An Overview of Pompe Disease and Clinical Manifestations

Alex R. Kemper, MD, MPH, MS
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Pompe Disease

- Deficiency of acid α-glucosidase (GAA), which leads to the accumulation of lysosomal glycogen
- Autosomal recessive disorder
- More than 300 mutations have been described
- Broad spectrum of illness

Classification of Pompe Disease

Infantile: Most severe
- Onset ≤12 months of age
  - Infantile Onset with Cardiomyopathy (“Classic Form”) – progressive hypotonia and cardiomyopathy; without treatment, death usually within the first year of life
  - Infantile Onset without Cardiomyopathy (“Nonclassic Form”) – typically no cardiomyopathy; longer survival, but without treatment, death in early childhood

Late-onset: Variable Presentation
- Clinical onset >12 months of age
- Most seek care for symptom onset in adulthood (>18 years)
- Diagnosis ~8-10 years later, and death ~27 years later
- May have mild weakness in childhood that can go unrecognized
- Slowly progressive myopathy
- Variable long-term outcomes without treatment (e.g., wheelchair dependence; ventilator assistance; respiratory failure)
Enzyme Replacement Therapy (ERT)

Treatment: Replace alglucosidase alfa (GAA) deficiency

- Not curative
- Infusion typically every two weeks with central line
- Typical dose is 20 mg/kg infused over 2 hours
- Adverse Effects: Infusion Associated Reactions, Antibody Formation

<table>
<thead>
<tr>
<th>FDA Approval</th>
<th>Pompe Disease Form (Indication)</th>
<th>Drug</th>
<th>Wholesale Acquisition Cost per 50mg vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Infantile-onset (ERT start ≤ 3.5 years)</td>
<td>Myozyme</td>
<td>$975</td>
</tr>
<tr>
<td>2010</td>
<td>Late-onset (≥ 8 years)</td>
<td>Lumizyme</td>
<td>$725</td>
</tr>
</tbody>
</table>

Factors that Affect Detection

**Carriers**
- May have below normal GAA enzyme activity level and be identified through screening

**Pseudodeficiency**
- Low measured GAA enzyme activity level, but does not lead to Pompe disease
- High frequency in East Asian populations (3.9%)
- Can be identified by genotyping

Factors that Affect Treatment Response

**CRIM+ vs. CRIM–**
- Cross-Reacting Immunologic material – individuals make some endogenous enzyme, which may or may not be functional
- CRIM– can develop high titers of antibodies that neutralize ERT, leading to poor outcome
- Standard CRIM status detection: Western blot, however mutation analysis is usually helpful
- CRIM+: ~25% of CRIM+ individuals can also develop antibodies to ERT, usually not as significant as antibody development among those who are CRIM–
Diagnosis

- Establish low functional GAA enzyme levels
- Genotyping
  - Rule out pseudodeficiency
  - Identify carriers
  - Predict infantile-onset vs. late-onset
  - Predict CRIM status

Expected Epidemiology in the United States

- Overall Incidence ~1/28,000
- Infantile-onset Pompe disease
  - ~28% of cases are infantile-onset Pompe disease
  - ~85% of infantile cases are classic Pompe disease
    - ~75% of cases of classic infantile-onset Pompe disease are CRIM+
- Late-onset Pompe disease
  - ~72% of cases are late-onset
- Pseudodeficiency occurs in <1% of births

Clinical Course Before ERT Availability: Infantile-Onset Pompe Disease

<table>
<thead>
<tr>
<th>Symptom Onset</th>
<th>Infantile- onset</th>
<th>Diagnosis</th>
<th>Mechanical Ventilation Assistance</th>
<th>Death</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile- onset</td>
<td>WITH cardiomyopathy</td>
<td>2.0 (0–12)</td>
<td>4.7 (0–48.3)</td>
<td>5.9 (1–59.1)</td>
<td>29</td>
</tr>
<tr>
<td>Infantile- onset</td>
<td>WITHOUT cardiomyopathy</td>
<td>4.4 (0–15.6)</td>
<td>6.0 (0–48.3)</td>
<td>5.9 (1–59.1)</td>
<td>29</td>
</tr>
</tbody>
</table>
Clinical Course Before ERT Availability: Late-Onset Pompe Disease

