



FDA Listening Session Neuronopathic Gaucher Disease

September 9, 2021

Objectives of Session:

1. Provide context to the FDA of the struggle for families living with neuronopathic Gaucher disease (nGD) and the lack of approved treatments for this disease.
2. Highlight the new research and clinical trials for Gaucher Type 2 and 3 and ask the FDA for careful review on efficacy and safety.
3. Engage and empower families in our community that often have no outlet for self-advocacy.

Summary of Topics Discussed:

Clinical Summary of Disease presented by Ozlem Goker-Alpan, MD

Dr. Goker-Alpan reviewed the background on Gaucher disease, diving deeper into nGD, its heterogeneity and end point challenges. The different Gaucher chromosomes were reviewed and the biological process of Gaucher described. Neuropathic GD presents therapeutic challenges because of cell death, immune dysregulation and inflammation. Although Gaucher is broken into three types, it is actually a continuum of neurologic phenotypes. The presentation included a definition of nGD and symptoms, review of rare presentations of nGD, clinical manifestations and clinical spectrum. Finally, Dr. Goker-Alpan reviewed the unmet medical challenges of nGD including: progressive disease despite intervention, seizures, myoclonic encephalopathy, hearing loss, cognitive impairment, behavioral and psychiatric problems.

Patient and Caregiver Presentations

Three different nGD families spoke about their experiences living with nGD.

Family 1 (13 year old female with nGD and her mother)

- Mom discussed diagnosis, starting infusions, 9 surgeries total to date with bones in bad shape and severe fractures in hip, like having a football injury. Daughter had a wheelchair and walker and is now grateful that she is released from using them on a regular basis, but now still uses them when in pain or having difficult days. Daughter

receives weekly infusions and has shown some improvement in blood levels. After starting Ambroxol this past March more improvement has been shown.

- Daughter diagnosed with epilepsy and takes anti seizure medications. She has needed surgeries for eyes to align; has hearing aids because of severe hearing loss in each ear; lost all hearing in left ear and had surgery to bring some of her hearing back.
- Family is waiting for a cure someday, but in the meantime they would love to take a pill instead of infusions and a port, and they would love Ambroxol in this country for easy access to help the neurological symptoms of nGD.

Family 2 (25 year old male with nGD and his mother):

- Patient introduced himself and explained that he was first diagnosed with leukemia. He likes watching TV and eating good burgers, going to the Monster Games, and going to the park and zoo. He stated that he gets very frustrated with all his medications and sometimes throws them on the floor because he can't take the frustration anymore. Having seizures is very, very frustrating. He used to be more independent, but now he can't be anymore due to his seizures. It's very hard and he gets angry sometimes.
- Mom is a full-time caregiver. She explained that her son can't be alone because of seizures and risk of falling. He started having trouble at 6 years old with vomiting and diarrhea. Doctors told mom that he was fine. As a mother, she always knew something wasn't right even though they were sent away with no diagnosis. As he got older he developed a large spleen and liver and had to wear a turtle shell to protect his spleen. He got sick all the time, so he was home schooled to protect from exposure. Yet through all this he was still undiagnosed. At 7.5 years, he finally got diagnosed with type 1 Gaucher. Started bi-weekly ERT right away, but was diagnosed as type 1, even though he had obvious type 3 issues. Mom decided to take him out of state to consult with a Gaucher specialist and was finally diagnosed with type 3.
- Many problems getting appropriate care. He had severe lung disease and chronic infections. Some aspects are under control, but the seizures have gotten worse and are the most frustrating aspect of his disease. One of the medications for his seizures is causing him to have lack of control for walking so he needs to use a wheelchair.
- Family hopes for a better treatment without needles. Gene therapy might be a good option someday. Mom worries about what there will be for her son and others with neuronopathic Gaucher in the future. Treatment is limited by ERT because it doesn't cross the blood-brain-barrier, and there is no access to Ambroxol in the US. His disease takes a toll on the entire family.

Family 3 (7 year old female and her mother):

- Child is nonverbal and on a ventilator and mom is very tired from all the care she has to give. It is a 24/7 job. Mom sensed something was wrong from the moment of birth. Baby would wake up in the middle of the night screaming in pain. Many types of physicians all told mom nothing was wrong. At 3 months, the baby's eyes started crossing, but the physician still said she was fine. At 5 months, after gaining no

weight, she was diagnosed but recommended not to go on ERT because she was not having any of the type 1 symptoms. Next she was diagnosed with Type 2. Baby had a g-tube insert followed by a tracheostomy. After starting ERT and Ambroxol, her eyes stopped crossing and no longer has vagel episodes.

