Long-term follow-up of 64 children with classical infantile-onset Pompe disease since 2004: a French real-life observational study

M. Tardieu, C. Cudejko, A. Cano, C. Hoebeke, D. Bernoux, V. Goetz, S. Pichard, A. Brassier, M. Schiff, F. Feillet, et al.

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Marine Tardieu[1] | Céline Cudejko[2] | Aline Cano[2] | Célia Hoebeke[2] | Delphine Bernoux[2] | Violette Goetz[1] | Samia Pichard[3] | Anaïs Brassier[3] | Manuel Schiff[3] | François Feillet[4] | Paul Rollier[5] | Karine Mention[6] | Dries Dobbelaere[6] | Alain Fouilhoux[7] | Caroline Espil-Taris[8] | Didier Eyer[9] | Frédéric Huet[10] | Ulrike Walther-Louvier[11] | Magalie Barth[12] | Laurent Chevret[13] | Alice Kuster[14] | Jérémie Lefranc[15] | Julien Neveu[16] | Gaele Pitelet[16] | Juliette Ropars[17] | François Rivier[11,18] | Agathe Roubertie[19] | Guy Touati[20] | Catherine Vanhulle[21] | Emilie Tardieu[22] | Catherine Caillaud[23] | Roseline Froissart[24] | Murielle Champeaux[2] | François Labarthe[1,25] | Brigitte Chabrol[2]

1 Centre de Référence des Maladies Héréditaires du Métabolisme ToTeM, Service de Médecine Pédiatrique, Hôpital Clocheville, Tours, France

2 Centre de Référence des Maladies Héréditaires du Métabolisme, Service de Neurométabolisme Pédiatrique, Hôpital Timone Enfants, AP-HM, Marseille, France

3 Centre de Référence des Maladies Héréditaires du Métabolisme, Service de Métabolisme Pédiatrique, Hôpital Necker-Enfants Malades, APHP, Paris, France

4 Centre de Référence des Maladies Héréditaires du Métabolisme, Service de Médecine Infantile, Hôpital Brabois Enfants; Unité INSERM NGERE U 1256, Campus Babrois-Santé, Vandoeuvre-lès- Nancy, France

5 Service de Génétique Clinique, Site Hôpital Sud, Rennes, France

6 Centre de Référence des Maladies Héréditaires du Métabolisme, Service Néphrologie, Endocrinologie, Maladies Métaboliques et Hématologie Pédiatrique, Hôpital Jeanne de Flandre, Lille, France

7 Centre de Référence des Maladies Héréditaires du Métabolisme, Service d'Endocrinologie et de Diabétologie Pédiatriques et Maladies Héréditaires du Métabolisme, Hôpital Femme-Mère-Enfant, Hospices Civils de Lyon, Bron, France

8 Centre de Référence des Maladies Neuromusculaires AOC, Service de Neuropédiatrie, Hôpital des Enfants Pellegrin, Bordeaux, France

9 Service des Maladies Métaboliques, Hôpital de Hautepierre, Strasbourg, France

10 Centre de Compétence des Maladies Héréditaires du Métabolisme, Service de Pédiatrie Multidisciplinaire, Hôpital d'Enfants, Dijon, France

11 Centre de Référence des Maladies Neuromusculaires AOC, Service de Neuropédiatrie, Hôpital Gui de Chauliac, Montpellier, France

12 Centre de Compétence des Maladies Héréditaires du Métabolisme, Service de Génétique, CHU Angers, Angers, France

13 Service Pédiatrie et Urgences Pédiatriques, CH Saint-Brieuc, Saint-Brieuc, France

14 Centre de Compétence des Maladies Héréditaires du Métabolisme, Service de Réanimation Pédiatrique, CHU Nantes, Nantes, France

15 Service de Neuropédiatrie, Hôpital Morvan, Brest, France

16 Service de Neuropédiatrie, Hôpitaux Pédiatriques de Nice, CHU Lenval, Nice, France

17 Centre de Référence Maladies Neuromusculaires AOC, Service de Neuropédiatrie, Hôpital Morvan, Brest, France

18 PhyMedExp, Université de Montpellier, INSERM, CNRS, Montpellier, France

19 Centre de Compétence des Maladies Héréditaires du Métabolisme, Service de Neurologie Pédiatrique, Hôpital Gui de Chauliac; INM, INSERM U 1298, Université de Montpellier, Montpellier, France

20 Centre de Référence des Maladies Héréditaires du Métabolisme, Service de Gastro-$ entérologie, Hépatologie, Nutrition et Maladies Héréditaires du Métabolisme Pédiatrique, Hôpital des Enfants, Toulouse, France

21 Service de Néonatalogie et Réanimation Pédiatrique, Hôpital Charles Nicolle, Rouen, France

22 Service de Santé Universitaire, Université Lumière Lyon 2, Lyon, France

23Service de Biochimie Métabolique, Hôpital Necker-Enfants Malades, APHP, Paris, France

24Service de Biochimie et Biologie Moléculaire, Centre de Biologie et de Pathologie Est, Hospices Civils de Lyon, Bron, France

25 Inserm U1069, N2C, Université de Tours, Tours, France

Correspondence

Chabrol B, Centre de Référence des Maladies Héréditaires du Métabolisme,
Service de Neurométabolisme Pédiatrique, Hôpital Timone Enfants, AP-HM, Marseille, France.
Email: brigitte.chabrol@ap-hm.fr

K E YWORDS

enzyme replacement therapy, immunomodulation, infantile-onset, Pompe disease, long-term, outcomes

Abbreviations:

CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy.

