JID: NMD [m5+;January 3, 2020;21:57]

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Neuromuscular Disorders xxx (xxxx) xxx

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Discontinuation of enzyme replacement therapy in adults with Pompe disease: Evaluating the European POmpe Consortium stop criteria

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Received 13 June 2019; received in revised form 17 October 2019; accepted 18 November 2019
Available online xxx

Abstract

Enzyme replacement therapy for Pompe disease received market authorization in 2006. To implement this costly treatment in the Netherlands in the most sensible way, a multidisciplinary expert committee was installed. We evaluated decision making in adult patients in relation to the European POmpe Consortium stop criteria. Of 125 adult Pompe patients, 111 started treatment; subsequently treatment stopped in 24 patients (21%). In 10 patients, treatment was discontinued for medical or personal reasons, as defined in the six stop criteria (median treatment duration: 2.1 years, range: 0.3–14.6 years). Three of these patients continued follow-up (follow-up: 1.3–8.0 years), these patients did not display a more rapid decline after discontinuation. In 14 of 24 patients, therapy ended at time of death. In 10 patients death was related to Pompe disease (median treatment duration: 7.2 years, range: 0.4–10.3 years). All 10 patients were severely affected at start of treatment, treatment had elicited positive effects in eight. The European POmpe Consortium guidelines worked well in decision making on stopping treatment. However, (re)evaluation of the rationale for continuation of treatment in advanced disease stage is not addressed. We suggest to add this to the treatment evaluation and to handle treatment decisions in a multidisciplinary expert team.

Keywords: Pompe disease; Enzyme replacement therapy; Adult patients; Treatment guidelines; Treatment discontinuation; Start and stop criteria.

1. Introduction

Pompe disease (glycogen storage disease type II or acid maltase deficiency, OMIM ID: 232300) is a rare inherited metabolic and neuromuscular disorder, which presents as a clinical spectrum, ranging from the rapidly progressive classic infantile form, to more slowly progressive phenotypes in children and adults [1-5]. Enzyme replacement therapy (ERT) with alglucosidase alfa for Pompe disease, was in 2006 the first therapy for a neuromuscular disorder that received market authorization. In adults, ERT has shown to improve or stabilize muscle strength, pulmonary function and daily life activities, and has resulted in increased survival [6–13].

In the Netherlands, all patients with Pompe disease are referred to the Center for Lysosomal and Metabolic diseases of the Erasmus University Medical Center, the national designated center of expertise for Pompe disease. To implement the costly therapy in our country in the most sensible way, a multidisciplinary expert committee was installed to decide on starting and stopping of ERT. Our center contributed to the realization of the European POmpe Consortium (EPOC) consensus recommendation for starting and stopping ERT in 2017, and implemented these criteria in our expert committee consultation [14]. The consensus

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https://doi.org/10.1016/j.nmd.2019.11.007

guidelines imply that all patients undergo a fixed battery of assessments to evaluate the effects of the therapy [15]. Reasons to consider discontinuation of ERT comprise infusion associated reactions (IARs), high neutralizing antibody titers, non-compliance to the treatment and/or assessment protocol, the patient's wish to stop ERT, other life-threatening illness or the lack of any clinical stabilization or improvement in the first 2 years of treatment. The guidelines advise to consider restart of ERT if a patient deteriorates faster after ERT discontinuation than during ERT.

In our experience, decisions regarding stopping ERT are often difficult, even when the EPOC stop criteria are met, particularly because ERT is currently the only available treatment for Pompe disease. Moreover, since the effects of stopping ERT on disease course are largely unknown, both physicians and patients usually fear for a relatively rapid decline after discontinuation of ERT, particularly when treatment has been effective.

