TK2d Patient Listening Session – Monday, January 31, 2022

What is a Patient Listening Session?

Patient Listening Sessions are small, informal, non-regulatory, non-public meetings that allow participants to connect with U.S. Food and Drug Administration (FDA) staff first-hand about their experiences, perspectives, and needs related to their health or a disease.

FDA Patient Listening Sessions can help inform medical product development, clinical trial design, patient preferences, and shape FDA's regulatory thinking. During a Patient Listening Session, FDA staff will either ask questions or simply listen to better understand your experiences and perspectives. Only the FDA, patients, caregivers, advocates, and community representatives participate in the session.

The Office of Patient Affairs works in partnership with the National Organization for Rare Disorders (NORD) and the Reagan-Udall Foundation for the FDA.

TK2d Patient Listening Session

On Monday, January 31, 2022, the FDA invited patients and caregivers of patients with Thymidine kinase 2 deficiency (TK2d), to speak about their personal experience.

The session – cohosted by The United Mitochondrial Disease Foundation (UMDF), MitoAction and TK2 Cures – featured four caregivers of affected youth, three adult patients, clinician Dr. Michio Hirano of Columbia University and speakers from the advocacy groups.

Brian Harman, President and CEO of the United Mitochondrial Disease Foundation, welcomed the group, thanking patients and caretakers for sharing their story and the FDA staff for the opportunity to speak.

Kira Mann, CEO of MitoAction, shared results from a January 2022 Tk2d "Voice of the Patient" survey. The survey queried TK2d patients or caretakers on symptoms, disease progression, current medications, desired outcome for treatments and more. Portions of the survey results are included in this report.

About TK2d

Thymidine kinase 2 deficiency (TK2d), TK2d is a mitochondrial disease and enzyme deficiency defined by muscle weakness, breathing difficulty, limb weakness that impairs gait or causes loss of ability to walk, droopy or saggy eyelids, and trouble chewing and swallowing that is often treated with feeding tubes.

Most TK2d patients experience symptom onset in the pediatric age group, while occasionally onset is in adulthood. Early onset patients tend to progress more rapidly and suffer early mortality.

As a rare depletion/deletion syndrome, TK2d is likely underdiagnosed. Estimates of the number affected individuals varies. **Research[1] released even since this listening session now suggests a prevalence of 600-2700 patients in the United States, although many of these are not yet identified.** As therapeutic options for TK2d advance, so does the opportunity to accelerate diagnosis.

Beyond the physical symptoms in this report, testimony noted TK2d is also a disease with tremendous economic and social consequences – including severe isolation, depression and anxiety.

Patients reported utilizing a significant range of services to help with the TK2d effects, including physical therapy, adaptive devices, occupational therapy, speech therapy, and mental health services.

Based on survey results, over half of TK2d patients have undergone surgery to assist with eating (tube-fed nutrition) or breathing (tracheostomy.)

1. Advances in Thymidine Kinase 2 Deficiency: Clinical Aspects, Translational Progress, and Emerging Therapies - PubMed (nih.gov): https://pubmed.ncbi.nlm.nih.gov/35094997/

The burden of living with TK2d

In this report, we've highlighted four major areas discussed by nearly every patient or caretaker, including the progressive nature of the disease, the most frequent symptoms of the disease, the lack of FDA approved treatments, and desired outcomes should a treatment become available. We've noted responses where participants answered specific FDA staff questions.

TK2d is "devastatingly progressive."

There is no doubt that TK2d symptoms progressively worsen – often quickly. Patients and caregivers used words such as "devastatingly progressive," "relentless," and "degenerative" to describe the disease.

> *"This severely progressive devastating disease called TK2d simply kills time, and again … time is the one thing people simply wish they had more of."*

Said Dr. Michio Hirano of Columbia University, who joined the call to give a clinician perspective: "Regardless of the age of onset, this disease is **recklessly progressive, debilitating, and in most cases, lethal**."

Given the lack of FDA approved treatments, parents reported doctors encouraging them to make their children "comfortable" in preparation for death.

