Adult Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia a Patient-led Listening Session by Sisters' Hope Foundation
01/17/2024

Initial meeting goals and topics accepted by the FDA:
Proposed Meeting Goals:

1) Provide understanding of disease - its severity, difficulty in diagnosing, and its inheritance pattern
2) Share the impact of symptoms on patient and caregiver
3) Share the impact of disease on family
4) Share our community's clinical trial experiences
5) Share our community's hope for treatments

Proposed Meeting Topics:

1) A clinician will present an overview of challenges with diagnosis, disease severity, and treatment challenges.
2) A caregiver will share the realities and impact of the 5 most burdensome symptoms on patients and caregivers.
3) A young woman who lost her mother to ALSP will give insight into the lasting impact of the disease on the family unit.
4) A caregiver/asymptomatic carrier will share experiences of experimental and clinical trials.
5) A caregiver will express expectations and willingness of patients to participate in clinical trials as well as limitations of patients ability to participate.

Summary of topics discussed:

Speaker A, Introduction to Listening Session and Clinician

Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia, also known as ALSP is the disease that brings us before the FDA. Here are the cold hard facts that make ALSP so horrific and devastating. It is a debilitating disease that hits the young in the prime of life, symptom onset typically occurs between 30-50 years of age, leaving in its wake a life cut short, financial ruin, and shattered families. It is rapidly progressing. Once symptoms appear, there is no plateau. It is a continuous decline of the mind and the body. Death happens between 1 to 6 years after symptoms onset. And this nightmare doesn't happen just once in a family. It happens over and over and over because it is an autosomal dominant hereditary disease. Every child of an affected parent has a 50/50 chance of inheriting the genetic mutation responsible for causing ALSP, and only one copy of the mutation is needed for the disease to manifest. Families live through the nightmare time and time again, generation after generation.

Speaker B, clinician

Topics of Discussion Include:

1. Disease severity

2. Diagnosis difficulty – including that it used to be an autopsy diagnosed disease and there is typically a long diagnosis odyssey
3. Inheritance pattern - an autosomal dominant disease
4. Highly variable presentation - 4th to 5th decade of life similar to FTD, can also look like Parkinson's or MS, women can present 7 years earlier than men
5. Current standard of care - symptom management, no disease-modifying treatment at this time

Speaker C, caregiver, representing 3 family members:
There is a range and a variety of symptoms that ALSP patients experience - gait, coordination and mobility problems, cognitive changes, behavioral issues, communication difficulties, urinary and fecal incontinence, seizures, skin issues, and respiratory challenges. It's a full body, whole person disease. There are multiple organ systems involved and affected. Medications and therapies are used in an attempt to manage symptoms, but universally these medications and therapies provide little to no benefit in slowing progression or effectively managing symptoms.

According to a recent survey of the ALSP community conducted by Sisters' Hope Foundation, the top 5 most burdensome symptoms are: cognitive changes, behavioral disruptions, gait and mobility problems, incontinence, and seizures. It is nearly impossible to focus on the absolute most burdensome symptom. There are multiple reasons for this. Initial symptoms of ALSP patients vary from person to person, even within members of the same family, and generally, patients exhibit multiple symptoms simultaneously as the disease takes hold and progresses. No two manifestations are the same.

The speaker then provided real life examples of ALSP patients living with these top 5 symptoms

From the patient perspective these symptoms are terrifying. They rob the person of independence, privacy, dignity, self-control, activities they love, and so much more.

From the caregiver perspective, these symptoms are overwhelming, surprising, and shocking. Generally, the loved one declines so rapidly, it is hard for the caregiver to adapt and adjust to the ever emerging symptoms.

An added layer and struggle with some caregivers is the notion that this eventually could be them. When you are caring for a parent or a sibling with a hereditary disease, there is the question - "Do I also carry this mutation and will I develop this disease?" As they care for their loved one, they are simultaneously watching what could be their own death play out in front of their eyes. They are vicariously living their loved one's death as if it could be their own.

Speaker D, caregiver, representing 1 family member:

ALSP is a disease that doesn't just affect individuals; it affects families. The implications to family are deep and far reaching. Symptoms can cause financial damage, scandals of reputation, and wedges in relationships.

ALSP brings with it major life disruptions, family conflict, and long-term breakdowns of the family unit. ALSP devastates families. It has devastated my family multiple times over. It changes family dynamics, it strains family relationships, and it shatters the stability of families.

And it doesn't just wreck and destroy families once. It does it over and over, generation after generation.

The speaker gave real life examples of how ALSP has impacted the family unit.