In this study, we specifically focus on adult patients who discontinued therapy and evaluate the motives, clinical course, and the applicability of the EPOC treatment guidelines on stopping ERT. Furthermore, to gain insight in treatment decisions in patients with advanced Pompe disease or comorbidity, we evaluate the clinical course, treatment effect and causes of death of patients in whom ERT ended at time of death, with special regards to whether we should have considered discontinuation of ERT earlier in the course of disease in some. We aim to address important clinical dilemmas regarding discontinuation of ERT in adults with Pompe disease, with the intention to add to the use and optimization of the present EPOC treatment guidelines.

2. Methods

2.1. Study design

We analyzed data of patients who participated in a prospective, cohort study which includes all patients with Pompe disease in the Netherlands, which started in 2004. We also included patients who started to receive ERT even before that. The Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam serves as the single reference center for Pompe patients with a confirmed diagnosis. The diagnosis was confirmed by enzyme analysis in leukocytes and/or fibroblasts and by mutation analysis. Patients were included in the current study if they discontinued ERT for any reason, between start of ERT and January 1st 2017. All patients gave their written informed consent.

2.2. Procedures

Clinical assessments were performed on a regular basis (every 3–6 months) and included the following parameters:

2.2.1. Skeletal muscle strength and muscle function

Skeletal muscle strength was measured by manual muscle testing using the Medical Research Council (MRC) grading scale (range 0–5) [16,17]. Muscle groups tested comprise the neck flexors, neck extensors, shoulder abductors, shoulder adductors, shoulder exorotators, shoulder endorotators, elbow flexors, elbow extensors, hip flexors, hip extensors, hip abductors, hip adductors, knee flexors and knee extensors.

Muscle function was assessed using the Quick Motor Function Test (QMFT), which evaluates 16 motor skills that are specifically challenging for patients with Pompe disease [18]. This was recorded on video. For the MRC and QMFT, sum-scores were derived as described previously [19]. If values for three or more items were missing, no sum-score was calculated. The use of a wheelchair was registered at each visit.

2.2.2. Pulmonary function

Forced vital capacity (FVC) was measured in upright and supine positions according to ATS/ERS standards. Results were expressed as a percentage of the predicted normal values [20]. The use of mechanical ventilation was registered at each visit.

2.3. ERT multidisciplinary expert committee

With the reimbursement of ERT in the Netherlands in 2006, a multidisciplinary expert committee was installed at Erasmus MC, to decide on starting and stopping of ERT in patients with Pompe disease. The team comprises various medical experts (i.e. pediatricians, neurologists, internists), a hospital pharmacist, a medical ethicist, a molecular biologist, research physicians (Ph.D. students), and nurses. The committee has an independent chair. Every newly diagnosed patient with Pompe disease is evaluated by this team, to determine whether ERT should be started. Decisions are based on careful consideration of the patients' clinical condition, comorbidity and ability to comply to the treatment protocol, following the EPOC guidelines [14]. For treated patients, the effects of ERT are evaluated after the first two years of treatment by evaluating a set of outcome measures (MRC, FVC, QMFT), including video recordings of the patient performing the QMFT. The committee also advises on possible discontinuation of ERT. Reasons to advise on discontinuation are (lack of) efficacy, new comorbidity that largely interferes with the effects of ERT, high neutralizing antibody titers or infusion associated reactions.

3. Results

In total, 125 adult patients with Pompe disease were evaluated and included in the ongoing study. Fig. 1 shows an overview of the study population. In 111 of 125 (88.8%) patients ERT was started. Of this group, 24 patients stopped receiving ERT (21.6%) and qualified for the current analyses. In 10/24 patients treatment was discontinued for medical or

