2019 Update in Neuronopathic GD

Pramod K Mistry, MD, PhD,
Professor of Medicine and Pediatrics

Annual NYC Meeting,
Museum of the City of New York
October, 29, 2017
Disclosures

• Received research funding from
  - NIH R01/K24
  - Gaucher Generation Program Senior Investigator Award
  - National Gaucher Foundation
  - Sanofi Genzyme, a Center of Excellence for Treatment of Gaucher Disease
  - Shire

• Travel support and honoraria from Genzyme,
  Pfizer and Shire

• Chair of the Project Hope Humanitarian Program for Gaucher disease

• Chair of the International Gaucher Registry, ICGG
Update in Type 3 Gaucher disease - 2017

- Important global disease
- Long-term response to enzyme replacement therapy
- Unmet needs:
  - remains a disabling and life-threatening disease
  - lung disease
  - spinal deformity
  - abdominal lymphadenopathy
  - neurological signs
- New clinical trial of brain-penetrant SRT
Gaucher Disease Classifications

Type 1 (nonneuronopathic)
- Panethnic (~1:60,000)
- Prevalent in Ashkenazi Jews (~1:850)
- Onset in childhood or adulthood

Type 2 (acute neuronopathic)
- Panethnic (~1:100,000)
- Onset in infancy, death < 2 years

Type 3 (chronic neuronopathic)
- Panethnic (~1:100,000)
- Onset in childhood

Weiss K et al, Mol Genet Metab, 2015
Story of GD3 began in Northern Sweden –
First cluster of GD3 Described in Norbotten
and Vasterbotten

Hillborg and Svennerholm, Acta Paeditrica, 1960
First descriptions of Gaucher disease in Norrbotten
- Severe life-threatening disease starting in childhood
- Severe liver/spleen enlargement, low blood counts, growth failure
- And neurological symptoms

Svennerholm L et al, 1982, Progr in Biol Res

Extreme variability from lethal disease in childhood to adults with skeletal abnormalities
In one family one child died in infancy but other survived until 46 yrs age.
Pedigree for Norrbotten branch of Gaucher disease
All GD3 patients (filled circles) descended from common ancestors
Yet, highly variable disease severity

Several groups working to identify modifiers that lead to variable severity

Svennerholm L et al, 1982
Asymptomatic

Type 1

Skeletal disease
Visceral disease
2° neurologic involvement
Parkinsonian manifestations
Hydrocephalus, cardiac valve calcifications
Eye-movement disorder

Type 3

Neurologic manifestations

Type 2

Hydrops fetalis
Congenital ichthyosis
Progressive neurologic degeneration
Myoclonic epilepsy

Multiple syndromes of GD due to single gene, single enzyme deficiency

- GD1/pulmonary HTn
- GD1/Asplenic
- GD1/severe visceral disease/mild skeletal disease
- GD1/Asplenic
- GD1/Parkinson's Disease
- GD1/Cirrhosis, HPS
- N370S homozygous GD1 - non-expressing
- GD Multiple Myeloma/Cancers
- GD2 Congenital ichthyosis
- GD2 Congenital ichthyosis
- GD2 Hydrops fetalis
- Severe skeletal disease/mild visceral, hematologic disease
- Asplenic GD1/Cirrhosis, HPS
- Type 2
- Type 3a
- Type 3B
- Type 3c

Yale SCHOOL OF MEDICINE
Global distribution of GBA genotypes by phenotype in ICGG Registry

Presence of at least one N370S allele precludes neuronopathic GD

GD1: 3,902 patients

- N370S/N370S
- N370S/L444P
- N370S/Δ55bp Deletion
- N370S/other

GD3: 283 patients

- L444P/L444P
- L444P/other
- Rare mutations
- D409H/D409H

GD2: 35 patients

- L444P/L444P
- Rec/Rec or Rec/other
- Rare mutations

ClinicalTrials.gov NCT00358943

Global distribution of Gaucher disease mutations

Neuronopathic Gaucher disease (NGD) is rare: ~1 in 100,000 individuals
However, world-wide, there are many more NGD patients than GD1
Worldwide prevalence varies substantially
US, Europe and Israel: 5% of GD patients classified as GD3 and 1% as GD2
Egypt, Korea, Taiwan, and China: at least one-third of GD patients classified as GD3 or GD2

