Thérapeutique chez l'enfant répondeur et non répondeur

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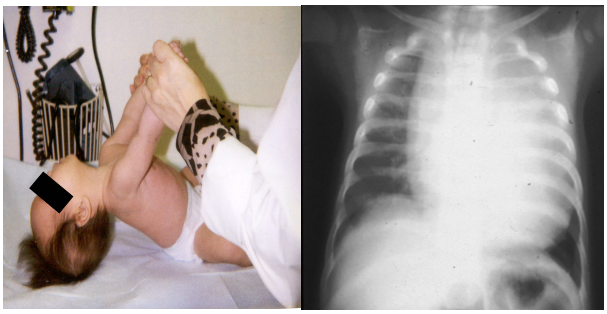
Infantile Onset Pompe Disease Main Features

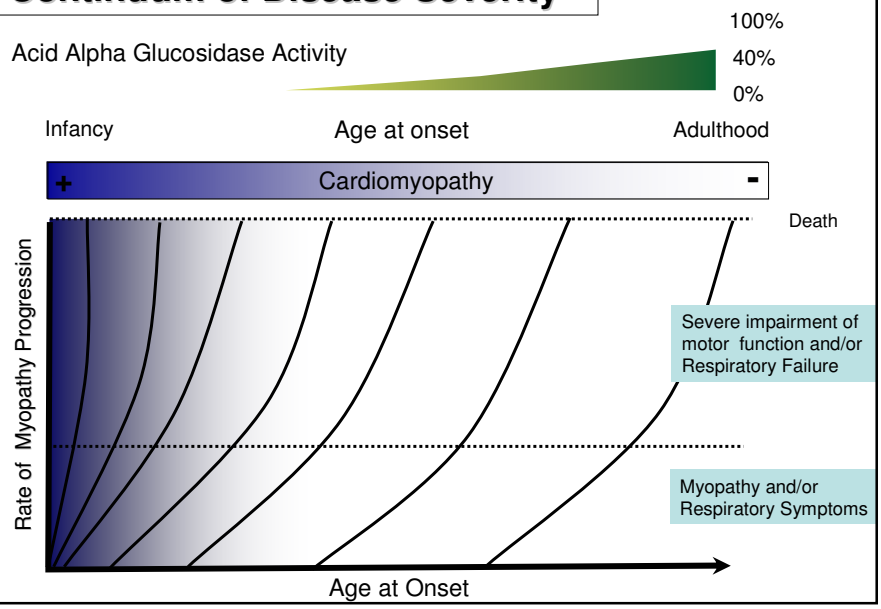
A Lysosomal Storage Disorder
(acid-alpha-glucosidase deficiency)

Glycogen accumulation in muscle cells



Progressive muscle weakness/hypotonia
Progressive cardiomyopathy → Respiratory and Heart Failure
Death usually in 1st year of life

Pompe Disease: Continuum of Disease Severity



Pompe Disease Phenotypes

	Phenotypes[1]			
	Classical Infantile	Non-classical Infantile	Childhood & Juvenile	Adult
Age @ Onset (years)	<0.5	<1	>1 - teens	>2nd decade
Age @ Death (years)	<1	1st decade	>1st decade	>2nd decade
GAA Activity[2] (%)	<1	< 1	~ 2 - 6	~ 7 - 23
	Infantile Onset		Late Onset	

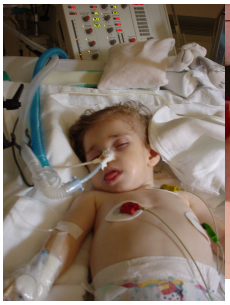
[1]Hirschhorn R, Reuser AJJ. The Molecular & Metabolic Basis of Inherited Diseases, 2001
[2]Reuser AJJ et al. Muscle Nerve 1995; Suppl 3:S61-S69

