Leveraging insights about the Rett syndrome patient experience to inform development of clinical trials

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INTRODUCTION

Over the years, caregivers become Rett syndrome experts. It is important that their needs, perspectives, experiences, and priorities are captured and incorporated in gene therapy research and development. Working with caregivers early in the research process can help improve study design, support recruitment, enhance the impact of findings, improve trial knowledge, and build meaningful relationships with communities for ongoing collaboration.1

Regulatory authorities—including the US Food and Drug Administration, European Medicines Agency, Health Canada, and Medicines and Healthcare products Regulatory Agency—encourage the inclusion of the caregiver and patient viewpoints in the product development and regulatory processes.2,3

PARTICIPANTS/METHODS

Caregivers of females with Rett syndrome were recruited from the US, Canada, UK, and Israel with the assistance of patient advocacy groups to share insights in an online survey.4

N=318 across participating countries:
- United States: N=112
- Canada: N=64
- United Kingdom: N=115
- Israel: N=79

Survey addressed challenging symptoms, meaningful clinical outcomes of potential treatments, and thoughts on gene therapy for caregivers of loved ones aged 2-10 years. Deeper qualitative insights were captured through online questionnaire, discussion forum, and live video focus group. N=10 US caregivers of females with Rett syndrome aged 2-41 years

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CAREGIVER INSIGHTS

CAREGIVER-REPORTED IMPACT OF SYMPTOMS ON QUALITY OF LIFE

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of speech</td>
<td>90%</td>
</tr>
<tr>
<td>Loss of purposeful use of hands</td>
<td>80%</td>
</tr>
<tr>
<td>Loss of ability to walk independently</td>
<td>70%</td>
</tr>
<tr>
<td>Loss of mobility</td>
<td>60%</td>
</tr>
<tr>
<td>Involuntary hand movements such as hand-wringer</td>
<td>50%</td>
</tr>
<tr>
<td>Gait disturbances</td>
<td>40%</td>
</tr>
<tr>
<td>Gastrointestinal issues/constitution</td>
<td>30%</td>
</tr>
<tr>
<td>Loss of muscle tone (hypotonia)</td>
<td>20%</td>
</tr>
<tr>
<td>Seizures or Rett “episodes“</td>
<td>10%</td>
</tr>
<tr>
<td>Scans/look or Rett episode</td>
<td>0%</td>
</tr>
<tr>
<td>Motor rigidity (spasticity)</td>
<td>0%</td>
</tr>
<tr>
<td>Anxiety or other mood disturbances</td>
<td>0%</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>0%</td>
</tr>
<tr>
<td>High muscle tone (hypertonia)</td>
<td>0%</td>
</tr>
<tr>
<td>Hyperventilation, breath holding, or swallowing, etc</td>
<td>0%</td>
</tr>
<tr>
<td>Behavioral issues</td>
<td>0%</td>
</tr>
<tr>
<td>Impaired respiratory function, speech</td>
<td>0%</td>
</tr>
<tr>
<td>Teeth grinding</td>
<td>0%</td>
</tr>
<tr>
<td>Social withdrawal/social assistance</td>
<td>0%</td>
</tr>
<tr>
<td>Slowed rate of growth for head, feet, hands</td>
<td>0%</td>
</tr>
</tbody>
</table>

Severe impact on quality of life
Moderate impact on quality of life
Mild impact on quality of life
Never experienced

Caregivers reported impact of Rett syndrome symptoms on quality of life

Caregivers hope for gene therapy varied based on their loved one’s age, with parents of younger children expressing more optimism compared to those caring for late teens and adults who are wary of a treatment that could potentially improve their loved one’s quality of life. Caregivers of late teens and adults were more concerned about how they would adapt to a treatment with unknown results and a long-term commitment. Caregivers also worried about how they, as caregivers, would adapt to a treatment with unknown results and a long-term commitment.

CAREGIVER-REPORTED DESIRED IMPROVEMENTS FROM GENE THERAPY

Communication

The most important improvement evaluated by caregivers is the patient’s ability to express their needs and opinions—this was identified as the most important need by 90% of respondents.

Mobility

Ability to stand and take steps became more concerning as patients age and become more difficult to carry and manage for caregivers.

GI issues

Dependence on medication and the ability to reduce overall pain and anxiety were the largest concerns; bowel issues were less concerning for respondents.

Overall Anxiety

As age and patients become more agitated, the crying and screaming fits become more challenging for caregivers and families to manage.

Breathing

Breath-holding and hyperventilation are highly concerning for caregivers as a key source of anxiety.

ATTITUDES TOWARD GENE THERAPY AND CLINICAL TRIALS

Nearly all caregivers indicated they would be willing to consider participation in a gene therapy clinical trial. Caregivers hope for gene therapy varies based on their loved one’s age:

- Those with a daughter aged 7-17 sought symptom reduction and halting or slowing disease progression in order to preserve or potentially improve their loved one’s quality of life.
- Caregivers of late teens and adults were wary of a treatment that only prolonged life span since this group tends to worry about what their family will do when they are no longer able to do so.

CAREGIVER INPUT INTO STUDY DESIGN

In developing the clinical trial protocols for 2 planned studies in females with Rett syndrome, endpoints were selected to reflect major concerns cited by caregivers:

- Communication: Observe/Report Communication Ability (ORCA)
- Hand use: Rett Syndrome Hand Function Scale (RSHFS)
- Mobility, Breathing, and Anxiety: Revised Motor Behavior Assessment (R-MBA); Functional Mobility Scale in Rett Syndrome, Rett Syndrome Behavior Questionnaire
- GI issues: Gastrointestinal Health Questionnaire for Rett Syndrome

Additional caregiver-centric assessments include:

- Parental Global Improvement—Improvement
- Caregiver Top 3 Concerns Visual Analog Scale
- Rett Syndrome Caregiver Burden Inventory

CONCLUSION

Overall, caregivers reported that incremental improvements in speech, hand use, and mobility would improve the ability to communicate and perform daily tasks of living. It is important to consider caregivers’ insights when designing clinical trials, and caregivers are experts in caring for people living with Rett syndrome.