N370S is the most common GBA mutation
L444P and other pseudogene mutations most common GBA Mutation
Two ICGG Gaucher Registry* Studies of Neuronopathic Gaucher Disease (NGD)

Largest cohorts of NGD studied to date

<table>
<thead>
<tr>
<th>Neurological Outcomes Subregistry ¹</th>
<th>GD3 Treated with Imiglucerase Starting &lt;18 Years Old ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>• N=131</td>
<td>• N=253</td>
</tr>
<tr>
<td>• Initiated in 2004, captured full worldwide spectrum of NGD</td>
<td>• All GD3 patients in the ICGG Registry as of 4 September 2015 who started alglucerase/imiglucerase at &lt;18 years of age</td>
</tr>
<tr>
<td>• All patients in ICGG Registry with confirmed GD diagnosis and neurologic manifestations</td>
<td>• Baseline: value closest to treatment initiation up to 2 wks after</td>
</tr>
<tr>
<td>• Baseline: data point closest to diagnosis date within ±2 years</td>
<td>• Data analysis: annually from baseline through treatment year 5</td>
</tr>
<tr>
<td>• Data analysis: patients enrolled in the Subregistry as of 1 June 2007</td>
<td></td>
</tr>
</tbody>
</table>

*ICGG Registry: International Collaborative Gaucher Group Gaucher Registry


NGD Demographics and Clinical Characteristics in the ICGG Registry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neurological Outcomes Sub-registry (2010)(^1) N=131</th>
<th>GD3 Patients Started on Imiglucerase &lt;18 years Old (2016)(^2) N=253</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61 (47%)</td>
<td>126 (49.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>70 (53%)</td>
<td>127 (50.2%)</td>
</tr>
<tr>
<td>Age at GD Diagnosis (Years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.2 (6.2)</td>
<td>2.7 (2.81)</td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>1.0</td>
<td>1.7 (0.0, 16.7)</td>
</tr>
<tr>
<td>Age of onset of Neurological Manifestations, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 years</td>
<td>61 (47%)</td>
<td>57%</td>
</tr>
<tr>
<td>≥ 2 years</td>
<td>54 (41%)</td>
<td>NR</td>
</tr>
<tr>
<td>Unknown</td>
<td>16 (12%)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Neurological manifestations often appear before 2 years of age.

NGD Neurologic Manifestations: Neurological Outcomes Sub-registry

The most common neurological signs and manifestations are brainstem abnormalities and fine motor dysfunction.

Natural Course of Neuronopathic Manifestations in Gaucher Disease

### Birth-2 years
- Visceral disease
- Stridor
- Swallowing difficulties
- Pincer grasp
- Muscle weakness
- Walking ability (needs assistance/non-ambulatory)
- Chewing difficulties
- Slow object tracking
- Head movement rather than eye movement
- Convergent squint
- Ability to look to extreme up or down
- Ability to look to extreme left or right
- Head thrusting
- Wide base gait

### 2-5 years
- Retroflexion of head
- Myoclonus
- Extrapyramidal features
- Spasticity
- Dysarthria
- Rapid finger tapping

### 5-10 years
- Seizures
- Extensor plantar response
- Tremor when reaching
- Tremor at rest

#### Age of onset of Neurological Manifestations (N=131)

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<thead>
<tr>
<th>Age</th>
<th>Count</th>
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Devastating visceral and hematologic disease with growth failure in GD3