Different types of response to treatment

Good response

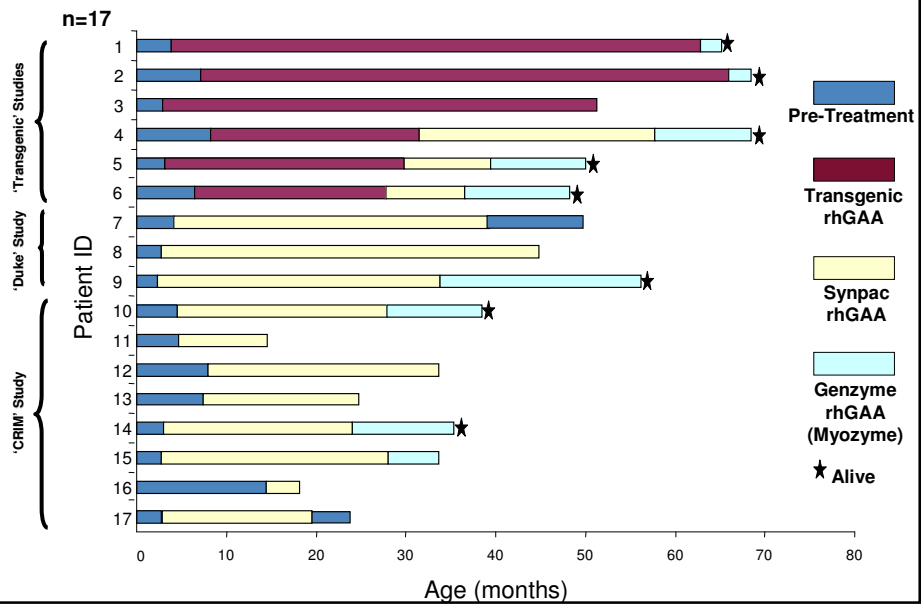
Poor response

Point of non return



Secondary aggravation

Early ERT Trials in Infantile-Onset Pompe Disease



ERT Trials in Infantile-Onset Pompe Disease

- « Additional studies are needed to further evaluate the efficacy of rhGAA »
  - **AGLU-017O2**: 21 patients enrolled
  - **AGLU-01602**: 18 patients enrolled

Studies Using ERT in Infantile 0nset Pompe:
General Design

Criteria	Study 1602* n=18	Study 1702** n= 21
Age	<6 months	6-36 months
Symptoms by 1 year of age	Yes	Yes
Cardiomyopathy	Yes	Yes
Minimal GAA activity (skin fibroblasts)	Yes	Yes
Ventilator Use Allowed	No	Yes
Cardiac Failure (Echo & Clinical)	No	No
Congenital Malformations	No	No
Dose:	***20 or 40 mg/kg qow***	***20 mg/kg/qow***

Infantile-onset GSD II : personal experience in clinical trials from 2001

Study	Patient	Patient's origin	DOB	Date treatment started	Outcome (†=deceased)
001	N-J	France	26 may 01	21 Aug 01	† 20 Jan 04
1602	A-K JGG L-L	France Italy France	25 Dec 02 13 Jul 03 15 Dec 03	26 May 03 21 Nov 03 27 May 04	
1702	G-B S-S L-B B-H N-JE	Italy Slovenia Italy France Germany	18 Feb 02 04 Jul 03 24 Jul 03 03 Dec 02 29 May 02	20 Mar 03 02 Apr 04 3 May 04 28 May 04 28 Aug 03	† 27 Jul 03 † 06 Apr 04

GSD II French patients treated with ATU *Autorisation temporaire d'utilisation* = Temporary authorization for use; no expanded access program in France)

Patient (phenotype)	DOB	Date treatment started	Site	Outcome († = deceased)
E-R (infantile)	06 May 03	Nov 04	Bordeaux	
C-G (childhood onset)	10 Jul 99	Feb 05	Lyon	
N-S (infantile)	03 Sept 04	Feb 05	Strasbourg	† 15 Apr 05
F-F (childhood onset)	01 Oct 73	March 05	Lyon	
R-L (childhood onset)	02 Jul 90	March 05	Lille	
M-S (childhood onset)	19 Jan 87	March 05	Lille	
S-ND (infantile)	24 March 05	April 05	Marseille	
I-C	15 Dec 04	May 05	Nancy	

Patients receiving Myozyme (Sept. 2005)

- 159 patients on treatment
  - 37 patients enrolled in studies

Infantile-Onset Pompe Disease: ERT Trials using Myozyme

AGLU-01602

Study started May 2003

Inclusion Criteria

- Be ≤ 6 months of age
- Residual GAA activity <1% of normal mean (skin fibroblasts)
- Have abnormal left ventricular mass (LVM) by echocardiogram
  - Defined as LVM >2 SD above normal mean
- Be free of any ventilator support

Summary of Baseline Characteristics

- **Gender**
  - **11 males: 7 females**
- **Ethnicity**
  - 7 Caucasian
  - 4 African American
  - 3 Hispanic
  - 2 Asian
  - 2 Other
- **Mean age at 1st symptoms**
  - 1.6 months (range 0 -5.5 months)
- **Mean age at 1st infusion**
  - 4.6 months (range 1.2 – 6.1 months)
- **Cross-reactive immunological material (CRIM)**
  - 15 CRIM (+): 3 CRIM (-)