Abstract

Background:

Classical infantile-onset Pompe disease (IOPD) is the most severe form of Pompe disease. Enzyme replacement therapy (ERT) has significantly increased survival but only a few studies have reported long-term outcomes.

Methods:

We retrospectively analyzed the outcomes of classical IOPD patients diagnosed in France between 2004 and 2020.

Results:

Sixty-four patients were identified. At diagnosis (median age 4 months) all patients had cardiomyopathy and most had severe hypotonia (57 of 62 patients, 92%). ERT was initiated in 50 (78%) patients and stopped later due to being ineffective in 10 (21%). Thirty-seven (58%) patients died during follow-up, including all untreated and discontinued ERT patients, and 13 additional patients. Mortality was higher during the first 3 years of life and after the age of 12 years. Persistence of cardiomyopathy during follow-up and/ or the presence of heart failure were highly associated with an increased risk of death. In contrast, cross-reactive immunologic material (CRIM)-negative status (n = 16, 26%) was unrelated to increased mortality, presumably because immunomodulation protocols prevent the emergence of high antibody titers to ERT. Besides survival, decreased ERT efficacy appeared after the age of 6 years, with a progressive decline in motor and pulmonary functions for most survivors.

Conclusions:

This study reports the long-term follow-up of one of the largest cohorts of classical IOPD patients and demonstrates high long-term mortality and morbidity rates with a secondary decline in muscular and respiratory functions. This decreased efficacy seems to be multifactorial, highlighting the importance of developing new therapeutic approaches targeting various aspects of pathogenesis.

INTRODUCTION

Pompe disease, also known as glycogen storage disease type II, is a rare progressive metabolic myopathy resulting from autosomal recessively inherited lysosomal acid α-glucosidase (GAA) deficiency [1].

Pompe disease has a wide spectrum of clinical phenotypes that differ according to age of onset and rate of progression [2]. Although there is no official classification of the different

phenotypes, three forms are commonly accepted: infantile-onset Pompe disease (IOPD), juvenile, and adult-onset Pompe disease. Classical IOPD was described by Joannes Cassianus Pompe in 1930 in a 7-month- old girl. Classical IOPD patients present before the age of 12 months, and often in the first 6 months of life, with hypertrophic cardiomyopathy and muscular hypotonia. Natural history studies suggest that the median age of death is 6–9 months due to cardiorespiratory failure [3]. An atypical form of IOPD has been described. [1, 4] Onset is also in the first year of life, but the cardiac involvement is more moderate at diagnosis and survival is enhanced. Pompe disease is a rare disease, and the incidence varies from 1 in 100,000 for the infantile form to 1 in 40,000 for all forms as a whole [5]. The rate of disease progression, and thus severity, is overall inversely correlated to the degree of residual GAA activity [2]. IOPD patients have been classified into two subgroups: the cross-reactive immunologic material (CRIM)-positive (CRIM+) group that preserves synthesis of a non-functional form of GAA and the CRIM-negative (CRIM−) group that is completely unable to form any kind of native enzyme [6]. CRIM status is determined by analyzing the GAA enzyme by western blot. Alternatively, it can be deduced from the results of genotyping if the effects of a specific variant on protein synthesis have been characterized [6].

Enzyme replacement therapy (ERT) with recombinant human (rh) GAA (alglucosidase alfa, Myozyme®) has been available in France for the treatment of Pompe disease since 2004. In IOPD forms it has been shown to substantially prolong survival by reducing muscular and cardiac damage [3], the result being more effective if the treatment is started early. However, the production of high levels of IgG antibodies against rhGAA is a factor that leads to a reduction in the effectiveness of the treatment, and CRIM− patients have a much higher risk of developing high antibody titers directed against rhGAA than do CRIM+ patients [6]. In France, follow-up according to the national guidelines [7] and access to treatment is supervised by the Comity for the Evaluation and Treatment of Pompe disease (CETP), which validates the indication of ERT for Pompe patients. Indications for treatment are assessed on a case-by-case basis. For children with immediately severe cardiac and/or respiratory failure, the decision not to initiate ERT is the result of a concerted ethical decision. To our knowledge, large cohorts [8–10] and very long-term follow-up [11–13] information on ERT efficacy in classical IOPD patients, excluding atypical or juvenile forms of the disease, are rare. In the present study we retrospectively analyzed the outcome of 64 patients with classical IOPD diagnosed in France between 2004 and 2020.

POPULATION AND METHODS

Data from patients with classical IOPD were provided by the French expert centers for rare diseases, coordinated by the French networks for rare diseases (G2m network for inborn errors of metabolism diseases and FILNEMUS network for neuromuscular diseases). Data from this multicenter study were collected from 2004 (when ERT became available in France) until April 2021. The only inclusion criterion was confirmed diagnosis of classical IOPD, with or without ERT. Data collected retrospectively were: date of birth, gender, familial case, consanguinity, age at diagnosis, symptoms at diagnosis, GAA activity, CRIM status, GAA genotype, ERT initiation, age at treatment initiation, vital status, evolution with motor function information (particularly age of acquiring walking ability and age of losing the ability to walk), nutritional (use of nasogastric tube or gastrostomy) and ventilatory support (non-invasive or tracheostomy-assisted ventilation) information, treatment information, and scholar status.

GAA sequencing of classical IOPD patients was performed using the Sanger method following polymerase chain reaction (PCR) amplification of the 20 GAA exons. Pathogenicity of variants was determined according to the recommendations of the American College of Medical Genetics (ACMG) [14]. Blood-based CRIM assay was done by western blot analysis as described previously [15]. GAA variants and their corresponding CRIM status were all compared with data present in the Pompe disease GAA variant database (http://www.pompe varia ntdat abase.nl/).