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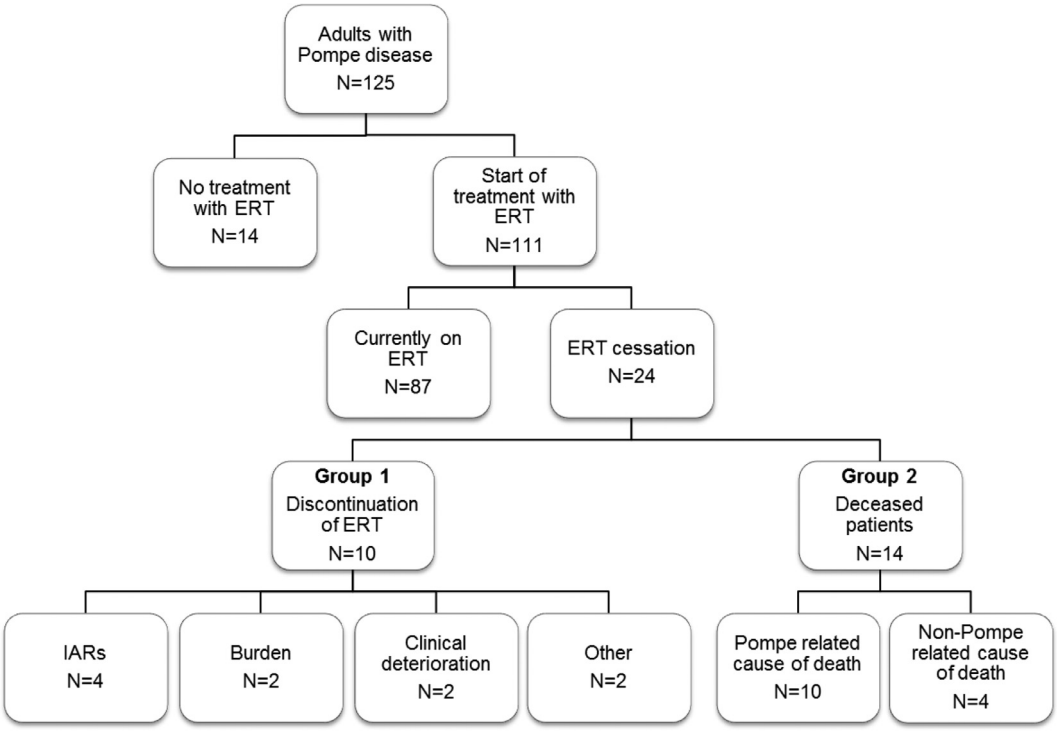

Fig. 1. Flowchart of the study population.
Overview of 125 adult Pompe patients participating in our nationwide, prospective, cohort study. *N*: number of patients; ERT: enzyme replacement therapy; IARs: infusion associated reactions.

Table 1
Applicability of the European POmpe consortium (EPOC) criteria for stopping ERT on the patients who discontinued ERT in our cohort.

EPOC stop criteria	*N* in our cohort
1. The patient suffers from severe infusion-associated reactions that cannot be managed properly.	4
2. High antibody titers are detected that significantly counteract the effect of ERT.	1
3. The patient wishes to stop ERT.	2
4. The patient does not comply with regular infusions or yearly clinical assessments.	1
5. The patient has another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate.	1
6. There is no indication that skeletal muscle function and/or respiratory function have stabilized or improved in the first 2 years after start of treatment, as assessed using clinical assessments.	1

ERT: enzyme replacement therapy; *N*: number of patients.

personal reasons (group 1). In 14/24 patients, ERT ended when the patient died (group 2).

3.1. Group 1: reasons for discontinuation of ERT for medical or personal reasons

In Table 1, the reasons for discontinuation of ERT for the patients in our cohort are summarized, listed according to the six EPOC stop criteria. In four patients (3.6% of all treated patients), ERT was discontinued because of infusion associated reactions (IARs) (stop criterion 1). Usually, IARs can be managed by decelerating the infusion schedule and/or starting pre-medication with clemastine and hydrocortisone. However, in these four patients, IAR symptoms and/or side effects of pre-medication remained unacceptable for the patient and therefore ERT was discontinued. Most frequent IARs were hyperthermia/fever and chills, (generalized) exanthema, hypertension and chest pain. In one patient ERT was discontinued because high antibodies that counteracted the effect of ERT were detected (stop criterion 2) [21]. Two patients experienced the burden of the treatment as too high and requested to stop ERT, after 3 months and 5.9 years of treatment (stop criterion 3). In one patient we decided to discontinue ERT after 9 months, because of non-compliance to the treatment protocol (stop criterion 4). In one patient ERT was stopped because treatment for B-cell lymphoma was started (stop criterion 5). One patient discontinued ERT because of deterioration of clinical condition despite therapy (stop criterion 6). The characteristics of these 10 patients are summarized in Table 2 (Group 1). Median treatment duration was 2.1 years (range 0.3–14.6 years).

