Treatment Strategies for a Complex Neuromuscular Disease: The Pompe Story

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The Cure
Geeta Anand

How a Father Raised $100 Million and Bucked the Medical Establishment to Save His Children
EXTRAORDINARY MEASURES

BRENDAN FRASER
HARRISON FORD

INSPIRED BY A TRUE STORY

DON'T HOPE FOR A MIRACLE. MAKE ONE.
Initial Presentation of Pompe Disease: Fatal Cardiomyopathy in Infancy
Background: Spectrum of Disease

- Mutations in GAA gene with lysosomal accumulation of glycogen
  - Autosomal recessive
  - 1:40,000
- Heart disease: glycogen accumulation leading to increased cardiac mass and heart failure
- Musculoskeletal: severe weakness with early loss of motor milestones
- Respiratory disease: progressive loss of independent ventilation
Pompe Disease Spectrum

Age at onset

Infancy  →  Age at onset  ←  Adulthood

Rate of Progression

Respiratory
Cardiomyopathy
Myopathy

Acid Alpha-Glucosidase Activity

0%  →  40%  →  100%
Infantile-Onset Pompe Natural History Study: Kaplan-Meier Plot of Time to Death*

Median age at death: 8.7 months

Survival at 12 mos.: 25.7%
Survival at 18 mos.: 14.3%
Survival at 24 mos.: 9.0%
Survival at 36 mos.: 7.1%

*Based on n=163 with available data

Kishnani et al., 2005
Pathophysiology of Pompe Disease

- Weakness syndrome
- Congenital defect affecting both cardiac structure and function
Glycogen

Defect in glycogen degradation due to GAA deficiency
Neuromuscular disease progression from early affected muscle to permanent damage

Untreated Disease Progression

Early disease → Reversible muscle damage → ? Irreversible muscle damage → Damaged muscle

Healthy muscle fibre
Damaged muscle fibre
Healthy lysosome
Lysosome (w/ glycogen accumulation)
Released glycogen/enzymes
Fat deposits
Mouse Model of Pompe Disease

Patient data leads to an essential tool in preclinical evaluation of therapeutic strategies
GAA<sup>-/-</sup> Mouse Model: Essential tool in evaluation of therapeutic strategies

Raben et al., 1998
Cardiac Pathology – Loss of myofibrils with glycogen accumulation

129/B6  GAA\textsuperscript{−/−}
Pompe Disease

Investigational Treatments and Research Initiatives

• Enzyme replacement therapy
  – Supply enzyme by IV infusion
  – Clinical studies completed: 1702, 1602, LOTS
  – BMN-701 to begin in January 2011

• Gene therapy
  – Supply the patient with functional gene for GAA
  – IND issued August 2010, Enrolling

• Pharmacological Chaperone
  – Inhibition of enzyme activity rescues protein misfolding for missense mutations.
Development History

2003: Infant Natural History Studies completed

2004: Launched the Pompe Registry & Initiated Expanded Access Program

2005: Diagnostic Availability of Blood Testing (Chamois)

2005: Successful Infant Studies & LOPOS Completed

2006: Myozyme® Approved by EMEA and FDA

2007: MTAP/ATAP Initiated in US as Bridge to FDA Approval of Scale-up

2007: Importance of Mutation Status Recognized

2007: Successful LOTS study Completed

2007: Newborn Screening Pilot Successful in Taiwan

2007: Newborn Screening Pilot Successful in Taiwan
Development History

2007: High Dose/Dose Frequency Study completed

2009: Immune Tolerance Studies Initiated for CRIM NEG infants and those with high titers

March 2009: EMEA Approval of the Large Scale Process in Geel, Belgium

Early 2010: LOTS Published in NEJM and Prescribing Information Updated in Europe

May, 2010: FDA approval of Lumizyme®

August 2010: AAV Gene Therapy Study
Enzyme Replacement (ERT) Studies: AGLU 1602 and AGLU 1702

Goals
- To expand ERT experience in infantile onset Pompe patients treated from 6-36 months of age (1702) or <6 months (1602).