<table>
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<th>Parameters</th>
<th>Baseline</th>
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<tr>
<td>Hemoglobin (g/dL), mean (SD)</td>
<td>9.6 (1.92)</td>
</tr>
<tr>
<td></td>
<td>n=163</td>
</tr>
<tr>
<td>Platelet Count (x10^9/L), mean (SD)</td>
<td>127.4 (99.24)</td>
</tr>
<tr>
<td></td>
<td>n=161</td>
</tr>
<tr>
<td>Liver Volume (MN), mean (SD)</td>
<td>2.4 (1.28)</td>
</tr>
<tr>
<td></td>
<td>n=49</td>
</tr>
<tr>
<td>Spleen Volume (MN), mean (SD)</td>
<td>34.6 (15.26)</td>
</tr>
<tr>
<td></td>
<td>n=63</td>
</tr>
<tr>
<td>Height Z-Score, mean (SD)</td>
<td>-1.8 (1.43)</td>
</tr>
<tr>
<td></td>
<td>n=140</td>
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</tbody>
</table>

# Imiglucerase Improves Hematologic, Visceral and Growth Outcomes in children with GD3

*ICGG Registry, Started Imiglucerase <18 Years of Age*

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## Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>Years on ERT</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>&gt;0 to ≤1</td>
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Type 3 Gaucher disease: Response to ERT

At Diagnosis

Age 14 on imiglucerase ERT

With permission Dr El-Beshlawy
High Survival Probability with Imiglucerase in children with life-threatening visceral/hematologic disease

ICGG Registry, Started Imiglucerase <18 Years of Age

Unmet needs in GD3

- Neurologic disease
- Lung involvement
- Abdominal lymphadenopathy
- Spinal deformity
- Cardiac involvement (in Type 3c)
• Steve H
• Now 10 yrs old
• Diagnosed with GD3 at age 3,
  Massive HSM
  L444P/L444P
• On cerezyme since age 3
• IQ>130
• Doing Singapore math
• ADHD/autism

October 28, 2017
With permission Diana and Steven H
Tylan, now age 12
Genotype L444P/L444P
Massive liver/spleen enlargement, FTT, low blood counts
Started enzyme treatment age 2 in 2006
For past 2 years FTT again

Massive abdominal lymphadenopathy
With duodenal obstruction

With permission Tiffany and Tylan C
Enzyme Replacement Therapy (ERT) vs. Substrate Reduction Therapy (SRT)

- **Synthesis (S)** and **degradation (D) of glucosylceramide**

**Normal**

- **SRT:** affects all cell types

**Gaucher’s disease**

- **ERT:** macrophage-targeted
- **SRT:** affects all cell types

**Gaucher’s infusion**

- **+ ERT**

**Gaucher’s + SRT oral**

- **SRT**
- **ERT**

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Inflammation at the center of GD

• Inflammation is central to all types of GD  
  (Dr Grabowski’s key note lecture)
• Inflammation increases GCS enzyme activity that is involved in formation of Gaucher lipids
• This amplifies GD defect of decreased breakdown of glucosylceramide
Therapeutic Targets in GD: Synthesis and Degradation of GL1
SRT: Oral Treatment With GL1 Synthase Inhibitors to Correct System-Wide Metabolic Abnormality

- Reduces GL1 by partial inhibition of its synthesis

Ceramide + Glucose → Glucocerebroside (acid β-glucosidase) → GL1 synthase → GL1 (Glucocerebroside)

- Miglustat
  - \( IC_{50} \) 20-50 \( \mu \)M
  - \( IC_{50} \) for GBA2: 0.31 \( \mu \)M

- Eliglustat
  - \( IC_{50} \) 0.024 \( \mu \)M
  - \( IC_{50} \) for GBA2: 1600 \( \mu \)M

References:
ENGAGE cerdelga trial: Decrease in inflammatory lipids and markers of inflammation