3.1.1. Group 1: disease course after discontinuation of ERT

In seven patients, no follow up data after discontinuation of ERT were available. This was either because patients chose to stop clinical assessments after discontinuation, or because the patient's condition hampered clinical assessments. The disease course in these seven patients is shown in Fig. 2(A). In four patients (Patients 1a, 1c, 1e and 1g) ERT had been effective, improving or stabilizing motor and/or pulmonary

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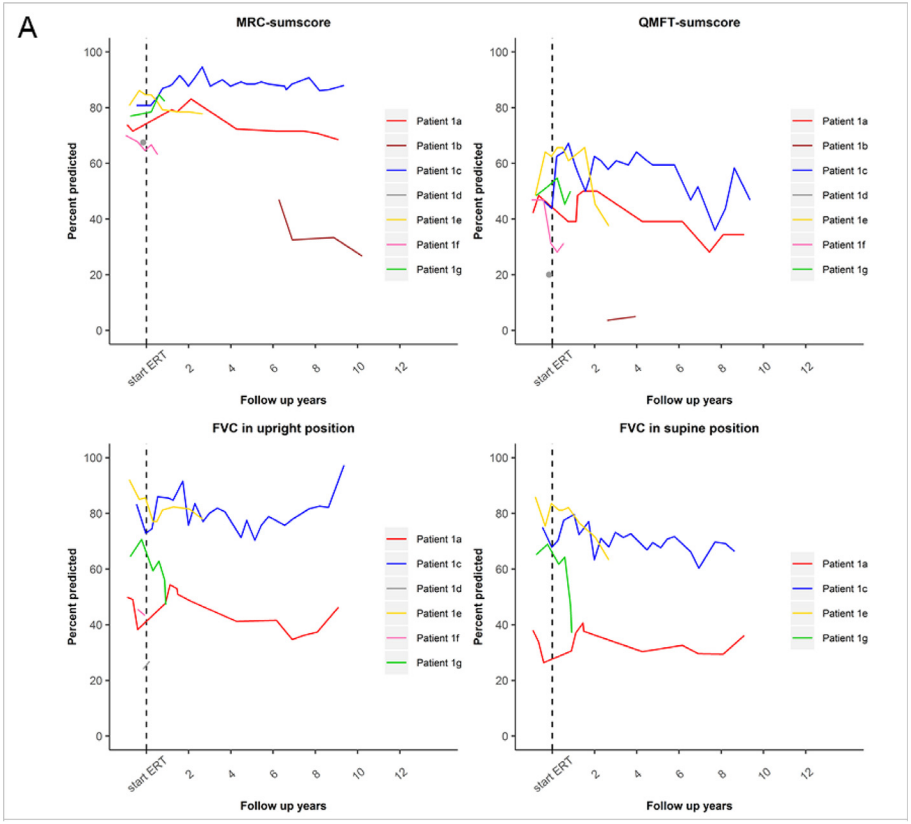
A
MRC-sumscore
QMFT-sumscore
FVC in upright position
FVC in supine position
Percent predicted
Follow up years
start ERT
Patient 1a
Patient 1b
Patient 1c
Patient 1d
Patient 1e
Patient 1f
Patient 1g

