Sebelipase alfa enzyme replacement therapy in Wolman disease

A nationwide cohort with up to ten years of follow-up

Tanguy Demaret, MD, PhD
Pediatrician, fellow in Medical Genetics in IPG, Gosselies

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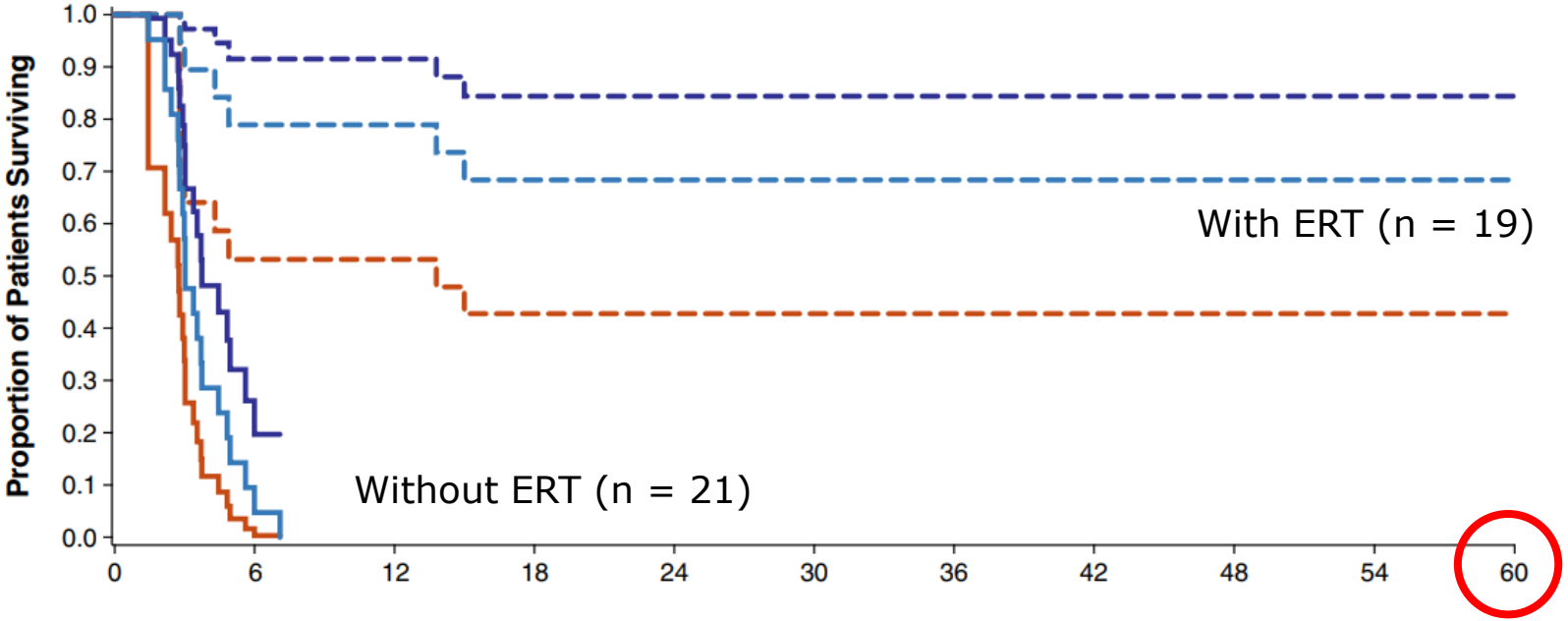
Wolman disease has dismal outcome without ERT

- Wolman disease (WD), AR, 1/1,000,000
  - Rapidly-progressive phenotype of lysosomal acid lipase deficiency
  - Neonatal presentation
  - Diarrhea, failure to thrive, hepatosplenomegaly, anemia

  ➔ Multi-organ failure and death before 12 months of age

- Sebelipase alfa (Kanuma®)
  - Enzyme replacement therapy (ERT)
  - 1x/week
  - Improved survival, growth and biological parameters

Sebelipase alfa was associated with higher survival compared with historical cohort.



Vijay, *et al.*, Orphanet J Rare Dis, 2021

FU & management data are lacking

- Long-term follow-up (> 5 years)
  - Biological parameters
  - Phenotype evolution
- Diet, (par)enteral nutrition, vitamins
- Venous access
- Health-related quality of life (HRQoL) evaluation

Nationwide (France), retrospective, study

- Medical file review + PedsQL questionnaire
- Inclusion criteria:
  - Sebelipase alfa treatment
    - 3 patients were previously included in LAL-CL03 trial
  - WD patients:
    - Abolished LAL enzyme activity

    and/or
    - Bi-allelic *LIPA* gene pathogenic variant
- Exclusion criteria:
  - Liver transplantation

  or
  - Hematopoietic stem cell transplantation

5 WD patients were included

- 3 patients had a previously affected sibling
  - ➔ clinically less affected at diagnosis
  - ➔ early diagnosis & ERT initiation (1 month of age)

