There is no current treatment to stop the progression of Arginase 1 Deficiency. Currently the only hope is to manage the progression by feeding a low protein diet and drinking terrible tasting formulas not just once but numerous times a day. This treatment method does not work for every child. G-tubes, liver transplants, scavenger drugs that do their own damage, wheelchairs and AFOs . . . this is the best that we

"Is there nothing we can do to save these families and children from a devastating future?"

can hope for? Our cry for help is urgent. The emotional and financial drain on everyday living for a family is tough but when these kids are in crises it is horrific. These families are so desperate to find help for their children that they are willing to risk off label drugs and difficult experimental therapies. Is there nothing we can do to save these families and children from a devastating future? Please help us find a path towards a cure or at the very minimum a treatment to stop the progression of this disorder. We need help now!"

In closing out the listening session, FDA DRDMG Director Kathleen Donohue thanked the patients and families and asked a question about how they fared during the CoVid 19 Pandemic. Jackson reiterated that he had to leave his job due to the pandemic and added that he is still on disability. He said ARG1-D weakened his immune system to the degree that he could not take the chance of contracting CoVid. His mother Leafy said the family went through many times their normal amount of supplies as they tried to keep everything in their household as sanitary as possible. Alexandra said the pandemic increased the anxiety around Josh having an ARG1-D crisis. She said they were able to have telehealth visits with Josh's 15 different specialists and they had started to venture out more at the time of the listening session.



Disclaimer

Discussions in FDA Rare Disease Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the account of the perspectives of patients and caregivers who participated in the Rare Disease Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of Arginase 1 Deficiency, 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 Arg1-D patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.