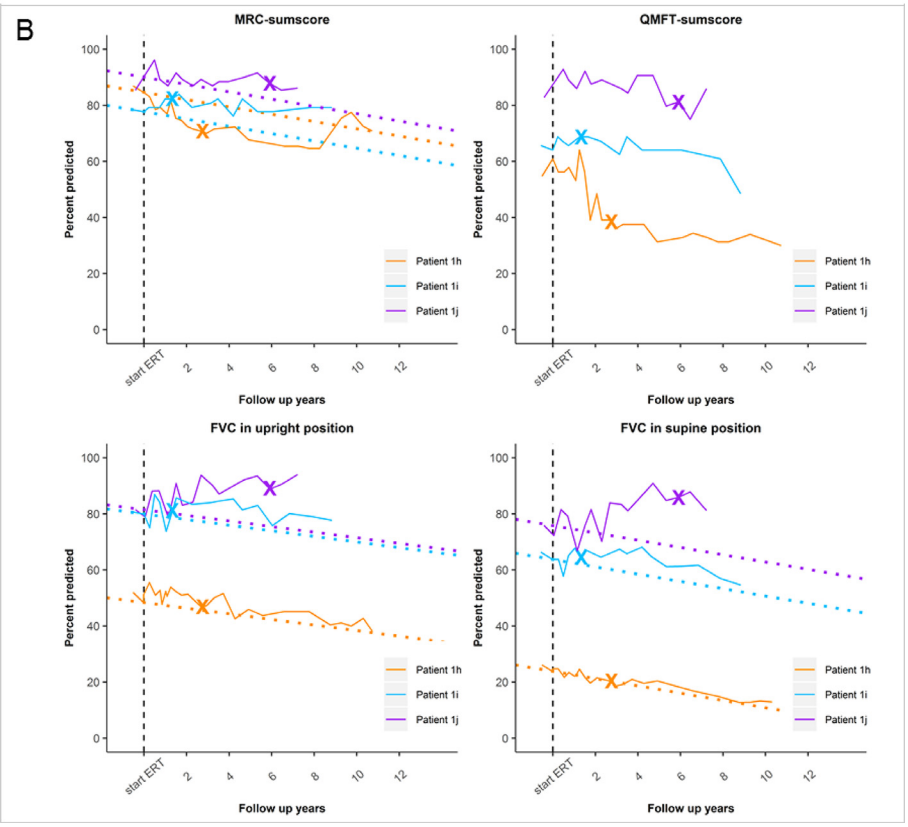
B
MRC-sumscore
QMFT-sumscore
FVC in upright position
FVC in supine position
Percent predicted
Follow up years
start ERT
Patient 1h
Patient 1i
Patient 1j

Table 2
Patient characteristics.

	Group 1	Group 2	
	Discontinuation of ERT ($N = 10$)	Deceased patients ($N = 14$)	
		Pompe related (N=10)	*Non-Pompe related (N=4)*
Gender, male *N* (%)	5 (50)	10 (100)	2 (50)
Current age in years	52.6 (40.8–83.5)[a]	–	–
Age at death in years	45.9 (30.7–56.2)[b]	65.4 (51.8–77.7)	69.1 (62.0–74.8)
Follow up time in years	7.1 (0.7–11.7)	7.2 (0.4–10.3)	3.8 (1.3–6.0)
Age at start of ERT	42.7 (28.7–74.0)	56.5 (51.0–76.0)	66.0 (61.0–70.0)
Disease duration at start of ERT in years	11.5 (5.3–29.1)	27.3 (15.6–46.7)	39.4 (30.5–40.0)
Treatment duration in years	2.1 (0.3–14.6)	7.2 (0.4–10.3)	2.7 (0.2–4.4)
Disability at start of ERT, *N* (%)			
No wheelchair or mechanical ventilation	4 (40)	1 (10)	1 (25)
Wheelchair use	4 (40)	–	1 (25)
Ventilation use	–	–	–
Both use of wheelchair and ventilation	2 (20)	9 (90)	2 (50)