Inclusion Criteria
- Age at ERT > 6 - 36 months (1702) or <6 months (1602)
- Pompe Symptoms ≤ 12 months age
- GAA in fibroblasts (4-MUG) < 2%
- Cardiomyopathy (+) pre-ERT (by echo)
- LVMI > mean + 2 SD for age
- Invasive ventilation allowed (1702 only)

rhGAA dose
- 20 mg/kg/q2weeks or 40 mg/kg/q2weeks (1602)
- 21 subjects enrolled in study 1702 and 18 subjects in study 1602.
AGLU 1602 Study Design

AGLU 1602:
Overall Survival at 18 Months of Age (1 yr ERT)

18/18 trial patients [100%]

1/62 untreated controls [2%; 95% CI: 0% - 6%]

Clinical Trial Patients
Untreated Historical Cohort
*** 95% Confidence Intervals
Baseline Echocardiography

**Measure z-score**
- LV mass: 8.5
- LV post wall: 10.7
- Mass:vol: 19.0
- EF (53%): -1.7
**Echocardiography Protocol**

- Data expressed as Z scores relative to BSA or age
- Core center for blinded interpretation of echo data
- Multiple readers
- Local training of echo staff for this specific protocol
LV MASS Z-Score Change with Myozyme

Long-term outcome in 38 subjects in 1602/1702 Myozyme studies

7 ventilator dependent at study start
- 2 died
- 5 alive at study end on ventilator
- 1 died
  - 16 alive and ventilator free at study end

31 without ventilator support at study start
- 14 became ventilator dependent
- 17 NOT ventilator dependent
  - 7 died
  - 7 alive on a ventilator at study end

Group A: alive/free of assisted ventilation 16/38 (42%)

Group B: death or assisted ventilation 22/38 (58%)
- 10/38 deceased; 12/38 alive and ventilated

*one subject died prior to 2nd infusion; not included
**Baseline LV mass predicts clinical outcome group**

<table>
<thead>
<tr>
<th>Baseline Echo Measures</th>
<th>Group A Alive and Vent Free (n=16)</th>
<th>Group B Ventilation or Death (n=22)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVED</td>
<td>2.41</td>
<td>4.29</td>
<td>0.073</td>
</tr>
<tr>
<td>EF z-score</td>
<td>-1.59</td>
<td>-1.67</td>
<td>0.915</td>
</tr>
<tr>
<td>LVM z-score</td>
<td>5.08</td>
<td>7.71</td>
<td>&lt;0.0001</td>
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<tr>
<td>MVR z-score</td>
<td>6.98</td>
<td>11.86</td>
<td>0.024</td>
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</tbody>
</table>
LV mass and mass:vol ratio are lower at 0 and 52 weeks in Group A

LV Mass

LV Mass/Volume

p=0.001

p=0.016
Age at 1st infusion does **not** predict cardiac remodeling in cohort as a whole

**LV Mass**

- Graph showing data with z-scores from 0 to 7.0, weeks of infusion from 0 to 55.
- "Age 0-11 months" and "Age 12+ months" lines.
- p-value: 0.44

**LV Mass/Volume**

- Graph showing data with z-scores from -4.0 to 16.0, weeks of infusion from 0 to 55.
- "Age 0-11 months" and "Age 12+ months" lines.
- p-value: 0.66
Summary of Cardiac Findings

- PR interval lengthens from baseline to near normal with ERT.
- LVM improves in the study population with some predictable minimal responders.
- EF improvement may depend on favorable wall stress.
- Survival data reflect overall improvement in cardiac function. Need to assess functional reserve and diastolic function.
Myozyme (for children <8 yrs and ex-US adults) Lumizyme (>8 yrs in US)
Increasing Capacity to Meet Needs Worldwide

Bioreactor Manufacturing Scale

160 L
Framingham, MA USA
Licensed in US and provides treatment for Children. Used in infant clinical studies.

2000 L
Allston, MA USA
Previously licensed outside of US. Intermediate scale is now obsolete and is no longer in production. Used in the older children & adults clinical studies (e.g. LOTS)

4000 L
Geel, Belgium
Licensed ex-US and provides treatment for all patients worldwide except children in the US, including adults treated in ATAP. Pending approval in the US and will be named Lumizyme.
Impact of Severe Hypertrophy on Respiratory Function
AGLU 1602:
Overall Survival at 18 Months of Age (1 yr ERT)

- **Clinical Trial Patients**: 18/18 trial patients [100%]
- **Untreated Historical Cohort**: 1/62 untreated controls [2%; 95% CI: 0% - 6%]

***95% Confidence Intervals***
AGLU 1602:
Survival Free of ANY Ventilation at 18 Months

12/18 trial patients
[67%; 95% CI: 45% - 88%]

1/62 untreated controls
[2%; 95% CI: 0% - 6%]

Clinical Trial Patients
Untreated Historical Cohort

** 95% Confidence Intervals
Late Onset Pompe Disease

Key to understanding results of current clinical studies
Late-Onset Pompe Disease