> "I was cautioned that the earlier the onset the more severe and devastatingly progressive it would be, meaning he was given a few months to live and they could only make his decline comfortable."
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> "She was completely healthy and now we had to make a decision on how she would die. The doctors gave us a couple of weeks due to her current condition and asked us whether we wanted her to be on a breathing machine once her lungs failed. We made the difficult choice to decline the breathing machine that would prolong her suffering. We then brought her home at 4-1/2 months old under hospice care living her last days."

Adult patients talked of losing all levels of independence.

"When I was first diagnosed, although I had symptoms, I was able to do my normal activities. Today I can't … TK2d has progressively taken away my physical strength and my ability to eat, swallow, and breathe."

"I went from an active and independent teenager to a 25-year-old who relies on help with absolutely everything. I cannot walk. I cannot cook for myself. I cannot pick out clothes from my closet and dress myself. I cannot get onto a toilet by myself. I cannot get in the shower without someone placing me there."

"It's hard being unable speak. But the worst part is knowing that every day I'll wake up weaker than the last. I cling desperately to every last bit of strength, and it still slips away."

"The worst thing is that this condition is degenerative. I know that it can only get worse. I have been living with this disease for at least 15 years now and nothing has helped me."

"Each day is different depending on my level of fatigue and weakness but I find each day I can do less and less. I used to have a job in the medical field that I loved but the effects of TK2d have robbed me of my career. I'm no longer able to work, nor live alone and have become dependent upon my loved ones to help with my care."

"The symptoms don't vary. Nothing makes them better. I am weaker every day. I know other diseases have ups and downs, peaks and valleys. But here there is only down, and it never reaches bottom."

"I've been dependent on a vent and wheelchair since I was three years old. I lost the ability to speak when I was around nine. Since then, it's been a slow decline with my hands and eyes. Ten years ago, I could write pretty well; not so much anymore. Three years ago, I didn't need to tape open my eyelids to see; now I do. I've also had some hearing problems start this past year, and after some testing it seems like it's from eustachian tube dysfunction. I suspect that's a progression of my disease."

The progressive nature of the disease is often compounded by problems getting a diagnosis. Dr. Hirano noted many patients have been on a "diagnostic odyssey for weeks, months or even years."

Problems breathing, eating, and walking – how muscle myopathy wreaks havoc on the lives of TK2d patients.

Many of the symptoms that most worry TK2d patients and caretakers – including swallowing difficulties, respiratory issues, chronic fatigue, and eye muscle problems– are directly related to skeletal muscle disorders, or myopathies.

> *"The tough thing about the disease is that it weakens not just one muscle, but all … that help us do little things like swallow, blink, smile, walk, hug and breathe."*

One-hundred percent of those surveyed chose muscle weakness as one of the symptoms that most impact daily quality of life. Similarly, every participant on the call cited muscle weakness as a symptom.

"When he was 8 months old, we noticed that he had muscle weakness and he couldn't stand like other infants his age. When he was 1.5 years old, he started to stand up alone and within a few months he would walk a short distance. By 2.5, he began to lose muscle strength and could no longer walk by himself. He would have to hold on to the tables and couches to support himself."

"Living with TK2d means having a plethora of symptoms, but the general weakness and loss of my motor skills is so insurmountable that I truly wouldn't wish it on anyone."

Many participants cited muscle fatigue as the number one goal of any potential treatment. Over 80% of those surveyed chose "reduced muscle weakness" as one of the top priorities for anything designed to improve symptoms.

The effects of TK2d-related myopathy are far reaching, affecting nearly every aspect of life, including:

- Breathing
  Respiratory related issues were cited by half of respondents as a top symptom in the survey. Similarly, nearly 60% of respondents choose "Improved Respiratory Function" as something they would want a possible treatment to target.

  "For the last two months, Andrew has needed to use the BiPap machine during the day every 2-3 hours for 15 to 20 minutes. We pray that he doesn't get any worse which would require him to use the machine more often during the day and a definite indication that his disease is progressing."

  "My breathing is severely impacted and I spend most of my day on my BiPAP machine for the simple relief of not having to work so hard to continue the most basic function that keeps us all alive. Imagine how it feels when you get out of breath; now imagine feeling that way all day every day."