All data are median (range) unless otherwise specified. *N*: number of patients; ERT: enzyme replacement therapy.
[a] $N = 7$, other patients deceased.
[b] $N = 3$, patients died 1.0–3.3 years after discontinuation of ERT.

function. Patient 1b deteriorated despite ERT. Two patients were treated too short to determine the effects of ERT (Patients 1d and 1f). Three patients (Patients 1d, 1e and 1f) died 1.0–3.3 years after discontinuation of ERT. Their median age at death was 45.9 years (range 30.7–56.2 years), causes of death were respiratory insufficiency, autoimmune hepatitis and lymphoma.

Three patients continued follow-up after discontinuation of ERT (1.3–8.0 years), their disease course is shown in Fig. 2(B) (Patients 1h, 1i, and 1j). Patient 1h displayed high sustained antibody titers that counteracted the effect of treatment, explaining the observed treatment failure and IARs [21]. Patient 1i showed a stable disease course during treatment, but had to discontinue ERT because of unmanageable IARs. Patient 1j displayed stabilization of motor function and improvement of pulmonary function, but requested to stop because of the burden of the treatment. Individual natural disease progression in these three patients could not be estimated due to limited data on disease course prior to treatment with ERT. Previous studies on natural disease progression at group level in our cohort showed an estimated yearly decline in pulmonary function (FVC) in sitting and supine position of 1.0% and 1.3%, and in muscle strength (MRC) of 1.3% [22]. For the QMFT, no estimated yearly decline was calculated previously. We compared the disease course after treatment cessation in these three specific patients with estimated natural progression rates and observed a stable disease course, or a slow decline similar to the estimated progression rate. No unexpected (rapid) decline in any of the outcome measures was observed in these patients.

3.2. Group 2: deceased patients

In 14 patients, treatment with ERT ended when the patient died. We distinguished patients with a Pompe related cause of death, and patients with causes of death probably not related to Pompe disease. The characteristics of these patients, are summarized in Table 2 (Group 2).

In 10 of 14 deceased patients (71.4%) the cause of death was, certainly or most likely, related to Pompe disease. All 10 patients were male. Their disease history and causes of death are shown in the lower part of Fig. 3 (Patients 2a–2j). Nine of these 10 patients were already wheelchair and ventilator dependent when ERT was started (shortly after reimbursement in 2006). The duration of treatment with ERT varied widely from 0.4 to 10.3 years. The clinical course of these patients can be found in the Appendix. Eight patients were treated for more than 2 years, all showed improvement or stabilization of at least one outcome measure (MRC, FVC and/or QMFT). The most common cause of death was acute-on-chronic respiratory insufficiency ($n = 7$). Five of these patients were dependent on invasive ventilation, in most patients an obstruction or unintended disconnection of the

Fig. 2. Clinical course of patients who discontinued ERT.
Clinical course of patients who discontinued ERT without follow up data after discontinuation (A) and clinical course of patients who discontinued ERT with available follow up data after discontinuation (B). Each line represents an individual patient. For each outcome measure, only the patients of whom data were available are depicted. All outcome measures are expressed as percentages of predicted normal values. The *X* depicts the moment of discontinuation of ERT for each individual patient. The dotted lines indicate estimated natural progression rate at group level [22]. The reasons for discontinuation of ERT in these patients were the following: clinical deterioration and IARs in the presence of high sustained antibody titers (Patient 1h), IARs (Patient 1i) and burden of treatment (Patient 1j). ERT: Enzyme Replacement Therapy; MRC: Medical Research Council; FVC: Forced Vital Capacity; QMFT: Quick Motor Function Test.