Speaker E, asymptomatic patient, caregiver, representing self and 2 family members:

We have shared stories highlighting the challenges of symptom management using already available FDA approved medications. Most of the readily available medications do little to curb the devastating symptoms of this disease. We have seen simple medical devices such as catheters and feeding tubes improve quality of life when used. However, these devices are not readily prescribed for use in the United States.

Despite these challenges, progress toward viable treatments has been made in the last 3 years within the ALSP space. Researchers are interested and invested in ALSP, and pharmaceutical companies are hoping to use research to create treatments. There's currently a drug trial in process! Some of our patients have been offered the option of an experimental bone marrow transplant. The use of these experiments and this research has created even more complexities and challenges to our patient and family community.

We now have three separate groups that need treatments within our community. We have asymptomatic carriers. These people have the gene mutation that will likely cause ALSP. They are in need of preventative treatments. We have chronic patients. These are the people who have undergone and survived the experimental bone marrow transplant. Their disease progression has stopped, but all are left with varying degrees of disability. Most are unable to work, and many require full-time care. They are chronically ill. They need medications that can effectively manage their symptoms, and they are hopeful for treatments that will repair the damage in their brain and restore their ability to fully function in daily life. Finally, we have terminally ill patients. These are the people who are so far advanced in their symptoms that they do not qualify for potential treatments or the treatments are not working to stop the progression of the disease.

The speaker shared experiences - both pros and cons - of experimental treatment and clinical trial.

Speaker A, caregiver, representing 4 family members:

Our community desperately wants viable treatments and a cure. We know that your role at the FDA is an important piece of making this a reality. So, when considering the disease course, the disease impact, and all the long term implications of this disease, our community is quite unified in what we expect from clinical trials and treatments.

Our community is passionate and dedicated to finding a viable treatment and cure for this disease. Our patients are willing to take on enormous risk for themselves to find a viable treatment. To be clear, when our community says viable treatment, they are speaking of a treatment that is highly effective in slowing the progression of the disease and improving the quality of life of the patient.

As a rare disease, clinical trials come with their own challenges based on the inherently low number of people able to participate in any given trial. To combat this problem, we believe that in clinical trial design it is important to consider the following things.

First, it is important to make participation as easy as possible for the patients. This includes things such as considering convenience for patients. If possible, limit the amount of travel they must do. Make sure they are fairly compensated for their participation in the trial.

Secondly, consider eligibility requirements carefully, making sure to include as many patients as possible. We believe it is important to offer the treatment to all participants. Natural history studies can hopefully offer a control group rather than giving some participants of the trial a placebo. It is imperative to allow studies to continue even with a small sample size. While our community may look small, we are mighty, our disease affects multiple generations, and we believe this disease is highly underdiagnosed.

Thirdly, when writing clinical study protocol, we recognize that it is important to have clear, concise requirements and measurements. That being said, we are requesting that those protocols not be so stringent that they overshadow the human aspect and experience.

Finally, considering the rapid progression of ALSP, we need a rapid response. We ask you to consider accelerated approval for all potential treatments that produce data showing positive impact on slowing disease progression and increasing quality of life for our patients.

Our community is open to all methods of treatment whether that be a pill, an infusion, gene therapy, or any other idea that researchers may bring forward. We embrace innovation and creativity, and we will support anyone willing to work within this space and on the behalf of our patients and families.

Now is the time to find a treatment. Sisters' Hope is working to make a positive impact by supporting our patients and families living with ALSP. We are working to bring awareness and education to the wider community of clinicians and researchers. And we are always working to instill hope for all living with, and fighting, this disease.

This is the most important thing of all: Our community has hope. It is HOPE that keeps each of us going. It is HOPE that pushes the researchers forward in their work. It is HOPE that propels you at the FDA forward as you work to make a difference in the lives of families impacted by disease. It is HOPE that keeps us all motivated and fit for fighting. We hope for more understanding. We hope for better care. We hope for more support. We hope for viable treatments. We hope for a cure.

FDA comment 1: I wanted to take a moment to say thank you for taking the time to share your personal experience. It is impactful to hear your stories and lived experience and the extent that your families have been impacted. We thank you for taking the time to come today. I wanted to tell you that we are listening. It is helpful to hear the range of experiences. There is a variety of different presentations of disease. It is helpful to hear firsthand how different it is from family to family. It makes it difficult for drug companies because they want to capture one endpoint. It is hard when they have different most burdensome symptoms. It is hard to pinpoint what that one endpoint could be. I think you answered a lot of hard questions. It is helpful to understand what you would consider in terms of risk.

FDA question 1: It sounds like there might be a treatment that might stop progression as opposed to reverse symptoms, such as the bone marrow transplant. Is that something that would be meaningful? Is there a way to capture what is most meaningful if you can't reverse?