  "We were on 24-hour watch with both of us restless beyond imagination because she couldn't breathe unless we constantly sucked the mucus and saliva out of her. We tried our hardest to take care of her. We were happy we were able to spend a little more time with her than what the doctors gave us, but it was extremely tolling on our family and trying to our marriage."

  "We were discharged from the hospital with a BiPap machine that is critical for Andrew to breathe. He must use the machine all night while he sleeps or his oxygen saturation will drop to a dangerously low level. My wife cares for Andrew around the clock and this really takes a toll on her. We have alarms that are set to wake us in the event his oxygen levels drop during the night."

  "His respiratory system was too weak and he could no longer breathe on his own, so now ventilators help us buy more time. They stitched his esophagus and wrapped it to prevent him from vomiting and taught me all about his g-tube. I became a doctor, a nurse, a therapist, an advocate and a medical mom in what seemed like overnight."

"It is challenging for me to walk and breathe at the same time. I have pain in my chest that is almost like a burning sensation and muscle spasms all over my body."

- Eating

Swallowing difficulties were cited numerous times in comments on the listening session. Amongst those surveyed, more than 60% chose "Swallowing Difficulties" as one of the most impactful symptoms.

"The focus a lot of the time are his three main areas that are all justifiably intertwined – his respiratory system, his feeding ability, and his mobility."

"I can no longer swallow to eat or drink. I miss drinking water. I feel thirsty all the time, so I have a g-tube to get nutrition and water. I have sores near my peg placement that are very uncomfortable."

"It can take up to an hour to eat because my mouth and facial muscles are weak making it harder to chew and swallow liquids or solid foods. I have no suction to keep my mouth closed when I'm chewing and the weakness in my throat makes it hard to swallow without choking. I had to learn different ways to compensate, for instance, eating slower and taking smaller bites, and not eating chewy or hard foods."

- Mobility

Of those surveyed, approximately three out of four respondents said they had limited or no ability to walk, meaning they were reliant largely on others to complete every day tasks. When asked to choose what specific activity was most important that TK2d impacts, two of the top four answers related to mobility.

"Andrew continues to struggle with many symptoms because of TK2d such as muscle weakness, difficulty breathing and difficulty accomplishing gross motor skills such as walking and standing without support."

"When I was able to walk upstairs, my legs would get so tired. I always thought that I could climb the stairs when I grew older because my legs would be taller and stronger. But going upstairs became more and more difficult with time. Since then, hope has become part of my character; hope was our only way to deal with this situation. Fighting is the only thing we can do, and the things we fight for are getting more and more severe with time."

"I'm not able to walk very far without getting extremely fatigued and out of breath. I try to do general chores around the house and some sort of exercises like walking or Pilates."

Outcomes and Treatments

TK2d is a disease without any FDA approved therapy. Dr. Hirano noted: "Current TK2d treatment efforts are mainly focused on supportive care, which requires multi-disciplinary efforts through physical, occupational and speech therapy."

Respondents take a variety of medications to help manage symptoms and more than 30% are taking experimental medications as part of a clinical trial.

"When I am tasked with the question of what I want from a treatment for my condition I say 'I want absolutely anything. Anything that can help me stay stable. Anything that can help me have a semblance of a life again.'"

> "The supplements are the "mitochondrial cocktail" prescribed by my neurologist. I suppose in theory it's meant to reduce muscle fatigue or something. I'm not convinced it does much, but there's no alternative."
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> "We hope that one day the story that we will tell will be of a cure for TK2d. For now, we take one day at a time, struggling with the fact that unlike other 3-1/2 year-old boys, there are so many things Andrew can't do. We are blessed that he is still here with us, but we need a treatment."
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> "I know the FDA, those researching -- everyone needs time. Sadly for those with the disease, their fate doesn't have time. Time is personal, nobody quite understands it unless they experience it, unless they experience the loss and grief that comes along with the uncertainty of it."
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> "I have no treatment available to me, but I hope that I can participate in a clinical trial that will help make my life and other TK2d patients' lives more fruitful and help with the production of energy. I also hope that one day with treatment, I will be able to form a smile and speak without any difficulty. My symptoms have rapidly progressed in the last three years. What worries me most about my condition is that I'll be unable to eat and breathe on my own."

