2019 Update in Neuronopathic GD

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Professor of Medicine and Pediatrics

National Gaucher Foundation

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Museum of the City of New York
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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

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

Svennerholm L et al, 1982, Progr in Biol Res
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
Phenotype Continuum

Type 1
- Asymptomatic
- Skeletal disease
- Visceral disease

Type 3
- Parkinsonian manifestations
- Hydrocephalus, cardiac valve calcifications
- Eye-movement disorder

Type 2
- Congenital ichthyosis
- Progressive neurologic degeneration
- Myoclonic epilepsy

Neurologic manifestations

Sidransky E. *Disco Med*. 2012;14:273-81;
Multiple syndromes of GD due to single gene, single enzyme deficiency

- GD1/severe visceral disease/mild skeletal disease
- Asplenic GD1/pulmonary HTn
- GD1/Asplenic GD1/Cirrhosis, HPS
- GD1/Parkinson's Disease
- Severe skeletal disease/mild visceral, hematologic disease
- GD1/Multiple Myeloma/Cancers
- N370S homoz GD1 - non-expressing
- GD1/Hydrops fetalis
- GD2 Cong ichthyosis
- GD2
- Type 3a
- Type 3B
- Type 3c
- Type 2
- Asplenic GD1/Cirrhosis, HPS
- Asplenic GD1/pulmonary HTn
- Hydrops fetalis
- Cong ichthyosis
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
- Rare mutations
- Rec/Rec or Rec/other
- L444P/other

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 Old²</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

<table>
<thead>
<tr>
<th>Birth-2 years</th>
<th>2-5 years</th>
<th>5-10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral disease</td>
<td>Retroflexion of head</td>
<td>Seizures</td>
</tr>
<tr>
<td>Stridor</td>
<td>Myoclonus</td>
<td>Extensor plantar response</td>
</tr>
<tr>
<td>Swallowing difficulties</td>
<td>Extrapyramidal features</td>
<td>Tremor when reaching</td>
</tr>
<tr>
<td>Pincer grasp</td>
<td>Spasticity</td>
<td>Tremor at rest</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Dysarthria</td>
<td></td>
</tr>
<tr>
<td>Walking ability (needs assistance/non-ambulatory)</td>
<td>Rapid finger tapping</td>
<td></td>
</tr>
<tr>
<td>Chewing difficulties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow object tracking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head movement rather than eye movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convergent squint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability to look to extreme up or down</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability to look to extreme left or right</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head thrusting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wide base gait</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age of onset of Neurological Manifestations (N=131)

<table>
<thead>
<tr>
<th>Age</th>
<th>Count</th>
<th>Percentage</th>
</tr>
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<tr>
<td>&lt;2 years</td>
<td>61</td>
<td>(47%)</td>
</tr>
<tr>
<td>≥2 years</td>
<td>54</td>
<td>(41%)</td>
</tr>
</tbody>
</table>
Devastating visceral and hematologic disease with growth failure in GD3

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<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 ($\times 10^9$/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>
</tr>
</tbody>
</table>

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

ICGG Registry, Started Imiglucerase <18 Years of Age

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>Years on ERT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&gt;0 to ≤1</td>
</tr>
<tr>
<td>Hemoglobin (g/dL), mean (SD)</td>
<td>9.6</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>(1.92)</td>
<td>(1.68)</td>
</tr>
<tr>
<td></td>
<td>n=163</td>
<td>n=143</td>
</tr>
<tr>
<td>Platelet Count (x10^9/L),</td>
<td>127.4</td>
<td>182.0</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>(99.24)</td>
<td>(94.32)</td>
</tr>
<tr>
<td></td>
<td>n=161</td>
<td>n=139</td>
</tr>
<tr>
<td>Liver Volume (MN), mean (SD)</td>
<td>2.4</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>(1.28)</td>
<td>(0.80)</td>
</tr>
<tr>
<td></td>
<td>n=49</td>
<td>n=33</td>
</tr>
<tr>
<td>Spleen Volume (MN), mean (SD)</td>
<td>34.6</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>(15.26)</td>
<td>(12.29)</td>
</tr>
<tr>
<td></td>
<td>n=63</td>
<td>n=43</td>
</tr>
<tr>
<td>Height Z-Score, mean (SD)</td>
<td>-1.8</td>
<td>-1.6</td>
</tr>
<tr>
<td></td>
<td>(1.43)</td>
<td>(1.43)</td>
</tr>
<tr>
<td></td>
<td>n=140</td>
<td>n=118</td>
</tr>
</tbody>
</table>

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 life-threatening visceral/hematologic disease

ICGG Registry, Started Imiglucerase <18 Years of Age

- **Patients at Risk:**
  - n=253
  - n=169
  - n=91
  - n=37
  - n=14

- **Probability of survival after starting imiglucerase:**
  - 5 years: 92%
  - 10 years: 82%
  - 20 years: 76%

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 vs. Substrate Reduction Therapy

Synthesis (S) and degradation (D) of glucosylceramide

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

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

Glucocerebrosidase (acid β-glucosidase)

Ceramide + Glucose

GL1 synthase

GL1 (Glucocerebroside)

Miglustat

IC$_{50}$ 20-50 μM

Eliglustat

IC$_{50}$ 0.024 μM

IC$_{50}$ for GBA2: 0.31 μM

IC$_{50}$ for GBA2: 1600 μM

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>
</thead>
<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>

-62% GM3
-71% MIP-1β
-79%GL-1
-82% Chito
-84%Lyso GL-1

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

Raphael Schiffmann, MD,1 Edmond J. FitzGibbon, MD,2 Chris Harris, PhD,3 Catherine DeVile, MD,4 Elin H. Davies, MSc,4 Larry Abel, PhD,5 Ivo N. van Schaik, MD,6 William S. Benko, MD,1 Margaret Timmons, MD,1 Markus Ries, MD, PhD, MHSc, FCP,1 and Ashok Vellodi, FRCPCH4

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 (e.g., 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 Yang¹, Masako Chen¹, Donald Y. Ye⁶, Russell R. Lonser⁶, Roscoe O. Brady², and Zhengping Zhuang²

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)

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

Benjamin McMahon, Elma Aflaki, Ellen Sidransky*

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 Matushita², Chisako Fukuda³, Norika Kubota³, Rumiko Takayama³, Hideo Shigematsu⁶, Anri Hayashi⁶, Tomohiro Kumada⁶, Kotaro Yuge⁷, Yoriko Watanabe⁸, Saori Kosugi⁹, Hiroshi Nishida⁸, Yukiko Kimura⁸, Yusuke Endo⁹, Katsumi Higaki¹⁰, Eiji Nanba¹⁰, Yoko Nishimura¹, Akiko Tamasaki¹, Masami Togawa¹, Yoshiaki Saito¹, Yoshihiro Maegaki¹, Kousaku Ohno¹ & Yoshiyuki Suzuki¹¹

Repeated-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.