- Child is doing better on Ambroxol now. She has no seizures as long as she's on medication. But she has scoliosis and is on a ventilator.
- Mom hopes that children will have a better outcome if the medical community listens to parents more and understands that there is still a human there, even though they have a disease.

nGD Registry presented by Tanya Collin-Histed, CEO, International Gaucher Alliance (IGA)

- Tanya is first and foremost mother to Maddy who has type 3. She explained that support from other families is so important to rare disease patients.
- Tanya reviewed the new nGD patient registry, GARDIAN. The goal is to show evidence for improved outcomes and disease management and improve patients' lives. There is a massive challenge for the global phenotype and this will help find the right endpoints for further research for emerging drugs for nGD.
- Patient Portal: Various doctors will be engaged with this portal and use the data from patients and caregivers on a global survey to develop a global patient registry. The registry will be in 7 different languages and collect and store data on a platform to provide evidence-based data to improve outcomes for our patient community.
- When treatments are approved in the US, it affects other countries because decisions are used as a model for other countries. GARDIAN welcomes the expertise of the FDA and encourages exchange of information. With small patient numbers in other countries, there is difficulty with running clinical trials;
- IGA and GARDIAN hope that everyone together can best address these issues and ultimately improve innovation and get treatment access for patients.

nGD Community asks for the FDA presented by Aviva Rosenberg, Co-President GCA

- Hope this is only the beginning of a conversation between the community and FDA.
- ERT is approved for only Type 1; by not having approval for nGD, this places another burden on families because it must be prescribed off label. This causes additional insurance hurdles and denial or alternatively incorrect medical record diagnosis to ensure the child receives ERT.
- Approve access to Ambroxol in the US, by funding studies. Currently, patient families have to find people in Europe to send treatment to them on a regular basis so that they can treat their children with the only thing so far that can cross the blood-brain-barrier to treat nGD.
- Fast track gene therapy trials and continue to push gene therapy trials forward to give more options to the nGD community.

Questions from the FDA

- How has COVID affected receiving care?
 - Patient family: Increased opportunity for telemedicine because going out is extremely dangerous with immunocomprised child.

- o Patient family: Used telemedicine as much as possible, but doesn't fully give the best care. Not as good as sitting directly in front of a doctor. Ultimate goal is to keep the child safe.
- Natural history study question regarding patient outcomes; why GARDIAN developed a PRO.
 - o There is a wide spectrum of nGD, GARDIAN recognizes that caregivers would sometimes need to respond in their point of view. It varies on how severe the patient's disease is. Whole process has been designed around the different types of scenarios.
- Would patients do a placebo trial?
 - o Dr. GA: Believes it would be unethical to do this because the data is there and cannot take nGD patients off of ERT.
 - o Clinical trials can have placebo control, but should be with only for adults because not much animal data. Cannot do placebo in children with nGD as they are ones who need therapy the most.
 - o If the FDA can be open to start clinical trials for investigational medical products for nGD, it would save many lives.

Gaucher Community Alliance Attendees

Cyndi Frank, Gaucher Community Alliance, Co-President

Aviva Rosenberg, JD, Gaucher Community Alliance, Co-President

Ozlem Goker-Alpan, M.D., LDRTC

Tanya Collin-Histed, International Gaucher Alliance

Three separate nGD patients and their parent caregivers

FDA Divisions Represented

Office of the Commissioner (OC) – 5 offices

- OC/OCPP/PAS- Office of Clinical Policy and Programs/Office of Patient Affairs (*organizer*)
- OC/OCPP - Office of Clinical Policy and Programs
- OC/OCPP/OCP - Office of Clinical Policy and Programs/ Office of Clinical Policy
- 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 & Research (CBER) –2 offices/division

- CBER/OCD - Office of the Center Director
- CBER/OCBQ/DIS/PSB – Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Program Surveillance Branch

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

- CDER/OCD/PASES - Office of Center Director/Professional Affairs and Stakeholder Engagement Staff
- CDER/OND/ORPURN/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Division of Rare Diseases and Medical Genetics
- CDER/OND/ORPURN/DRDMG/DPMH – Division of Pediatrics and Maternal Health
- CDER/OND/ON/DNI - Office of New Drugs/Office of Neurology/Division of Neurology I
- CDER/OTS/OB/DBI – Office of Translational Sciences/Office of Biometrics/Division of Biometrics I
- CDER/OTS/OCP/DTPM - Office of Translational Sciences/Office of Clinical Pharmacology /Division of Translational & Precision Medicine

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 Gaucher Community Alliance's 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 nGD, 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 nGD patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.