On follow-up questions, respondents were asked what outcomes they value the most from potential treatment. Several parents pointed out that a power outage could lead to ventilator failure and the death of their child, making an exit from machine breathing a priority. Others focused on stopping the progression of the disease to allow for more time for future treatments – or even dreamed of regaining abilities lost. These comments largely mirror survey results in which 100% of those asked chose "prolong life" and "gain in function" for meaningful outcomes of a possible treatment.

> "Slow the progression, make him stronger and improve his quality of life. I would like for him to get off the ventilator."
>
> "This disease progresses every day. Stop the progression until there are more treatments in future."

"Something that would slow the progression but also reverse some of the issues. Get some energy to muscles so I have an easier time speaking, swallowing and eating without choking. For now, a lot of my day is spent eating. (A treatment) would allow me do other things – go for a walk, maybe even try to work again. Missing in my life as my work was central to my life and it contributes to my depression and anxiety."

"The goal of the treatment will help him to improve his muscle weakness. To improve his breathing."

On Controlled Studies

When asked if anyone would want to provide their thoughts about control trials, both patients and caregivers were clear with their concerns. All verbal responses favored eliminating controls and placebos – or at least limiting them as much as possible.

"The disease is hopeless as is. I would be discouraged if I might be getting a placebo because I would be left in the same hopeless situation I'm in now. But a 50-50 chance of getting the real medication is better than nothing. I already have nothing."

"Personally, I would disagree (with use of a placebo). Someone in the control would die without these medications. As a parent, I disagree."

"The sooner you start, the better your chances are. If there were to be a placebo, it needs to be for the shortest time possible."

"One of the good things is there are different markers to see if they are working. I don't think they would do well with withdrawal. Medication gives you a chance at a normal life. (Rather than a control) look at skills, mobility, and respiratory, feeding, and quality of life."

"I want it to be scientifically sound. If I'm going to get a placebo, time should not be long. Any placebo period should be short."

Closing Statement

Philip Yeske, Science & Alliance Officer for UMDF and parent of a deceased mitochondrial disease patient, thanked the patients and caregivers for helping to achieve the meeting goal of amplifying the voice of the TK2d patient. He noted that throughout the meeting TK2d was described with terms such as "relentless" and "progressive" and emphasized that there are currently no treatments for TK2d.

He urged the FDA to:

- prioritize and accelerate drug reviews and apply regulatory flexibility on behalf of patients with Tk2d who have a very poor quality of life and no time to spare;
- allow Tk2d patients access to potential therapies that may halt the progression of their symptoms or reverse them;
- ensure the Tk2d patient voice is included at every stage of drug development and approval.

FDA staff from 15 different offices/divisions across four centers attended this listening session, including:

Office of the Commissioner (OC) – *4 offices*

- OC/OCPP/OPA – Office of Clinical Policy & Programs/Office of Patient Affairs *(organizer)*
- OC/OCPP – Office of Clinical Policy & Programs
- OC/OCPP/OOPD – Office of Clinical Policy & Programs/Office of Orphan Products Development
- OC/OCPP/OPT – Office of Clinical Policy & Programs/Office of Pediatric Therapeutics

Center for Biologics Evaluation & Research (CBER) – *2 offices/divisions*

- CBER/OD – Office of the Director
- CBER/OTAT/DCEPT/GMBI – Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharmacology & Toxicology /General Medicine Branch I

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

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

Center for Drug Evaluation and Research (CDER) – *8 offices/divisions*

- CDER/OD – Office of the Center Director
- CDER/OND/ON/DNI – Office of New Drugs/Office of Neurology/Division of Neurology I
- CDER/OND/ORDPURM/DPMH – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology & Reproductive Medicine/Division of Pediatrics & Maternal Health
- CDER/OND/ORDPURM/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology & Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBIII – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics III
- CDER/OTS/OB/DBIV – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics IV
- CDER/OTS/OCP – Office of Translational Sciences/Office of Clinical Pharmacology
- CDER/OTS/OCP/DTPM – Office of Translational Sciences/Office of Clinical Pharmacology/Division of Translational & Precision Medicine

Disclaimer: Discussions in FDA Patient 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 TK2d Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of TK2d, 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 TK2d patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.