<table>
<thead>
<tr>
<th></th>
<th>Median Baseline</th>
<th>Normal Range</th>
</tr>
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<tbody>
<tr>
<td>Plasma GL-1 (µg/mL)</td>
<td>10.4</td>
<td>&lt;2.0–6.6</td>
</tr>
<tr>
<td>Plasma Lyso GL-1 (ng/mL)</td>
<td>304</td>
<td>&lt;5</td>
</tr>
<tr>
<td>GM3 (µg/mL)</td>
<td>24.0</td>
<td>5–21</td>
</tr>
<tr>
<td>Chitotriosidase (nmol/hr/mL)</td>
<td>11,356</td>
<td>4–120</td>
</tr>
<tr>
<td>MIP-1β (pg/mL)</td>
<td>232</td>
<td>27–77</td>
</tr>
</tbody>
</table>

Mistry et al. WORLD 2017 presentation
Randomized, Controlled Trial of Miglustat in Gaucher’s Disease Type 3

Raphael Schiffmann, MD, Edmond J. FitzGibbon, MD, Chris Harris, PhD, Catherine DeVile, MD, Elin H. Davies, MSc, Larry Abel, PhD, Ivo N. van Schaik, MD, William S. Benko, MD, Margaret Timmons, MD, Markus Ries, MD, PhD, MHSc, FCP, and Ashok Vellodi, FRCPCH

Interpretation: Miglustat does not appear to have significant benefits on the neurological manifestations of GD3. However, miglustat may have positive effects on systemic disease (pulmonary function and chitotriosidase activity) in addition to ERT in patients with GD3.

Ann Neurol 2008;64:514–522
Limitations of current ERT and SRTs in GD3

- ERTs: most uptake in the liver, spleen and bone marrow, none in the brain
- SRTs: no neurological improvement
- Need next generation CNS penetrant SRT
CNS-accessible Inhibitor of Glucosylceramide Synthase for Substrate Reduction Therapy of Neuronopathic Gaucher Disease

John Marshall¹, Ying Sun²,³, Dinesh S Bangari¹, Eva Budman¹, Hyejung Park¹, Jennifer B Nietupski¹, Amy Allaire¹, Mary A Cromwell¹, Bing Wang¹, Gregory A Grabowski²,³, John P Leonard¹ and Seng H Cheng¹

¹Sanofi Genzyme, Framingham, Massachusetts, USA; ²Division of Human Genetics, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA; ³Department of Pediatrics, University of Cincinnati School of Medicine, Cincinnati, Ohio, USA.

Treatment of mouse models of nGD
- Reduced Gaucher lipids
- Reduced neurological symptoms
- Improved survival
Leap Trial: Gz/Sar402671 in Combination With Cerezyme in Adult Patients With Gaucher Disease Type 3

Purpose Primary Objective:
Part 1:
- Evaluate central nervous system (CNS) biomarkers in adult GD3 patients that distinguish GD3 from GD1.
- Screen adult GD3 who qualify for treatment with Gz/Sar402671 in Part 2.
Part 2:
- Evaluate the safety and tolerability of Gz/Sar402671 in adult GD3.
- Evaluate the change in cerebrospinal fluid (CSF) central nervous system, biomarkers from adult GD3 receiving Gz/Sar402671.

Secondary Objectives:
- Evaluate the pharmacokinetics of Gz/Sar402671 in adult GD3.
- Explore the efficacy of Gz/Sar402671 in infiltrative lung disease in adult GD3.
- Explore the efficacy of Gz/Sar402671 in systemic disease in adult GD3.
- Explore the efficacy of Gz/Sar402671 in neurological function and on exploratory CSF biomarkers in adult GD3.

ClinicalTrials.gov Identifier: NCT02843035
Inclusion criteria

- Has a clinical diagnosis of GD1 or GD3
- Hemoglobin level of $\geq 11.0$ g/dL for females and $\geq 12.0$ g/dL for males.
- Platelet count $\geq 100,000$/mm$^3$.
- Spleen volume $<$ 10 multiples of normal (MN).
- Liver volume $<$ 1.5 MN.
- No bone crisis and free of symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathological fractures within the last year.
- Received treatment with ERT for at least 3 years.
- Female of childbearing potential must have a negative pregnancy test
- If the patient has a history of seizures, except for myoclonic seizures, they are well controlled

Adult GD1 cohort only:
- GD1 patient is $\geq 18$ and $\leq 40$ years of age.
- Adult GD3 cohort only:
  GD3 patient is $\geq 18$ years of age.