<table>
<thead>
<tr>
<th>Symptom Onset (med. consult)</th>
<th>Diagnosis Median Age</th>
<th>Death Median Age</th>
<th>Estimated Survival Post-Diagnosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-onset</td>
<td>28 years</td>
<td>38 years</td>
<td>+27 years post-dx 95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+10 yrs 83</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>+20 yrs 65</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>+30 yrs 40</td>
</tr>
</tbody>
</table>

Effectiveness of ERT – Infantile Onset

- Compared to historical controls, ERT at 52 weeks (first infusion by 6 months of age)
  - Reduced the risk of death by 95%
  - Reduced the risk of death or invasive ventilation by 87%
- Overall survival at 36 months: 72%
- Overall ventilator-free survival at 36 months: 49%
- CRIM- status associated with worse outcomes
- Lower survival if ERT begun after 6 months of age

Pre-symptomatic Detection of Late-Onset Pompe Disease

- No trials of pre-symptomatic ERT for late-onset disease
- Treatment decisions based on presence of weakness or muscle damage (e.g., elevated CK). MRI can also show muscle damage.
- Recommendations for follow-up not standardized
- Potential harms of early identification include treatment with ERT, central line placement, economic cost of lifelong treatment, and psychosocial harm.
- There is evidence from an RCT of ERT for symptomatic individuals (mean age in the 40s) that ERT can improve respiratory status and motor function.
Pre-symptomatic Detection of Late-Onset Pompe Disease

- The effect of treatment begun after symptom development might be limited because muscle damage is irreversible. Treatment begun before symptom development might avoid muscle damage.

  - **Biologic plausibility for pre-symptomatic treatment**
    - Muscle damage cannot be reversed by ERT
    - Autophagic inclusion bodies persist after ERT even after reduction of glycogen in muscle cells

- Testing this hypothesis would require a prospective study that would take many years.

Summary

- About 1/28,000 have Pompe disease
- Most cases are late-onset
- There is good evidence that early identification of infantile-onset Pompe compared to clinical detection improves outcomes.
- There is no direct evidence that pre-symptomatic treatment leads to better outcome; however, there is biologic plausability.
- Most cases of infantile-onset Pompe disease are CRIM+.  
  - CRIM- is associated with worse outcomes
  - Immunomodulation appears to improve outcomes, and early immunomodulation may be more effective

Diagnostic issues in Pompe Disease

APHL Webinar
February 19, 2014

Olaf A Bodamer MD, PhD, FACMG, FAAP
Division of Clinical and Translational Genetics
Dr John T. Macdonald Foundation, Department of Human Genetics
University of Miami, Florida
obodamer@med.miami.edu
Case report Pompe Disease

- Female, 18 years
- Presented with progressive proximal myopathy
- Elevation of CK (670 U/L)
- Muscle biopsy showed vacuolar myopathy
- Late-onset Pompe Disease confirmed by enzyme analysis in fibroblasts followed by molecular analysis of GAA gene

Diagnostic avenues Pompe Disease

- Clinical symptoms
- General laboratory abnormalities
- Histology/histochemistry in muscle
- Analysis of α-glucosidase activity
- Molecular analysis of the GAA gene

Histology/histochemistry in muscle

- Vacuolar myopathy
- Vacuoles contain PAS(+), PASD(-), acid phosphatase
- Degree of pathologic change varies with disease severity, and with different muscles
- Analysis of acid maltase in muscle tissue feasible
- Muscle biopsy may miss diagnosis!
General laboratory abnormalities

• Elevation of CK (400-1000 U/L)
• Elevation of aldolase, AST and ALT (ratio=1)
• Elevations of AST and ALT may be misinterpreted as liver disease
Analysis of α-glucosidase activity

- Fluorometric assay
  - singleplex, high throughput
  - ideal for dried blood spots and leukocytes

- Tandem mass spectrometry
  - multiplex capabilities, high throughput
  - ideal for dried blood spots
  - 24-36 hour assay time

- Inhibition of maltase-glucoamylase by arcabose needed to avoid false negative results

Cross Reacting Immunological Material

- CRIM negative infants with Pompe disease mount an immune response against recombinant enzyme

- CRIM status can be determined in fibroblasts or peripheral blood mononuclear cells using Western Blot