- Excellent ERT tolerance (4/5)
  - One patient experienced an anaphylactic reaction
    - ➔requires systematic premedication

Table 1. Patients characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Median (min-max) or proportion
Age at diagnosis (months)	2	0	0	0	2	0 (0-2)
Follow-up (months)	120	83	37	84	14	83 (14-120)
Family history	-	+	+	+	-	3/5
Diet						
Enriched in MCT (at last FU)	-	-	+	+	+	3/5
NG tube (at diagnosis)	-	+	-	+	+	3/5
NG tube (at last FU)	-	-	-	-	+	1/5
Sebelipase alfa						
First dose (months)	4	1	0	1	2	1 (0-4)
Maintenance dose (mg/kg/d)	5	3	3	3	4	3 (3-5)
Frequency (/ X weeks)	2	1	1	1	1	1 (1-2)
Treatment duration (months)	116	82	37	83	12	82 (12-116)
Venous access						
CVAD (number)	2	6	4	2	3	3 (2-7)
Last CVAD use (month)	65	66	26	n.a.	n.a.	65 (26-66)
At last FU	PVC	PVC	PVC	CVAD	CVAD	

MCT: medium-chain triglycerides, FU: follow-up, NG: nasogastric, CVAD: central venous access device, n.a.: not applicable, PVC: peripheral venous catheter

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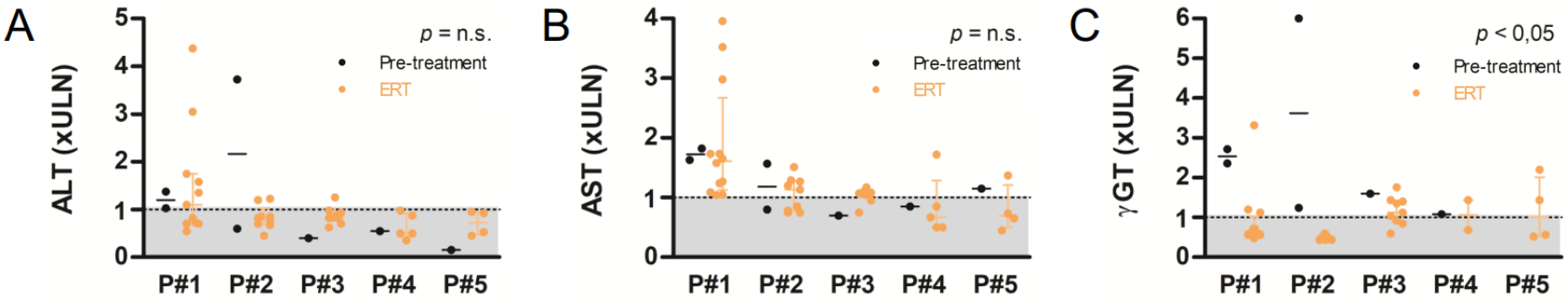
Liver enzymes remained nearly normal during ERT



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All patients survived under ERT

- 100% survival
- PedsQL questionnaires
  - 3 patients scored 61-80%
  - 4 parents scored 82-100%, 1 parent gave 51% (linguistic barrier ?)
- Three patients exhibited a neuromyopathic phenotype
  - Footdrop gait, waddling walk or muscle fatigue
  - EMG and muscle strength testing were normal
  - All showed spontaneous recovery
- Regular school attendance (n = 3)

Discussion

- Biological results are similar to clinical trials
- No lack of clinical response in our cohort (n = 3 in LAL-CL08, < auto-Ab)
- Slow increase of the ERT dose is required to avoid anaphylaxis
- Bi-weekly infusion will be evaluated in all patient
- One patient still requires tube feeding & parenteral nutrition (after AGE)

Conclusion & perspectives

- Sebelipase alfa enzyme replacement therapy in 5 WD patients:
  - Early diagnosis & ERT initation is the key — Newborn screening ?
  - 100% long-term survival
  - Improved bio-clinical parameters
  - Acceptable health-related quality of life — ERT 1x/2w after 5y ?
- Very-long term follow-up has to be done — Neuromyopathic phenotype ?
- Hematopoietic stem cell transplantation while under ERT ?

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tanguy.demaret@ipg.be

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Sebelipase alfa enzyme replacement therapy in Wolman disease: a nationwide cohort with up to ten years of follow-up

Tanguy Demaret[1,10*], Florence Lacaille[2], Camille Wicker[3], Jean-Baptiste Arnoux[3], Juliette Bouchereau[3], Claire Belloche[3], Cyril Gitiaux[4], David Grevent[5], Christine Broissand[6], Dalila Adjaoud[7], Marie-Thérèse Abi Warde[8], Dominique Plantaz[7], Soumeya Bekri[9], Pascale de Lonlay[3] and Anaïs Brassier[3*]