A standard anonymous form was sent to all expert centers, completed by the local investigator, and sent to our center for data to be entered into the database. Management and control of the data were performed by a clinical research associate using Microsoft Access® software.

Statistical analysis

Results were presented as number of patients (percentage, calculated from the number of available values) or median [minimum; maximum] as appropriate. Statistical analyses were carried out by a statistician using SPSS version 20.0 (IBM SPSS Statistics). Results were reported according to the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.

Ethics approval and consent to participate

No nominative, sensitive, or personal data on patients were collected. This study was registered locally, in our institution, under n0. 20_244. As the study was completely anonymous, no ethics committee approval was required under French law.

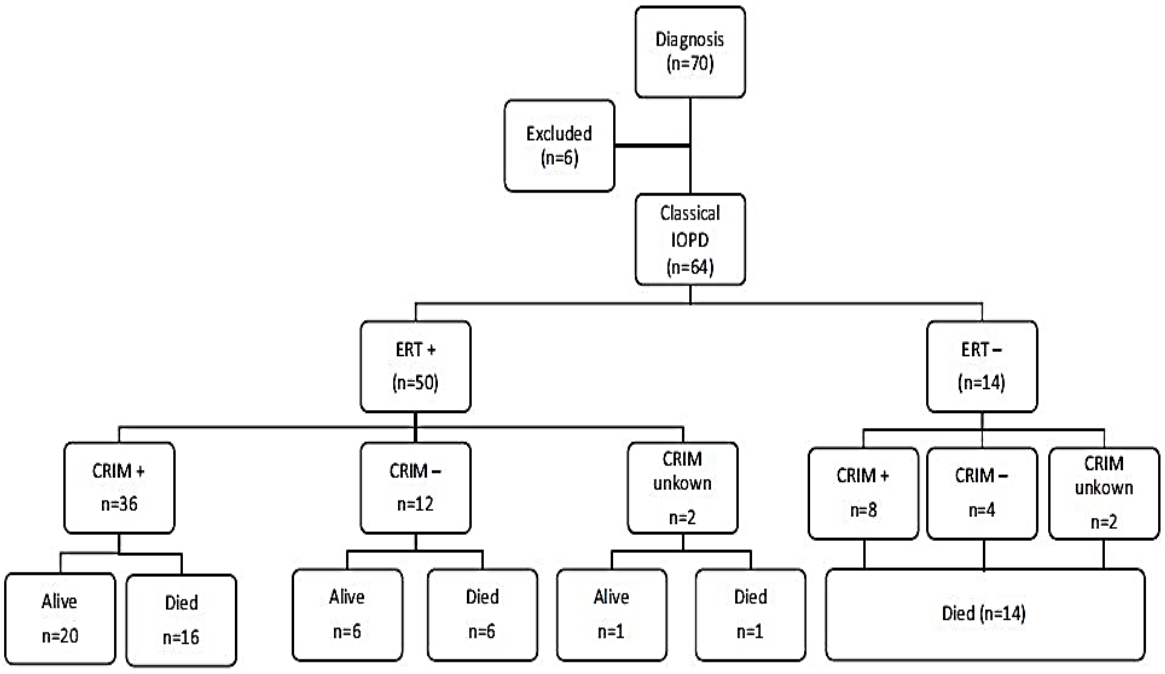

FIGURE 1 Flowchart of the French cohort of classical infantile-onset Pompe disease. CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease.

RESULTS

We identified 70 unrelated patients born between 2004 and 2020 followed for the diagnosis of IOPD (see flowchart in Figure 1). Six of them were excluded because of the absence of cardiomyopathy at diagnosis (n = 4, considered as early diagnoses of a juvenile form) or because diagnosis was made after the age of 12 months (n = 2, considered as atypical IOPD). Further analyses were performed on 64 patients with a confirmed diagnosis of classical IOPD. For 22 (37%) of these patients, their parents were consanguineous and there was a previous case of classical IOPD in the family for 8 (13%) patients. Familial cases (n = 8) were compared with other classical IOPD patients (n = 56). In this

subgroup, median age at diagnosis was earlier (0.5 [0; 2] vs. 4 [0; 12] months) and median age of treatment initiation was also advanced (1 [0; 2] vs. 5 [1; 15] months). All parameters of disease progression appear to be improved in the second children (n = 4) compared to the index cases (n = 4; e.g., global survival: 25% vs. 0%; survival free of any ventilation: 25% vs. 0%; acquisition of walking ability: 50% vs. 0%; median age at death: 11 [1; 69] vs. 8 [7; 24] months). However, the small size of each group does not allow any conclusions to be drawn. From 1 to 7 patients (median 3) were diagnosed each year at a median age of 4 [0; 12] months, which remained relatively constant over time (Figure 2). Characteristics of the patients are presented in Table 1. Cardiomyopathy was present in all the cases at diagnosis, with cardiac failure in 25 of 61 (41%) patients. Cardiomyopathy was hypertrophic in most cases (n = 56, and/or genotype in 61 (95%) patients. The result was negative in 16 (26%) cases, positive in 44 (72%), and undetermined in 1 (2%).