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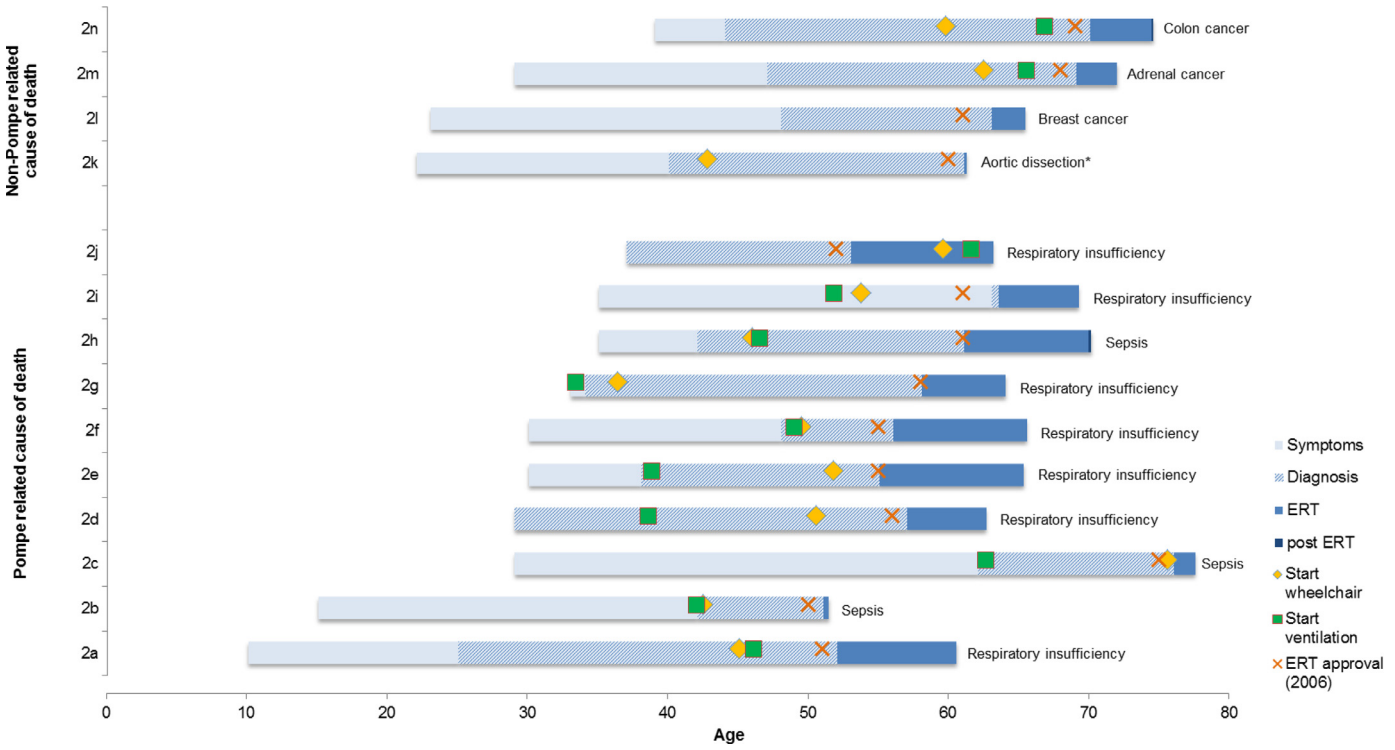

Fig. 3. Pompe disease history of deceased patients.
Each bar represents an individual patient, including cause of death. The lower part shows the patients who (most likely) deceased as a consequence of Pompe disease (Patients 2a–2j). In the upper part, the patients who did not decease as a consequence of Pompe disease are displayed (Patients 2k–2n). * Arterial dissection has been related to storage of glycogen in smooth muscle cells of the arterial wall. Therefore it cannot be ruled out that the aortic dissection was related to Pompe disease [23]. ERT: enzyme replacement therapy.

tracheal tube caused acute respiratory failure. Three patients died from sepsis, caused by severe decubitus as a result of immobilization, which we considered a lethal complication of Pompe disease. Median age at death was 65.4 years (range 51.8–77.7 years).