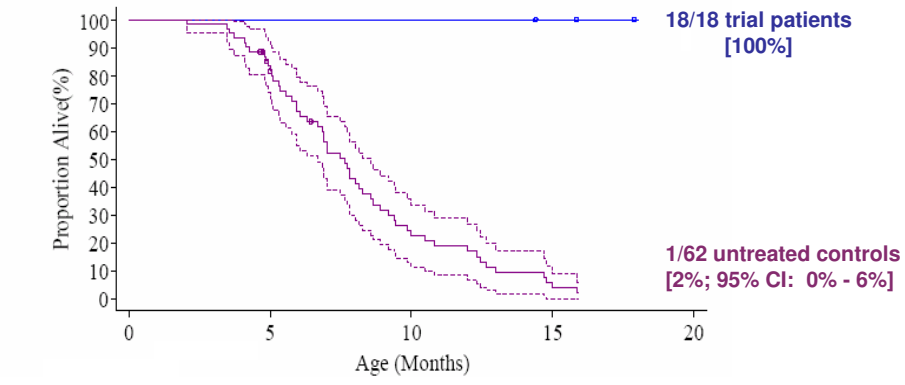
  (Evaluated by western blot from skin fibroblasts)

Study Design

- **Open label, multi-national, multi-center**
- **Patients randomized to 20 or 40 mg/kg/q2w**

End Points	Description
Primary	Survival free of invasive ventilator vs. Overall Survival in Untreated Historical Cohort (ventilated or not)
Secondary	Overall Survival
	Survival free of any ventilator use
	Changes in LVMI
	Changes in Growth
	Motor Development

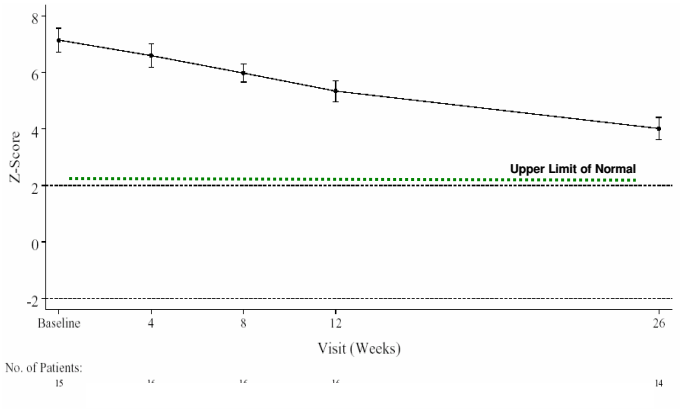
Overall Survival at 18 Months of Age



- Clinical Trial Patients
- Untreated Historical Cohort
- 95% Confidence Intervals

Changes in Left Ventricular Mass (LVM)

Mean decrease in LVM index of 53% at Week 26 (n=12)



•All patients had abnormal LV mass (z-scores > +2 by a Central Reader) at Baseline (n=18)

•100% patients with repeat measurement showed decrease in LV mass index & z-scores (n=14)

Motor Development

- Measured by
  - Alberta Infant Motor Scale (AIMS) and
  - Acquisition of Motor Milestones Checklist
- Results by Week 52
  - 13/18 patients (72%) with demonstrable gains
    - 7 patients walking
    - 2 patients crawling and standing with support
    - 2 patients sitting independently
    - 2 patients sitting with support
  - 5/18 patients (28%) with minimal or no gains
    - All 5 patients required ventilator support
      - 3 patients invasively ventilated
      - 2 patients non-invasively ventilated

Safety Findings Summary

- 15/18 patients (83%) seroconverted by Week 12
- By Week 52, most patients' titers plateau or decreased
  - Titers ranged from 1:100 to 1:204,800 in all but one patient
    - » 1 CRIM (-) patient with high anti-rhGAA antibody titers (1:1,638,400) and 12% inhibitory activity by an *in vitro* assay (assay variability approx. 10%)
- 11/18 patients (61%) had IARs, majority mild and managed symptomatically with success
  - No discontinuations due to intolerance
- Dose groups:
  - Similar proportion of patients with IARs in both dose groups
    - » 5 patients at 20 mg/kg/qow vs. 6 patients at 40 mg/kg/qow
  - Trend towards higher antibody titers in 40 mg/kg/qow group
  - Trend towards more IARs/per patient in 40 mg/kg/qow group

Sept. 2005: 1602 study update

- 2 patients have died
- CNS: no complication
- 7 patients with invasive ventilation
  - 4 patients with 40 mg/kg/qow
  - 4 patients CRIM+

1602 Study: conclusions

- Administration of ERT with Myozyme has been in general, safe and well tolerated
- ERT with Myozyme in patients with infantile onset Pompe disease receiving 20 40 mg/kg/qow for 6 to12 months have changed the natural history of the disease:
  - Significantly improved survival
  - Marked reversal of cardiomyopathy parameters
  - Prevention of failure to thrive
  - Continuous acquisition of motor milestones in a subgroup of patients
- Long term clinical and immunological follow up is necessary