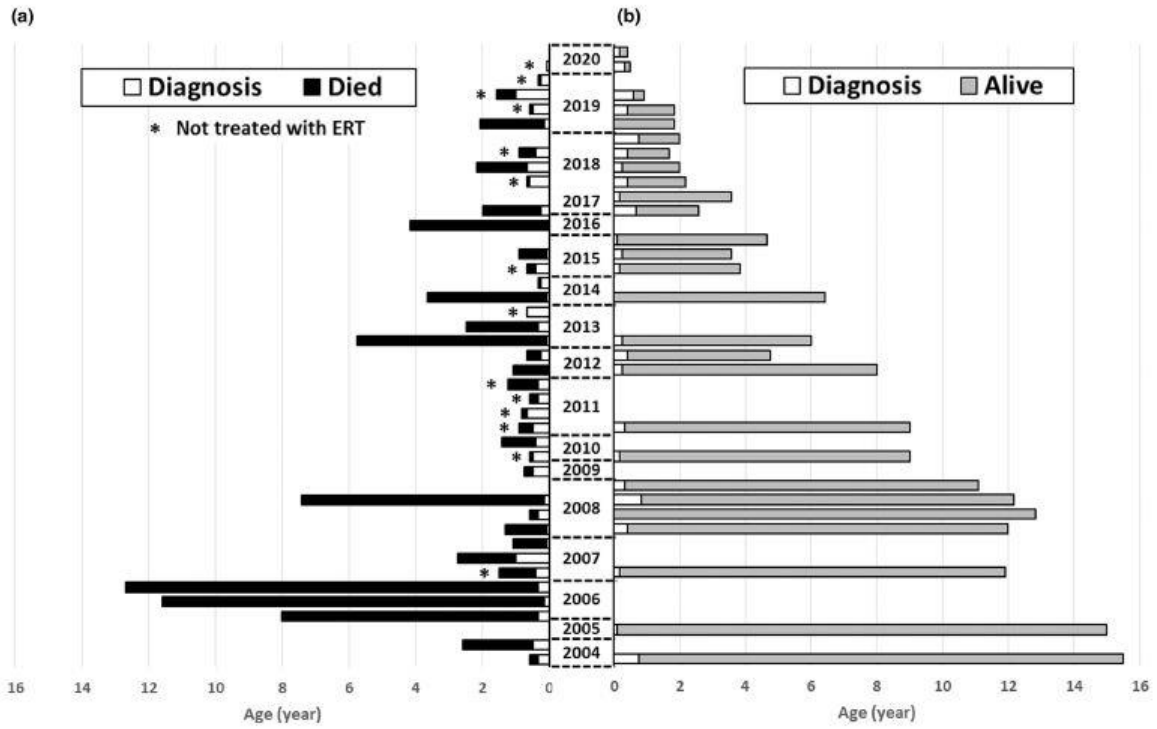

FIGURE 2 Age structure of the French cohort of classical infantile-onset Pompe disease. Age structure of the classical infantile-onset Pompe disease (IOPD) patients who died (a) or were still alive (b) at last visit per year of birth. White box represents age at diagnosis for each patient. ERT, enzyme replacement therapy.

Specific ERT treatment was initiated in 50 (78%) patients at a median age of 4 [0; 15] months. ERT was not started in 14 (22%) patients with regard to the severity of disease at diagnosis, as illustrated by the older age (5.5 [1; 12] vs. 3.0 [0; 12] months, $p < 0.05$) and the higher percentage of patients with heart failure (11 of 12 [92%] untreated patients vs. 14 of 48 [29%] treated cases, p = 0.0001), whereas the percentage of patients with negative CRIM status was similar (4 [33%] vs. 12 [25%], not significant). For patients treated with ERT, an increased dosage (mostly 20 mg/kg/week) was used at initiation in 20 (40%) cases. The use of an increased dosage right from the ERT initiation was a recent practice, as demonstrated by a shorter duration between ERT initiation and the end of our study (April 2021) for patients receiving an initial increased dosage compared to the conventional dosage of 20 mg/kg/every other week (5.9 ± 0.8 vs. 10.6 ± 0.9 years, respectively, p = 0.0007). An immunomodulation protocol was used for 13 (27%) patients, with a preventive protocol in 9 cases (7 CRIM− and 2 CRIM+) and a curative protocol for high IgG antibody titer against ERT in 4 cases (1 CRIM− and 3 CRIM+). ERT was stopped because of an observed deterioration suggesting that ERT was not effective in 10 (21%)

patients at a median age of 22 [3; 141] months. Indeed, of these 10 patients, the 2 (20%) patients who had acquired walking ability lost it at a median age of 81 [78; 84] months. 2 (20%) patients had non-invasive ventilation, 2 others (20%) had a tracheostomy, and 8 (80%) had nutritional support (nasogastric tube or gastrostomy). Death occurred at a median age of 3 [0; 11] months after ERT discontinuation.