- CRIM status may be predicted based on genotype in the majority of CRIM (-)

B(+) – Blood positive CRIM
F(+) – Fibroblast positive CRIM
S – Protein Standard
F(-) – Fibroblast negative CRIM

Molecular analysis of the GAA gene

- GAA gene spans 28kb on 17q25.3; 20 exons
- >250 pathogenic mutations (www.pompecenter.nl)
- Common pathogenic mutations include:
  - c.-32-13T>G (Caucasian)
  - p.R854X (African-American)
  - p.D645E (Chinese)
- Pseudodeficiency variant p.G576S (20% enzyme activity)

Clinical suspicion Pompe Disease
(spectrum of disease, infantile...adult onset)

CK, ALT, AST
(cardiac echo, X-Ray, lung function based on clinical indication)

Analysis of alpha-glucosidase (dried blood spot, leukocytes)
in specialized laboratory

Confirmation of Pompe Disease (plus CRIM status)
Low alpha glucosidase activity and identification of 2 pathogenic GAA mutations

Evaluation of organ manifestations and identification of treatment goals

Pompe Disease staging

MRI / MRI Angiogramm
(in selected patients)

Chest X-ray, Echo, ECG

Blood tests:
CBC, chemistry, CK, GOT, GPT, LDH
rhGAA antibody titer, CRIM
Serum, plasma, dry blood spots, urine
(storage for future biomarker analysis)

Physical/neurologic examen
Quality of life
Family history

Hearing/cochlear fct
(in infants on ERT)

Lung function
Sleep studies
(older children...)

Muscle function test
(older children...)

Neurodevelopmental tests

Evaluation of organ manifestations and identification of treatment goals
Summary and conclusions

- Diagnosis of Pompe disease has to be timely to maximize the benefit of therapy
- Laboratory abnormalities include moderately elevated CK and transaminases in most patients
- Muscle biopsy is obsolete for the diagnosis of Pompe disease
- Diagnostic test of choice is analysis of α-glucosidase activity in dried blood or leukocytes followed by molecular analysis of the GAA gene (cave pseudodeficiency!)
- Diagnostic testing should be done in CLIA/CAP certified laboratory with high sample load

Contact information

Olaf Bodamer MD PhD FACMG FAAP
Division of Clinical and Translational Genetics
Dr John T. MacDonald Foundation
Department of Human Genetics
obodamer@med.miami.edu
Office: 305 243 6056
Fax: 305 243 2704

BGDL:
biochemgenlab@med.miami.edu
Pompe Disease: Treatment
Neena Champaigne, MD
Medical Biochemical Geneticist
Director, Metabolic Treatment Program
February 19, 2014

Treatment Targets for Pompe Disease

Glycogen → α-glucosidase → Glucose

Substrate Reduction Therapy
Enzyme Replacement Therapy (ERT)
Chaperones
Gene Therapy

Supportive Care For:
Heart Function
Respiratory Function
Muscle Function
Improved Quality of Life

PubMed Articles on Treatment for Pompe Disease

# of Publications per Year

0 20 40 60 80 100 120 140
Treatment Strategies

Initial Clinical Trials with rhGAA

4 patients treated for 36 weeks with rhGAA from Rabbit Milk

Clinical Outcomes
- Cardiac function – improved
- Motor function – improved
- Respiratory function – variable
- Survival beyond 1 year – all

Muscle Biopsy
- α-glucosidase activity – normalized
- Glycogen material – decreased

3 patients treated for 1 year with rhGAA from CHO cells

Clinical Outcomes
- Cardiac function – improved
- Motor function – variable
- Respiratory function – variable
- Survival beyond 1 year – all

Muscle Biopsy
- α-glucosidase activity – improved
- Glycogen material – variable

ERT for Infantile-Onset Pompe Disease (IOPD)

- Multiple clinical trials demonstrated:
  - Survival rate - improved
  - Invasive ventilation-free survival rate – improved
  - Cardiac function – improved
  - Motor function – improved

- Treatment response is variable and correlates with:
  - Age at onset of symptoms
  - Stage of disease at ERT initiation
  - CRIM status

References:
CRIM Status in Pompe Disease

- Cross-reacting immunologic material (CRIM)
  - Negative status: 20% of infantile-onset form
    - No endogenous GAA enzyme produced
    - Develop high-sustained antibody titers (HSAT)
    - Reduced survival
    - Reduced invasive ventilator-free survival
    - Decreased cardiac response
    - Regression/loss of motor development

Immune Toleration Induction (ITI)

- Prevent or eliminate immune response to rhGAA
- Immune modulation with:
  - Rituximab
  - Intravenous immune globulin (IVIG)
  - Methotrexate
  - Gene Therapy?