Speaker C response: The bone marrow transplant stops progression, but it is not for everyone. Stopping progression is not ideal because the patient remains incapacitated, and it is not improving the quality of life for the patient and caregiver.

Speaker E response: I agree. If it is found in the patient earlier, then it would be helpful. At the late stage it is not as helpful. My brother has doubts that getting the treatment was a good thing to do.

Speaker C response: Someone in the community who had a bone marrow transplant earlier, this patient still has pretty significant disability. She can work and hold down a job, she still needs care. That isn't the best-case scenario and isn't ideal.

FDA question 2: When we have disease that is variable and we have patient reported outcome, how reliable would it be to ask how the patients are feeling? How much would rely on the caregiver?

Speaker C response: I would say those questions would need to be directed to the caregiver. They would know how they are feeling about life. My mom was able to communicate through most of her disease. It provided opportunities to have good conversation. She was wheelchair bound and said that if I ever got like this, I thought I wouldn't I want to live anymore, but that's not true. Thankfully, my mom was still able to engage in life. She could listen to music. She couldn't play music. She could watch her grandkids play, but she couldn't play.

Speaker A response: It is critical to involve the caregiver in every aspect of the journey. The patient gets to a point where they can't be their best advocate. They can't do it on their own. My twin sister was independent and single mom and insisted she could do it on her own. She would say that she is fine. She could barely speak and walk. At certain stages, we had to start carrying her. Every patient with ALSP must have their person, trusted individual to answer questions. They don't understand how bad it really is. To trust an ALSP patient at certain time frame of the disease is dangerous. You need their trusted person to answer the questions.

Speaker E response: With my middle brother, Jeffrey, he has good and bad days. When I do talk with him, there are days that he expresses himself. I don't want to die. I want more time with my wife. There are some days where he doesn't understand what is going on. He blames my sister-in-law. It is scattered. On days that he is himself, he can express that he is scared and aware that the disease is progressing.

FDA question 3: It seems that if genetic testing was done earlier, the patients could have earlier intervention. What are barriers to genetic testing?

Speaker C response: There are many barriers that contribute to people not getting tested. There are tangible barriers such as 1) doctors not recognizing genetic testing as necessary, 2) doctors not knowing what genetic testing to order, 3) cost of genetic testing being high, and 4) not being able to qualify for certain insurances. There are intangible barriers such as 1) family dynamics and opinions surrounding genetic testing and 2) personal emotions about genetic testing. Genetic testing is a complex and complicated decision. Doctors and genetic counselors don't always do a good job of explaining its necessity and preparing someone for the implications of potential results. Family relations can be strained over differing opinions and negative emotions such as fear and guilt accompany any test result.

Speaker A response: Even in my family, where we have spoken openly and honestly with the younger generation, there are still many members that are hesitant or absolutely refuse to get testing done. It is frightening to know you carry a mutation that will cause this devastating disease.

Speaker E response: When I got tested, it was shortly after we found out my sibling carries the mutation. I didn't really understand testing and the far reaching implications like the emotional impact and the financial impact. All of my siblings and myself have been tested, but there are still many, many cousins that refuse.

FDA Divisions Represented:
Office of the Commissioner (OC) - 1 office

- OC/OCPP/PAS – Office of Clinical Policy and Programs/ Patient Affairs Staff (organizer)

Center for Biologics Evaluation and Research (CBER) - 3 offices/divisions

- CBER/OCD – Office of the Center Director
- CBER/OCD/PS – Office of the Center Director/Policy Staff
- CBER/OTP/OCE/DCEGM/GMB2 - Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharmacology/Toxicology/General Medicine Branch II

Center for Devices and Radiological Health (CDRH) – 6 offices/divisions

- CDRH/OCD
- CDRH/OPEQ/OHTIII - Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHTIII/DHTIIIB - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III B
- CDRH/OPEQ/OHTV
- CERH/OPEQ/OHTV/DHTVB
- CDRH/OSOPTI/DAHRSSP/PSE - Office of strategic Partnership and Technology Innovation/Division of All Hazards Response, Science and Strategic Partnerships

Center for Drug Evaluation and Research (CDER) – 5 offices/divisions

- CDER/OCOMM/PASES/
- CDER/OND/ON/DNI – Office of New Drugs/Office of Neuroscience/Division of Neurology I

- CDER/OND/ON/DNII – Office of New Drugs/Office of Neuroscience/Division of Neurology II
- CDER/OND/ORDPURM/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DB I – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics I

Patients Represented
11 patients represented by 4 caregiver speakers.

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 Sisters' Hope Foundation's 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 ALSP, 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 ALSP patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.