Co-creating a gene therapy clinical trial with GM2 gangliosidosis caregivers: a virtual approach to patient engagement

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BACKGROUND

- Advancements in gene therapy technologies enable the development of therapies for devastating genetic diseases with few to no effective therapeutic options[1]
- GM2 gangliosidoses are a group of autosomal recessive, neurodegenerative, lysosomal storage disorders caused by gene mutations that result in deficiency of beta-hexosaminidase A (Hex A) enzyme activity that may be amenable to gene therapy[1]
- GM2 disorders include Tay-Sachs disease, caused by mutations in the alpha subunit (HEXA) of Hex A and Sandhoff disease, which is caused by mutations in the beta subunit (HEXB) of Hex A[1]
- A novel bicistronic gene therapy that delivers copies of both genes in a single AAV9 vector is being developed that could address the underlying causes of both Tay-Sachs disease and Sandhoff disease[2]
- The US Food and Drug Administration (FDA) is increasingly focused on including the patient voice in drug development, demonstrated by its guidances on patient-focused drug development[3]
- Engaging the community in the research process improves study design, recruitment, the impact of findings, and health knowledge and strengthens partnerships for future collaborations[4]
- In-person engagement can be a challenge for individuals with caregiving or other responsibilities. Further, COVID-19–related limitations on gatherings and travel created additional challenges. Therefore, a virtual approach was used to seek caregiver input

OBJECTIVE

- To gather caregiver perspective on the GM2 gangliosidosis patient experience (including the most challenging symptoms and caregiver views on a potential gene therapy clinical trial) to help inform the development of a clinical trial protocol and its supporting materials

METHODS

- Participants were selected to represent different phases in the patient journey (from diagnosis to bereavement) to provide a range of perspectives
- Caregivers spent at least 5 hours on the project
- The study design is shown in Figure 1

Participants

- 7 caregivers participated
- 4 caregivers of children with Tay-Sachs disease participated
  - Living children were aged 14 months to 2.5 years
  - 1 child was deceased at age 23 months
- 3 caregivers of children with Sandhoff disease participated
  - Living child was aged 2 years
  - 2 children were deceased at ages 15 months and 2 years

REFERENCES

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METHODS

Figure 1. Study design

Recruitment
Partnered with the National Tay-Sachs and Allied Diseases Association, a leading patient advocacy organization, to identify and recruit caregivers of children with GM2 gangliosidosis

Online Survey
The following key information was collected in an online survey:
- Caregiver introduction
- Details of patient diagnosis and key clinical milestones
- Burden of illness

Online Forum
- Asynchronous online forum was open for 1 week
- Activities included
  - Individual tasks
  - Guided written discussions between caregivers

Content Analysis
- Survey and forum outputs were analyzed to identify topics to discuss in greater detail during the video focus group

Video Focus Group
- Live discussion led by a trained moderator
- Included an unstructured Q&A session between caregivers and the clinical investigator

Data Analysis and Report
- Key learnings compiled into a report shared with key internal stakeholders to inform the trial design and its supporting materials

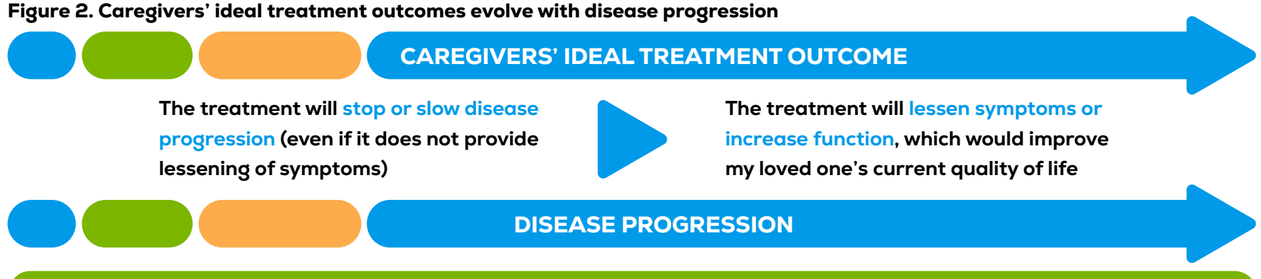
RESULTS

Key insights

Journey to diagnosis
- Initial signs were missed milestones (eg, not sitting up) and low muscle tone at 4 to 6 months
- Pediatricians recommended watchful waiting or referred to physical therapy (PT) and occupational therapy (OT)
- As symptoms progressed despite PT or OT, a neurology referral was made and a genetic cause was suspected (~9 months)
- The average age at diagnosis was 10 months (range 2 to 16 months)

Endpoints of value to caregivers
- The symptoms considered most challenging were highly dependent on the stage of disease progression, and included
  - Swallowing difficulties
  - Decrease in muscle tone/decline in motor skills
  - Contracture/muscle spasms
  - Sleep issues
  - Seizures

Figure 2. Caregivers' ideal treatment outcomes evolve with disease progression



Attitudes toward clinical trial participation
- In the first few months after diagnosis, caregivers were eager to explore clinical trials to improve outcomes
- At later stages of disease progression, caregivers turned to palliative care because they worried about participation in a clinical trial and its impact on quality of life and questioned the benefits of treatment (ie, "Is it fair to prolong such a difficult life?")

CONCLUSIONS

A web-based approach revealed key insights from caregivers of patients with GM2 gangliosidosis, including the impact of GM2 gangliosidosis on quality of life, desired treatment outcomes, barriers to clinical trial participation, and strategies to support trial participants.

Insights were leveraged to develop a patient-centric clinical trial protocol, including the selection of caregiver-valued outcomes. Insights informed the design of recruitment and retention methods, including strategies to mitigate barriers to clinical trial enrollment and meaningful ways to support enrolled families.

> "I deeply appreciate that you want to hear the real experiences and desires of the families you seek to help. They should be at the forefront of your mind with every step you take. I think this platform is a useful tool for getting to the truth of our experiences."
>
> –Caregiver Participant

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