Key Clinical Manifestations

• Progressive proximal muscle weakness, especially in trunk and lower limbs
• Gait abnormality
• Respiratory symptoms
  – Shortness of breath, fatigue on exertion, obstructive sleep apnea
• Morning headache
• Daytime somnolence
• Scoliosis
• Scapular winging
• Low back pain

Return to the Mouse Model of Pompe Disease

Patient data prompts a further evaluation of respiratory deficiency
Diaphragm Involvement in Pompe (Gaa−/−)

PAS Staining of Glycogen

Gaa−/− Diaphragm
Normal Diaphragm

(Rucker, Development, 2004)
Ventilation

Frequency (f): breaths per minute

Tidal Volume: Amt of air moved in/out of lungs with each breath (mL/breath)

Minute Ventilation: Freq * Tidal Volume (mL/min)

Peak Inspiratory/Expiratory Flow: Maximum inflow/outflow of air per sec (mL/sec)
Respiratory Assessment Protocol

baseline
60 min
normal air

hypercapnia
10 min
6.4% CO₂ / 94.6% O₂

Tidal volume, Frequency, Minute Ventilation
Response to respiratory challenge is blunted in Gaa−/− mice
Muscle Specific Expression of hGAA in GAA^-/- Mice
Spinal Cord Glycogen Quantification

Phrenic Motor Pool (C₃-C₅)

- **Control**
- **GAA⁻/⁻**

![Graph showing glycogen quantification across different time points (6 months, 12 months, >21 months) for control and GAA⁻/⁻ groups. Asterisks indicate significant differences.](image-url)
Neural deficits dominate respiratory dysfunction

**Figure B**

- **X-axis:** Baseline vs. Hypercapnia
- **Y-axis:** Minute Ventilation (ml/min)
- **Bars:**
  - Black: B6/129
  - Dashed: Muscle specific
  - White: Gaa-/-

**Figure C**

- **Control**
- **Gaa-/-**
- **Muscle specific**

Spectrograms showing baseline vs. hypercapnia conditions.
Why Gene Therapy in Pompe?

- Single gene defect with well defined pathophysiology.
- Ability to provide a single dose therapeutic with a systemic effect.
- Endogenous source of gene product.
  - Avoidance of circulating Ab / CTL
  - Differential fiber type processing
- Gene transfer to motor neurons.
Comparison of AAV9 at ~9.8 Å Resolution to AAV2, AAV4 and AAV8.
GAA Vector Map: rAAV1-hGAA

p43.2- hGAA
Systemic AAV delivery – Left ventricular mass

- All treatments significantly decrease LV mass at 3 months post-treatment.
- No differences at one month were detected.

Falk et al, unpublished
Phrenic Nerve Burst Amplitude is Improved post-injection with AAV-CMV-GAA (2.52 x 10^{10} particles)
Very little positive PAS staining at site of rAAV-GAA injection

Robust PAS staining in moto-neurons at site distant from rAAV-GAA injection

GAA+ neurons at the site of rAAV-GAA injection
Correction of Ventilation Deficit

Minute Ventilation (ml/min)\(^{\text{-1}}\) g\(^{-1}\)

- \(Gaa^{-/-}\) with spinal AAV5-GAA
- \(Gaa^{-/-}\) with spinal AAV5-GFP
- B6/129

Time post spinal vector injection:
- 30 days
- 70 days
- 130 days
Phase I/II: rAAV1-hGAA

- Single site (UF)
- Open label
- Single dose in three injection sites
- Dose escalation between groups
- Intramuscular administration with direct vision by thoracoscopy
- N = 6 (2 cohorts of 3 subjects)

<table>
<thead>
<tr>
<th>Cohort #</th>
<th>1</th>
<th>2</th>
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</thead>
<tbody>
<tr>
<td>Dose, vg</td>
<td>$1\times10^{12}$</td>
<td>$5\times10^{12}$</td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
**Time Line: Phase I/II rAAV1-hGAA**

- **ERT**

- **Vector Injection**

- **Day**
  - -14
  - 0
  - 3
  - 14
  - 30
  - 45
  - 60
  - 75
  - 90
  - 180
  - 365

- **Blood PCR**

- **Immune response profile to AAV and hGAA**

- **Respiratory function studies done up to 180d**

- **General safety studies done throughout up to 365d**
Pompe Disease

Summary

• Pompe disease is a **continuum** of clinical phenotypes, ranging from rapidly progressive infantile-onset to more slowly progressive, late-onset disease.

• All patients share a common pathophysiology: deficiency in GAA, leading to **glycogen accumulation**.

• **Early diagnosis** is the key to optimal patient management.

• Current management consists of **multidisciplinary** supportive measures.

• Pivotal study of ERT completed and **next generation** studies are underway.
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