Impact of Early ERT for IOPD

  - 206,088 newborns screened
  - 6 cases IOPD diagnosed and treated with ERT
  - After 14-32 months of treatment
    - Normal cardiac size
    - Normal respiratory status
    - Normal motor development
ERT for Late-Onset Pompe Disease (LOPD)

- Respiratory function – stabilized or improved
- Muscle function – stabilized or improved
- Quality of life – improved

- Treatment response is variable and correlates with:
  - Age at onset of symptoms
  - Stage of disease at ERT initiation


ERT for LOPD

- Recommended for symptomatic LOPD
  - Decreased pulmonary function
  - Demonstrable muscle weakness
- Efficacy should be assessed after 1 year to determine if symptoms have been
  - Slowed
  - Reversed
  - Stabilized
  - Prevented


Impact of Early Diagnosis/ERT for LOPD

- NBS in Taiwan: 2005 –2009
  - 344,056 newborns screened
  - 13 cases LOPD diagnosed (no cardiomyopathy)
  - 4 cases started on ERT (at 1.5 month to 3 years) due to:
    - Low muscle tone
    - Developmental delays
    - Elevated creatine kinase
  - 9 untreated cases monitored every 3-6 months

**FDA Approved ERT**

- **Myozyme® - 2006**
  - Approved for Infantile Pompe
  - 20 mg/kg IV every 2 weeks
  - 50 mg vial = $975*
  - Annual Cost: $50 – 400 K

- **Lumizyme® - 2010**
  - Approved for ≥ 8 years old without cardiac hypertrophy
  - 20 mg/kg IV every 2 weeks
  - 50 mg vial = $725*
  - Annual Cost: $300 – 600 K

*Commercial cost per Genzyme - February 2014

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**ERT Considerations/Limitations**

- Infusion-related reactions
- Antibody formation
- Unsatisfactory access to muscle cells
- New emerging neurological phenotype
- Life-long treatment
- Cost

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**Second Generation ERT**

- BMN-701 (BioMarin)
  - Alternative lysosomal targeting with IGF-2 linked to GAA
  - Phase 1/2 clinical trials

- Neo-GAA (Genzyme)
  - Synthetic bis-M6-P linked to GAA
  - Phase 1 clinical trials

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http://www.clinicaltrials.gov/
Chaperones

- Stabilize/rescue misfolded or unstable proteins
- N-butyldeoxynojirimycin (NB-DNJ)
  - Improved GAA transport from ER to lysosomes
  - Increased GAA activity
- Phase 2 Clinical Trial – Duvoglustat Hydrochloride (Amicus)
  - Administered 1 hour prior to ERT


Gene Therapy
Adeno-Associated Virus (AAV)

- Trials in GAA-KO mice
  - Target: Skeletal muscle
    - Limited systemic effects
  - Target: Liver
    - Efficient production, secretion and uptake in multiple tissues
    - Neutralization by anti-hGAA antibodies
  - Target: Diaphragm
    - Increased phrenic nerve activity and improved ventilatory function
- Phase I/II Clinical Trial– in progress


Other Adjunct Therapies

- Nutrition and Exercise
  - Low-Carbohydrate, High Protein Diet
    - Minimize glycogen accumulation
    - Increase muscle protein synthesis
- Daily Aerobic Exercise
  - Increase ratio of type I to type II muscle fibers

Supportive Treatments

Muscle & Nerve 2011;45 (3) 319 - 333.

Cardiac Monitoring

Neurological Monitoring

Care Coordinator

Physical therapy

Speech therapy


Psychosocial therapy

Occupational therapy

Nutritional & dietary therapy

Respiratory therapy

Care Coordinator

Patient/Family Support

Acid Maltase Deficiency Association
www.amda-pompe.org

International Pompe Association
www.worldpompe.org

www.pompregistry.com

United Pompe Foundation
www.unitedpompe.com