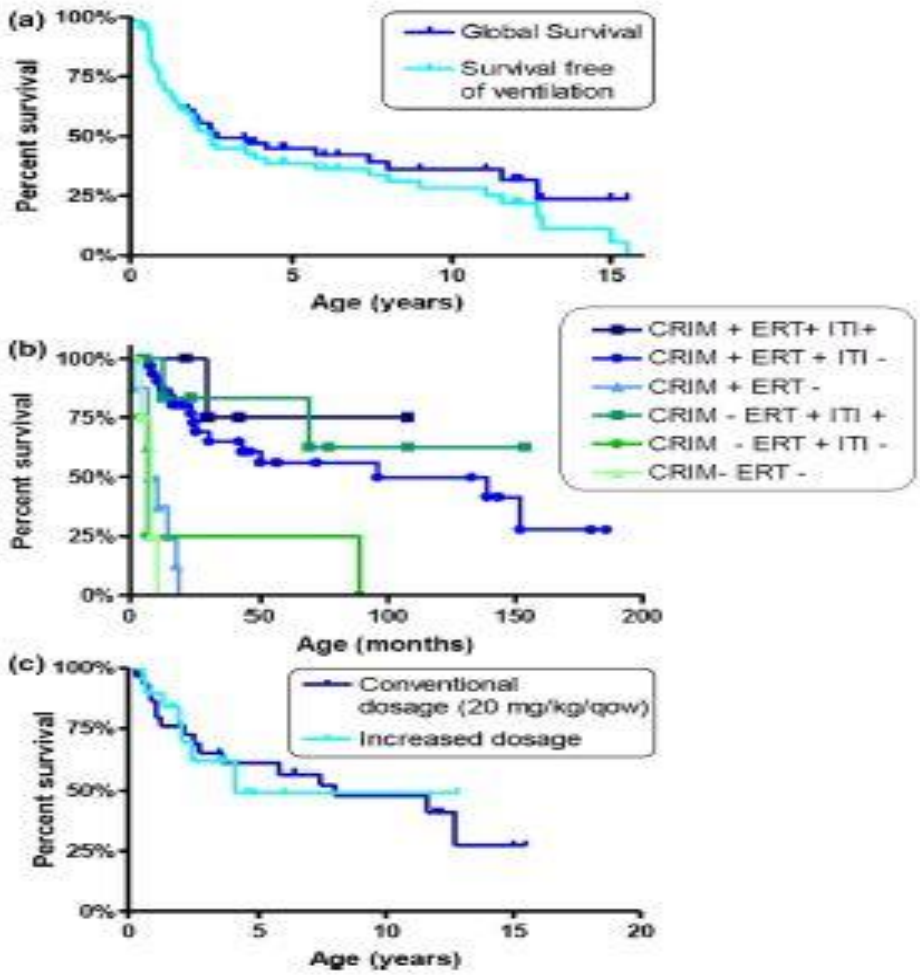

FIGURE 3 Survival analyses of the French cohort of classical infantile-onset Pompe disease (IOPD).(a) Kaplan–Meier survival curves for overall survival (dark blue line) and survival free of any ventilation (light blue line) of all the classical IOPD patients. (b) Kaplan–Meier survival curves for untreated CRIM+ or CRIM− patients (triangle, light blue and light green lines, respectively), CRIM+ or CRIM− patients treated with enzyme replacement therapy with immunomodulation (square, dark blue, or dark green lines respectively) or without immunomodulation (points, blue or green lines, respectively). (c) Kaplan–Meier survival curves for patients receiving an initial conventional dosage of 20 mg/kg/every other week (dark blue line) and patients receiving an initial increased dosage (light blue line). CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy; ITI, immune tolerance induction; qow, every other week.

Figure 3 presents survival curves according to selected factors (ventilation support, CRIM status, ERT, immunomodulation protocol, initial ERT dosage). Thirty-seven (58%) patients died during their follow-up, at a median age of 13 [1; 152] months, mostly during the first 3 years of life and after the age of 12 years. Deceased patients include all the ERT-untreated patients (n = 14) who died

prematurely (median age of 8 [1; 19] months) and 23 patients treated by ERT (who died at a median age of 25 [4; 152] months, $p < 0.01$, compared to untreated patients).

TABLE 1 Characteristics of the patients from the French cohort of classical infantile-onset Pompe disease.

Characteristics	Patients ($n = 64$)
Diagnosis	
Gender male	34 (53%)
Age at diagnosis (months)	4 [0; 12]
Clinical symptoms at diagnosis	
Cardiomyopathy	63 (100%)
Cardiac failure	25 (41%)
Hypotonia	57 (92%)
CRIM status negative	16 (26%)
Treatment	
Treated with ERT	50 (78%)
Age at first infusion (months)	4 [0; 15]
Increased dosage from initiation[a]	20 (40%)
Immunomodulation protocol	13 (27%)
Age at ITI start (months)	3 [0; 15]
Stopped ERT	10 (21%)
Follow-up and outcomes	
Age at last visit (months)	24 [1; 186]
Global survival	27 (42%)
Survival free of any ventilation	15 (23%)
Age at death (months)	13 [1; 152]
Persistent cardiomyopathy at last visit	33 (56%)
Cardiovascular medication use	25 (42%)
Non-invasive ventilation	17 (27%)
Tracheostomy and invasive ventilation	10 (16%)
Acquisition of walking ability	18 (28%)
Age of walking (months)	18 [12; 65]
Wheelchair using	13 (46%)
Electroneuromyography showing normal/myopathic/neuropathic/ myo + neuropathic patterns	3/20/2/2 (11%/74%/7%/7%)
Nasogastric tube and/or gastrostomy	34 (54%)
Age of starting enteral nutrition (months)	8 [0; 111]
Hearing loss	13 (28%)
Normal/special-needs schooling/not schooled (age >3 years)	5/13/4 (23%/59%/18%)

Note: Results are expressed as number of patients (%) or median [minimum; maximum] of available values, as appropriate.

Abbreviations: CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy; ITI, immune tolerance induction.

[a]Compared to conventional dosage of 20 mg/kg/every other week.

TABLE 2 Clinical status according to age of alive patients from the French cohort of classical infantile-onset Pompe disease treated with enzyme replacement therapy.