- Willing to abstain from consumption of grapefruit,
- Oculomotor apraxia characterized by a horizontal saccade abnormality.
- Cerezyme treatment every 2 weeks (minimum dose 30 U/kg every 2 weeks).
- Females of childbearing potential - effective methods of contraception.

ClinicalTrials.gov Identifier: NCT02843035
Exclusion criteria

- SRT or chaperone therapy for GD within 6 months prior to enrollment.
- splenectomy.
- The patient is blood transfusion-dependent.
- Severe liver, cardiac or renal disease
- history of cancer
- Has myoclonic seizures.
- Pregnant or lactating.
- Use of invasive ventilatory support
- Hypersensitivity to Cerezyme
- Has received strong or moderate inducers or inhibitors of CYP3A within 30 days or 5 half-lives from screening, whichever is longer, prior to enrolment in Part 2. This also includes the consumption of grapefruit, grapefruit juice, or grapefruit containing products within 72 hours of starting GZ/SAR402671 administration
- Has had a major organ transplant (eg, bone marrow or liver).
- The patient is unable to adhere to the requirements of the study.

ClinicalTrials.gov Identifier: NCT02843035
Treatments under investigation

• Need to conduct proper clinical trials for maximum benefit for patients to assess safety and effectiveness.
Future options to watch out for nGD families

Histone deacetylase inhibitors prevent the degradation and restore the activity of glucocerebrosidase in Gaucher disease

Jie Lu¹, Chunzhang Yang², Masako Chen³, Donald Y. Ye⁴, Russell R. Lonser⁵, Roscoe O. Brady⁶, and Zhengping Zhuang⁷,⁸

¹Surgical Neurology Branch and ²Developmental and Metabolic Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892-1414

Contributed by Roscoe O. Brady, November 22, 2011 (sent for review October 28, 2011)

NEURAL REGENERATION RESEARCH
November 2016, Volume 11, Issue 11

● PERSPECTIVE

Chaperoning glucocerebrosidase: a therapeutic strategy for both Gaucher disease and Parkinsonism

Benjamin McMahon, Elma Aflaki, Ellen Sidransky⁹

Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA
Ambroxol chaperone therapy for neuronopathic Gaucher disease: A pilot study

Aya Narita¹, Kentarou Shirai¹, Shinji Itamura¹, Atsue Matsuda¹, Akiko Ishihara², Kumi Matsushita², Chisako Fukuda³, Norika Kubota⁴, Rumiko Takayama⁵, Hideo Shigematsu⁶, Anri Hayashi⁶, Tomohiro Kumada⁶, Kotaro Yuge⁶, Yoriko Watanabe⁷, Saori Kosugi⁸, Hiroshi Nishida⁸, Yukiko Kimura⁸, Yusuke Endo⁹, Katsumi Higaki¹⁰, Eiji Nanba¹⁰, Yoko Nishimura¹, Akiko Tamasaki¹, Masami Togawa¹, Yoshiaki Saito¹, Yoshihiro Maegaki¹, Kousaku Ohno¹ & Yoshiyuki Suzuki¹¹

Repetitive-Dose Oral N-Acetylcysteine in Parkinson’s Disease: Pharmacokinetics and Effect on Brain Glutathione and Oxidative Stress

Lisa D. Coles, PhD¹, Paul J. Tuite, MD², Gülin Öz, PhD³, Usha R. Mishra, MS¹, Reena V. Kartha, PhD¹, Kathleen M. Sullivan, BS¹, James C. Cloyd, PharmD¹, and Melissa Terpstra, PhD³
Dedicated to all Gaucher disease
For more than 3 decades

Thank you
Questions?

With permission Veronica H.