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Considerations of preclinical and clinical data to support accelerated approval in treatment for rare diseases

Lawrence Charnas, MD
Shire Human Genetic Therapies
Rare pediatric neuro-degenerative diseases present special challenges for drug development

- Small numbers of patients present challenges to identify patients and get them to clinical trial sites
  - May not be easily or quickly recognized by generalist physicians
  - Dispersed patient population

- Pediatric patients with life threatening diseases makes trial design and conduct difficult
  - Typically no current treatment option
  - Pressure to treat patients in open-label, non-controlled trials
• The questions for development in these rare diseases are no different from standard drug development.

• But the methods to answer those questions may have to be different for these rare diseases.

• Need to use other sources such as:
  • Animal models
  • Natural history data
Animal models
Examples from Hunter and MLD programs

Preclinical data can demonstrate
• Impact on disease model
• Drug exposure
• Dose selection
Intrathecal (IT) I2S Administration Shows Therapeutic Effect In A KO Mouse Model

- Treatment Reduces cellular vacuolation (arrows) in gray matter
- EM confirms neuronal delivery and elimination of vacuolation

**Experiment Design**

- IT administered Idursulfase (0.21 mg)
- 2 weekly injections
- Sacrifice 1 hour after last injection

*I2S - idursulfase*
Intrathecal (IT) I2S Treatment Reduces Vacuole Size In Corpus Callosum And Fornix In KO Mouse Model

• IT delivery achieves “deep” white matter distribution
Can We Demonstrate Delivery Of Enzyme To Relevant Brain Regions In A Healthy NHP with delivery via the CSF?

- Punch locations in this coronal section
Dose Ranging Studies Of IT rhASA Allow Prediction Of NHP Brain Levels

- IT Delivery Of rhASA Gets To All Brain Regions
- Median rhASA levels after 1.8 mg IT dose are above therapeutic target for all regions tested
Targeted sampling in NHP allows dose ranging of rhASA and documents dose response.
Does IT-rhASA get to disease relevant cells?
IT Delivery Of 1.8 mg rhASA To NHP To Lysosomes In Deep White Matter

rhASA co-localizes with LAMP-1 in columns of cells in white matter, consistent with distribution to oligodendroglia.

Green = rhASA immunofluorescence
Red = LAMP-, a lysosomal marker
DAPI = 4’,6-diamidino-2-phenylindole, a nuclear marker
Animal models can provide surrogate information in rare diseases

- Data from Hunter and MLD programs show how animal models can provide
  - Preclinical Proof of Concept for the drug product
  - Proof of delivery to target tissues
  - Information on dose selection
  - Data supporting dose response
Natural history data
Data from MPSIII A Natural History Study

Natural history data can provide
• Insight into disease progression
• Insight into an appropriate patient population for trials of therapy
• Ability to identify candidate endpoints applicable in clinical trials
• Possibility to generate a high quality set of data with potential utility as a historical control
MPSIIIA (Sanfilippo A) is primarily a neurologic disease with impaired development leading to progressive dementia

- Autosomal recessive: mutations in *SGSH*, encoding heparan N sulfatase; over 70 mutations described
- Live birth incidence ~ 1 in 100,000
- Enzyme defect causes accumulation of heparan sulfate
- Clinical features are overwhelmingly neurological:
  - severe behavioral disturbances
  - progressive dementia
  - survival to late teens / early 20s
  - Phenotypic heterogeneity is primarily expressed in differences in rates of neurocognitive decline
Sensitive and validated measures of neurocognitive status are necessary to assess disease progression in MPSIIIA and potential responses to therapy.