Age (years)	2	4	6	8	10	12	14[a]
Expected patients treated with ERT (*n*)	45	37	32	28	20	17	7
Alive patients	35 (78%)	23 (62%)	17 (53%)	15 (54%)	10 (50%)	8 (47%)	2 (29%)
Cardiomyopathy	14 (61%)	5 (33%)	4 (33%)	3 (27%)	2 (29%)	1 (13%)*	1 (50%)
Ventilated patients	8 (23%)	7 (30%)	5 (29%)	7 (47%)	7 (70%)	7 (88%)**	2 (100%)
Walking patients	15 (43%)	13 (57%)	10 (59%)	7 (47%)	4 (40%)	3 (38%)	0
Wheelchair	10 (32%)	9 (45%)	7 (54%)	9 (64%)	7 (70%)	5 (63%)	2 (100%)
Enteral nutrition	14 (41%)	8 (36%)	7 (44%)	7 (47%)	4 (40%)	3 (38%)	0

Note: Results are expressed as number of patients (%), with the percentage calculated from the number of available values, except for "alive patients" that was calculated from the total number of expected patients (dead + alive) for age and treated with ERT.

Abbreviation: ERT, enzyme replacement therapy.

*$p < 0.05$, **$p < 0.01$, 2 vs. 12 years, Fisher's exact test.

[a]Note the small number of alive patients at the age of 14 years.

Focusing on alive patients, Table 2 describes the follow-up of ERT-treated patients according to age. The percentage of patients with cardiomyopathy decreased progressively with age (from 61% at age 2 years to 13% at age 12 years, $p < 0.05$). In contrast, the use of ventilation support increased in older patients (23% at age 2 years vs. 88% at age 12 years, $p < 0.01$). The need for a wheelchair also appeared to increase with age but the difference remained not significant. At age 14 years, only two patients survived, both requiring the use of a ventilation device and wheelchair, but the small staff does not allow a strong conclusion. Overall, at the last visit (median age 24 [1; 186] months, see Table 1), cardiomyopathy persisted in 33 (56%) patients and 25 (42%) patients were receiving cardiovascular medication. Only 15 (23%) patients were alive free of any ventilation. Twelve (19%) further patients were alive but required ventilation support (invasive or not). Tracheostomy was performed in 10 (16%) patients, mostly in older patients (all except one born before 2010), at a median age of 25 [3; 126] months. Only one tracheostomy has been performed since 2014. Most patients gained motor skills and 18 (28% of the total population) were walking at a median age of 18 [12; 65] months; 5 of them lost walking ability subsequently. Thirteen (46%) patients were wheelchair-bound at a median age of 48 [41; 156] months. An electroneuromyogram (ENMG) was performed in 27 (47%) patients, showing a myopathic pattern in 20 (74%) cases, whereas it was normal, neuropathic, or neuromyopathic in 3 (11%), 2 (7%) and 2 (7%) cases, respectively. About half of the patients required nutritional support. Finally, auditory tests were performed in 46 ERT-treated patients, with hearing loss reported in 13 (28%) patients who were significantly older than the 33 other patients (median age of 88 [24; 154] vs. 24 [3; 186] months, $p < 0.01$). Most of the patients who survived more than 3 years required special-needs schooling (i.e., presence of a school life assistant or adapted schooling such as localized units for school inclusion or motor education institute).

TABLE 3 Comparison between deceased and alive patients from the French cohort of infantile-onset Pompe disease.

Characteristic	Deceased	Alive	*P* value
Patients (*N*)	37	27	
Age at diagnosis (months)	4 [0; 12]	3 [0; 10]	0.59
Cardiac failure at diagnosis	19 (54%)	6 (23%)	<0.05
CRIM status negative	10 (29%)	6 (23%)	0.77
Treated with ERT	23 (62%)	27 (100%)	0.0001
Stopped ERT	10 (48%)	0 (0%)	<0.0001
Age at last visit (months)	12 [1; 144]	56 [5; 186]	<0.0001
Persistent cardiomyopathy at last visit	26 (79%)	7 (27%)	<0.0001
Cardiac failure at last visit	15 (48%)	0 (0%)	<0.0001
Cardiovascular medication use	19 (58%)	6 (22%)	<0.01
Non-invasive ventilation	8 (22%)	9 (33%)	0.4
Age for starting non-invasive ventilation (months)	9 [6; 32]	87 [2; 132]	<0.05
Acquisition of walking ability	4 (11%)	14 (52%)	<0.001
Age of walking (months)	21 [13; 65]	16.5 [12; 25]	0.06
Loss of walking ability	3 (75%)	2 (14%)	<0.05
Nasogastric tube and/or gastrostomy	25 (69%)	9 (33%)	<0.01
Age of starting enteral nutrition (months)	7 [0; 111]	21 [2; 63]	<0.05

Note: Results are expressed as number of patients (%) or median [minimum; maximum], as appropriate.Abbreviations: CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy.

In an effort to identify risk factors for mortality, we compared deceased and alive patients (Table 3). As expected, ERT treatment improved survival (all alive patients were treated compared to only 62% of deceased patients, $p = 0.0001$) and all the patients in whom ERT was discontinued subsequently died. Cardiac involvement, at diagnosis as during follow-up, was associated with a poor prognosis. Patients who died had a higher percentage of heart failure, at diagnosis ($p < 0.05$) and at the last visit ($p < 0.0001$), with a higher number of patients with persistent cardiomyopathy ($p < 0.0001$) requiring cardiovascular medication ($p < 0.01$). The absence of walking acquisition ($p < 0.001$) and early age for starting non-invasive ventilation ($p < 0.05$) or nutritional support ($p < 0.05$) were also associated with poor prognosis. In contrast, CRIM status was not related to survival. Survival curves of CRIM+ and CRIM− patients, according to ERT and immunomodulation treatments, are presented in Figure 3b. Untreated patients, whatever their CRIM status, had a higher mortality. Likewise, CRIM− patients treated with only ERT had a high mortality rate, whereas the use of an immunomodulation protocol appeared to improve survival. Finally, CRIM+ and CRIM− patients were compared (Table 4). CRIM− patients had a severe disease course, as reflected by a younger age for starting ERT, immunomodulation protocol, and nutritional support, but their mortality rate remained unchanged compared to CRIM+ patients. Global survival seemed to be slightly better with an initial increased dosage compared to the conventional dosage (65% vs. 47%, respectively, $p = 0.25$). However, this effect was only

due to a shorter duration of follow-up for the patients with an initial increased ERT dosage, as demonstrated by survival curves (Figure 3c, $p = 0.9$).

