Post-marketing experiences in Pompe disease

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TREAT-NMD meeting

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Pompe disease

Glycogen

Autophagy

Lysosome

Acid α-Glucosidase

ER-Golgi

Glucose
Pompe disease - a clinical spectrum

- No $\alpha$-glucosidase activity
- Hypertrophic cardiomyopathy
- Severe hypotonia
- † before 12 months of age
- Residual $\alpha$-glucosidase activity
- Slowly progressive
- Proximal myopathy
- Respiratory insufficiency
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1988</td>
<td>Cloning of the GAA gene</td>
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<td>1995</td>
<td>Knock-out mouse model</td>
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<td>1996</td>
<td>ERT successful in KO mice</td>
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<td>1999</td>
<td>First patient treated at the EMC</td>
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<td>2002</td>
<td>Start Pompe Survey</td>
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<td>2006</td>
<td>Registration FDA – EMA</td>
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Registration of Myozyme

Marketing authorization under ‘exceptional circumstances’
  – Preclinical and clinical data showed enough evidence of potential benefit

**Condition:** additional information needed after market approval
Challenges

Potential challenges studying the effects of a treatment in rare diseases:
- Small number of patients & variable expression
- Patients divided over individual centers and physicians
- Lack of standardized assessments
- Scarce natural course data
Initiatives

• Databases
  – Pompe registry
  – IPA/ Erasmus MC Pompe Survey

• International collaboration
  – European POMpe Consortium (EPOC)
Pompe registry

• Pharmaceutical sponsored clinical database
  – Physicians treating patients submit results of assessments
  – Most patients, but not very consistent follow-up
IPA/ Erasmus MC Pompe Survey

- Started in 2002 as an initiative of the International Pompe Association and Erasmus MC
  - Ongoing international questionnaire study
  - Continuous inclusion through patient organizations

- **Goal**: to gather information on the natural course of Pompe disease and evaluate treatment effects

- Unique collaboration between physicians, patient organizations and patients
IPA/ Erasmus MC Pompe Survey

- Survey consists of a disease-specific part and generic questionnaires
  - 14 Pompe relevant topics based on literature and expert/patient opinions
  - Rotterdam handicap scale
  - Fatigue severity scale
  - SF-36

- PROs increasingly important to regulatory authorities
  - Patients’ perspective
Current status

- Since 2002 over 450 patients from 14 countries have been included generating ~2300 responses
  - Annual response using a paper version and online platform

- Inclusion of patients through patient organizations
  - Motivated patients
Impact of late-onset Pompe disease on participation in daily life activities: Evaluation of the Rotterdam Handicap Scale

M.L.C. Hagemans a, d,e, P. Laforté e, W.J.C. Hop b, J.J.M. Merkies f, P.A. Van Doorn e, A.J.J. Reuser d, A.J. Van der Ploeg a

ORIGINAL COMMUNICATION

Fatigue: an important feature of late-onset Pompe disease

Late-onset Pompe disease primarily affects quality of life in physical health domains

Clinical manifestation and natural course of late-onset Pompe’s disease in 54 Dutch patients


Research

Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy

Deniz Güngör, Juna M. de Vries, Esther Brusse, Michelle E. Kruijshaar, Wim CJ. Magda Murawiska, Linda E.M. van den Berg, Arnold JJ. Reuser, Pieter A. van Doorn, Marloes LC. Hagemans, Ans T. van der Ploeg

Enzyme replacement therapy and fatigue in adults with Pompe disease

Deniz Güngör, Juna M. de Vries, Esther Brusse, Michelle E. Kruijshaar, Wim CJ. Magda Murawiska, Linda E.M. van den Berg, Arnold JJ. Reuser, Pieter A. van Doorn, Marloes LC. Hagemans, Iris Plug, Ans T. van der Ploeg

Impact of enzyme replacement therapy on survival in adults with Pompe disease: Results from a prospective international observational study

Deniz Güngör, Iris Plug, Ralph B D’Agostino Sr, Marloes LC. Hagemans, Ans T. van der Ploeg

Disease severity in children and adults with Pompe disease related to age and disease duration


Clinical manifestation and natural course of late-onset Pompe’s disease in 54 Dutch patients

Results from the IPA survey

>14 papers originated from the survey.
- More insight in natural course of disease
  - What are the problems patients face and how the disease progresses
- Decreased survival in untreated patients and positive effect of ERT
  - Important finding in the reimbursement discussion international
- Positive effects ERT on fatigue, participation and QoL
Results from the IPA survey

Fatigue

- Natural course: +0.01/year; p=0.80
- During ERT: -0.13/year; p<0.001

Participation

- Natural course: -0.49/year; p<0.001
- During ERT: -0.02/year; p=0.83

Güngör D et al: Quality of life and participation in daily life of adults with Pompe disease receiving enzyme replacement therapy: 10 years of international follow-up. submitted
Why the IPA survey worked

• Started early so we had data to compare a therapy to

• Large number of patients with consistent follow-up
  – Patients organizations & dedicated patients

• Additive to clinical data & patients’ perspective

• Benchmark to evaluate new developments / therapies
EPOC

European Network on Pompe disease
- Established in 2014
- Covers at least 1250 patients of all ages

- 42 Experts from 11 countries
  - Physicians
  - Epidemiologists
  - Basic scientist
  - Patient representatives

EPOC

Focus of the network:

- Data sharing & collaborating on research questions
- Develop standards of care & harmonize outcome measures
  - Developing of recommendations on starting and stopping ERT
- Responses to questions from health authorities

- Physicians remain in control over the data and have the ability to ‘go back to the patient’
- ‘Minimal datasets’ increases feasibility for smaller centers to participate
Summary

• International registries and collaboration are vital

• Standardization / ‘minimal datasets’

• Remaining in control of the databases increases potential

• PROs add to clinical data
  – Patients and patient organizations are reliable partners

• Start standardized follow-up before a treatment is available
Chair: Ans van der Ploeg

Neurology:
Pieter van Doorn
Esther Brusse
Hannerieke van den Hout
Nadine van der Beek

Pharmacy:
Peter Roos
Jan-Dietert Brugma

Internal Medicine
Janneke Langendonk

Diagnostics
George Ruijter

Pediatrics:
Esmee Oussoren
Hidde Huidekoper
Monique Williams

Clinical Genetics:
Arnold Reuser
Pim Pijnappel

Epidemiologists
Michelle Kruijshaar
Iris Plug

Care & Research