HGT-SAN-053 Natural History Study of MPSIIIA
- An observational study with no investigational treatment
- Enrollment criteria
  - Confirmed MPSIIIA diagnosis
  - Calendar age ≥ 1 yr
  - Developmental age ≥ 1yr, estimated using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
- Evaluations every 6 months for 12 months:
  - Comprehensive neurodevelopmental assessments
  - Brain imaging
  - Cerebrospinal fluid biomarkers
CSF GAG levels are increased in children with Sanfilippo Syndrome Type A

- Remained at comparable levels over observation up to 1 year
- 25 patients were enrolled in the MPSIIIA Natural History study
- 24 patients assessed over 12 months

Red symbols / lines indicate patients diagnosed ≤ 6 years

Healthy Controls (young adults)
Neurocognitive assessments are essential to the evaluation of MPSIIIA patients but present unique challenges

• Heterogeneous patient population with a wide range of neurocognitive impairment
  » Patients may be very low functioning, below the “floor” of most standardized tests
  » There may be physical or sensory disabilities, limiting the utility of some aspects of testing
  » Children may have disruptive, noncooperative behavior

• Considerations in selecting neurocognitive tests for assessing patients with MPSIIIA included
  » Dynamic range that covers the spectrum of disease stage and severity
  » Disease-relevant domains of content
  » Testing protocol should consist of familiar test(s), implementable in multiple centers in multiple countries

• No single instrument meets these criteria, so two different measures were used:
  » Bayley Scales of Infant Development, 3rd Edition (BSIDIII - birth to 42 months)
  » Kaufman Assessment Battery for Children II (KABCII - 3 to 18 years)
In natural history study, there is an apparent plateau in mental age achieved at 30 months in children diagnosed before age 6.

Plot of baseline mental age equivalence derived by BSID or KABC against calendar age.
Baseline DQ plotted against age shows steep age-related decline
Patients diagnosed after age 6 may exhibit different rate of decline

To standardize scores across the spectrum of disease, mental age equivalence was divided by calendar age to yield a “development quotient” (DQ)
Developmental age equivalence independently assessed by VABS-II shows strong correlation with age equivalence calculated by BSID or KABC, demonstrating concurrent validity of behavioral and cognitive assessment in these patients with MPSIIIA.
Automated segmentation and objective measurement of brain volumes is achieved with “Freesurfer” software.
Baseline cross-sectional data suggest decline in cerebral cortical volume with advancing age in children diagnosed before age 6

Automated brain magnetic resonance image (MRI) analysis using “Freesurfer” software

Note: green open symbols denote children under the age of 3.5 years, in whom grey/white matter contrast may be inadequate for reliable GM delineation
Cerebral cortical volume correlates with DQ
Baseline cross-sectional data

Note: green open symbols denote children under the age of 3.5 years, in whom grey/white matter contrast may be inadequate for reliable GM delineation
Decline Of DQ Within Individuals Correlates With The Loss Of Grey Matter Volume, suggesting that grey matter volume change may be able to serve as an objective surrogate of clinical disease progression

*Longitudinal data from natural history study*

**Change in DQ and Decline in Gray Matter**

- 7 patients were not included in this analysis of grey Matter Volumes
- 3 were either too young (under 2) or gray white differentiation was poor
- 2 patients data could not be analyzed because of severe atrophy
- 1 dropped out
- 1 had not yet had his 12 month visit at the time of this analysis
Conclusions

• CSF GAG levels are elevated in MPSIIIA, but do not appear to change as disease progresses

• DQ decline is measurable over 12 months of observation in untreated MPSIIIA patients of “rapid progressor” phenotype if carefully selected assessment tools are employed
  • These findings suggest that cognitive endpoints can be used to assess the clinical impact of therapy in the course of a 12 month clinical trial in MPSIIIA patients with disease expected to progress rapidly
  • Correlation with independent adaptive behavior assessment suggests concurrent validity of this approach to neurocognitive assessment

• Consistent declines in cortical grey matter volume over 12 months correlate with declines in cognitive status, suggesting that cortical grey matter volume may serve as a clinically meaningful biomarker of disease
Novel endpoints must be considered for rare diseases to get new therapies to patients

• Clinical endpoints often are not viable due to small numbers of patients and long clinical course

• We have shown that there are mechanisms to document the progression of disease that should lead to potential endpoints such as Biomarkers, Neurocognitive testing, and Imaging that can be validated for use in clinical trials

• Small patient populations with rare diseases need these opportunities to use novel endpoints that can be scientifically justified
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