TABLE 4 Comparison between cross-reactive immunologic material-positive (CRIM+) and CRIM-negative (CRIM−) patients from the French cohort of infantile-onset Pompe disease.

Characteristic	CRIM−	CRIM+	*P* value
Patients (*N*)	16	44	
Age at diagnosis (months)	3 [0; 8]	4 [0; 12]	0.18
Treated with ERT	12 (75%)	36 (82%)	0.72
Age at first infusion (months)	3 [0; 6]	4 [0; 15]	<0.05
Immunomodulation	8 (67%)	5 (14%)	<0.01
Age of starting immunomodulation (months)	2,5 [0; 12]	11 [2; 15]	<0.05
Died	10 (63%)	24 (55%)	0.77
Age at death (months)	8 [4; 89]	17,5 [1; 152]	0.07
Nasogastric tube and/or gastrostomy	7 (47%)	24 (55%)	0.77
Age of starting enteral nutrition (months)	3 [0; 5]	13 [2; 111]	<0.01

Note: Results are expressed as number of patients (%) or median [minimum; maximum], as appropriate.

DISCUSSION

This study reports the long-term follow-up of a large cohort of classical IOPD patients diagnosed in France since 2004. The first main result is the high mortality rate, including patients treated early with ERT, highlighting that classical IOPD remains a severe disease despite the substantial therapeutic progresses made within the last 16 years. The evolution of mortality seems to be in three phases, with a high mortality rate during the first 3 years of life (half of the patients died during this period in our study), followed by a relatively stable period from 3 to 12 years of age (mortality rate about 50%), and finally with a new increase in the mortality rate after the age of 12 years. All untreated patients died rapidly as expected, but also nearly half of the ERT-treated patients. Most of the previously published cohorts report this high mortality, especially during the first 2 or 3 years of life (about one-third of the ERT-treated patients died during this period). The mortality rate varies between studies from 34% to 83%, according to whether untreated patients were or were not considered and depending on the duration of the follow- up [8, 10, 13, 16–18]. Only the cohort of classical IOPD patients identified through newborn screening in Taiwan was reported to have a very limited mortality rate, probably due to earlier ERT initiation, but also because most of these patients exhibited the same variant with a likely attenuated phenotype [19]. The increased mortality after the age of 12 years was not reported, largely because the duration of follow-up was restricted in these previously published studies.

To identify risk factors associated with unfavorable outcomes we compared deceased and alive patients. The persistence of cardiomyopathy during follow-up and/or the presence of heart failure were highly associated with an increased risk of death. This may be partially explained by the inclusion of ERT-untreated patients who inevitably died with cardiac symptoms. However, even after exclusion of ERT-untreated patients, the presence of cardiomyopathy (14 of 21 deceased patients [67%] vs. 7 of 26 alive patients [27%], $p < 0.01$) or of heart failure (5 of 21 [24%] vs. 0 of 27, $p < 0.05$) at the last visit remained significantly higher in the group of deceased patients. Long-term improvement of cardiomyopathy and of cardiac function are major goals of ERT efficacy [20]. In our experience, the absence of improvement in cardiac symptoms with ERT is a risk factor for unfavorable outcome. Parameters related to walking ability, need of ventilation, and nutritional support were also associated with a poor prognosis.

Surprisingly CRIM-negative status did not appear to be one of the unfavorable prognosis factors in contrast to previous studies [8, 10, 13, 16, 17, 21]. In the initial scientific publications about CRIM status, a negative status was associated with a poor prognosis for survival and for ventilation-free survival, presumably related to the development of high titers of rhGAA antibodies [6]. To prevent the formation of antibodies, the use of prophylactic immune tolerance induction (ITI) before initiating ERT, with methotrexate, rituximab, and intravenous immunoglobulins in a short course over 5 weeks, has been proposed [6, 22]. The tolerance and efficacy of such an approach are proven [23]. This protocol is now routinely used for CRIM-negative IOPD babies in our country according to the 2016 French guidelines [7] and appears to improve their prognosis. Indeed, in our study, CRIM-negative patients who did not receive the ITI protocol died rapidly, whereas patients treated with ITI had a better survival, explaining why CRIM-negative status was not associated with peer prognosis.

Besides survival, a decrease in ERT efficacy appeared after the age of 6 years, with a progressive decline in motor and pulmonary functions for most of the survivors, as suggested by increasing need for ventilation and nutritional support, or wheelchair use during long-term follow up. Over the past decade, it has become increasingly evident that classical IOPD patients who initially respond well to ERT continue to have sustained cardiac benefits, but have a residual myopathy and respiratory decline that progresses despite therapy [24, 25]. The use of an increased dosage, reported in nearly half of our population (and especially in more recent patients), could contribute to a better outcome [25]. Recently, a multicenter, observational, cohort study from the European Pompe Consortium has been published assessing the effect of real-world ERT regimens on survival and walking ability in these patients. The authors observed that patients with classical IOPD treated with the high ERT dosage of 40 mg/kg/week exhibited significantly improved survival when compared with patients treated with the standard recommended ERT dosage of 20 mg/kg/every other week, suggesting that the currently registered dosage should be reconsidered [26].

The degree of weakness in classical IOPD patients has historically been attributed predominantly to muscle pathology but post mortem anatomopathological studies performed in the 1970s prior to ERT development also reported selective neuronal involvement, with the most evident signs of glycogen storage being found in the neurons of the spinal ganglia, anterior horns, and all motor nuclei of the brainstem [27]. In 2010, Burrow et al. [28] reported the case of a 2-year-old girl treated with ERT since the age of 5 months in which a severe motor neuron lesion was demonstrated at the age of 23 months, providing compelling evidence for a slowly progressive neurodegenerative process in classical IOPD patients affecting the motor neurons. This accumulation is consistent with the observation that ERT

does not effectively cross the blood–brain barrier and is suggestive of the need to develop strategies to improve drug delivery to the central nervous system (CNS) [29]. In our cohort, 47% of classical IOPD patients had ENMG. The results confirm a predominantly myopathic pattern in most of the patients, but a neuropathic involvement was also reported in four patients. In electroneuromyography, the association of spontaneous activities on needle ENMG examination and normal nerve conduction suggests a motor neuron dysfunction [28]. The presence of progressive motor neuron dysfunction could therefore favor the worsening of disease evolution in some children. Recently, the MUNIX (motor unit number index) has been shown to be an useful electrophysiological biomarker for disease progression in pediatric spinal muscular atrophy and for treatment response [30]. Korlimarla et al. [31] recently described in treated IOPD patients with longer survival, a new phenotype of CNS involvement. Neuronal losses in the brain and spinal cord with areas of gliosis are also reported which could be the cause of problems in white matter integrity, such as demyelination, observed in brain magnetic resonance imaging (MRI) scans in children with IOPD.

Deafness was recurrently reported in our cohort (13 of 46 [28%] ERT-treated classical IOPD patients who underwent auditory testing), mostly in older patients. The modified natural history compared to untreated historical controls is being better described [8, 10, 13, 16, 17, 21], with the persistence of a high frequency (from 30% to 90%) of hearing loss in IOPD patients in studies. Hearing impairment appears and persists despite ERT. This result emphasizes the need for careful monitoring of auditory function in classical IOPD patients, and the early fitting of hearing aids to protect speech and language development. In this way, auditory tests are now routinely proposed during follow-up. The most common type of hearing impairment is the sensorineural type, but conductive or mixed hearing impairment are also described [9, 13, 16, 32]. A recent study suggests that earlier initiation of ERT within 2 weeks after birth appears to contribute to an improvement in hearing function [32].

Despite improvements in knowledge and practices, the diagnosis of classical IOPD was performed at a median age of 4 months. Newborn screening can increase the efficiency of diagnoses and seems to be useful in improving the prognosis and has been developed in some countries [23] but some ethical questions remain unresolved, like the screening of late-onset forms or interpretation of unknown variants. The effects of ERT in our study are not as good as in some of the other reports in the literature with respect to survival, ventilator-free survival, and walking ability. This may be explained by the fact that: (i) our cohort was comprised exclusively of classical IOPD patients; (ii) all patients diagnosed in France were included, including those who were not treated and including those whose condition worsened with treatment; (iii) the study had a very long follow-up period; and (iv) initial doubling of the ERT dosage was not associated with a better outcome, in agreement with the European Pompe Consortium, which demonstrated a better prognosis only for a four-fold higher dosage [26].

Our study has several limitations. The management of classical IOPD patients occurs in multiple centers, with distinctive practitioners, and some disparity can occur in the examinations performed during the follow-up period. These differences are, however, balanced by the existence of the CETP, a group of experts that centralizes discussions and decisions concerning the management of all French Pompe patients, such as those about starting ERT and immunomodulation, but also about stopping ERT when the prognosis is worsening [33].

To summarize, this study reports the long-term follow-up of one of the largest cohorts of classical IOPD patients to our knowledge, excluding atypical or juvenile forms of the disease. The main results of our study were the high long-term mortality and morbidity rates, when after an initial improvement with ERT, there was a secondary decline in muscular and respiratory functions. This decrease in efficacy with time seems to be multifactorial, with factors including a restricted diffusion of ERT in muscle and CNS cells, a massive autophagy build-up, an immunological response to ERT, and other still unknown factors. This highlights the importance of developing new therapeutic approaches to target various aspects of pathogenesis and to improve long-term outcomes.

AUTHOR CONTRIBUTIONS

MT, FL, and BC designed the study. MT, CCu, DB, VG, FL, and BC were involved in the methodology. MT, CCu, AC, CH, BD, VG, SP, AB, MS, FF, PR, KM, DD, AF, CET, DE, FH, UWL, MB, LC, AK, JL, JN, GP, JR, FR, AR, GT, CV, ET, CCa, RF, and MC contributed to data collection. MT, CCu, DB, and FL were involved in data analysis. MT, CCu, AC, CH, FL, and BC participated in data interpretation. FL was responsible for the statistical analysis. MT, CCu, DB, CCa, FL, and BC wrote the first draft. CCu, FL, and BC were responsible review and editing. All co-authors have approved the final draft. All co-authors approved the data.

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CONFLICT OF INTEREST STATEMENT

In relation to the current work, M.T., A.C., C.H., and S.P. report personal fees as speakers at a conference from Sanofi Aventis France. M.T., A.C., C.H., S.P., A.B., P.R., and B.C. report support for attending meetings and/or travel from Sanofi Aventis France. A.C., A.B., F.F., and F.L. report personal fees as advisory board members from Sanofi Aventis France. R.F. reports a donation of laboratory equipment from Sanofi Genzyme. C. Cu, A.C., and C.H. report the offer of a lunch during a meeting from Sanofi Aventis France.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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