Four patients deceased from causes other than Pompe disease. The characteristics of these patients are shown in Table 2. The upper part of Fig. 3 shows the Pompe disease history and causes of death of these patients (Patients 2k–2n). Three patients died from malignancies (colon cancer, adrenal cancer and breast cancer). Median age at death was 69.1 years. Median duration of treatment was 2.7 years (range 0.2–4.4). The clinical course of these patients is shown in the Appendix. All patients showed a good response to ERT (stabilization or improvement of motor and/or respiratory function).

4. Discussion

In our study, all 10 of 111 treated patients who discontinued ERT met at least one of the EPOC stop criteria, indicating that the current EPOC guidelines work well in decision making on stopping ERT. Concerns about disease progression arise when discontinuation of ERT has to be considered for specific reasons (i.e. IARs, serious comorbidity), particularly when treatment has been effective. Long-term follow-up data after discontinuation of ERT were available of three patients in our cohort (follow-up: 1.3–8.0 years), in these patients a rapid decline after discontinuation was not observed. A Swiss study addresses the effect of temporary discontinuation of ERT in seven Pompe disease who had to stop ERT due to reimbursement issues [24]. In these patients, duration of treatment (3.1–61.1 months) and duration of treatment cessation (3.1–59.3 months) were quite variable, hampering direct comparison with the three patients who discontinued ERT in our cohort. The FVC rate of decline during cessation in the Swiss patients varied from −0.3 to −2.0% per month (median −1.4%). Muscle strength (MRC) did not decline significantly, although 6MWT did. Natural disease progression in our cohort is estimated −1.0% per year for FVC in upright position and −1.3% per year for MRC. The decline reported in the Swiss patients will at least in part represent natural disease progression, but to which extent remains unknown, as natural course data of these patients are not reported. Interestingly, clinical symptoms stabilized or improved after restarting ERT, also during long term follow up (36 months) [25]. This underlines the note in the EPOC stop criteria that restarting of ERT can be considered if the disease deteriorates faster after stopping than during treatment. Another study described four patients who discontinued ERT due to fatigue, inefficacy of ERT and incompliance, reporting a stable disease course after treatment cessation (with unknown follow up) [26]. This study did not refer to expected natural disease course either.

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In 14 patients, treatment ended at time of death, 10 of these patients died as a consequence of Pompe disease. In the majority of these patients, ERT was continued until death. We therefore evaluated treatment effect in these patients, with special regards to whether we should have considered discontinuation of ERT earlier in the course of these severely affected patients. All 10 patients who deceased as a consequence of Pompe disease started ERT shortly after reimbursement in 2006, when already being in an advanced stage of the disease (Fig. 3). Eight patients displayed improvement or stabilization of motor and/or respiratory function after start of ERT. Our findings support the previously reported beneficial effect of ERT in advanced Pompe disease and the EPOC recommendation that ERT can be started also in severely affected patients [27,28].

Sudden death from acute-on-chronic respiratory failure was reported in the majority ($n = 7$) of the patients who died from Pompe disease. Since these patients showed a positive response to ERT, there has never been a reason to consider discontinuation of ERT earlier in the course of disease. However, in our cohort one patient clinically deteriorated during ERT, which restrained him to visit our clinic for almost 18 months. Since this patient could not comply to yearly clinical assessments anymore (EPOC stop criterion 4), we could have decided to discontinue ERT earlier in this patient.

The EPOC consensus states that if there is no effect of ERT after the first two years of treatment, ERT in principle should be discontinued (stop criterion 6). In our practice, a growing number of patients is on ERT well over two years, also in a more advanced disease stage. We advise (re)evaluation of the efficacy of and rationale for continuation of ERT during long-term treatment, particularly in patients in an advanced stage of the disease. In the current EPOC guideline, start criterion 5 ("The patient should have residual skeletal and respiratory muscle function which is considered functionally relevant and clinically important for the patient to maintain or improve") aims to refrain from starting ERT in severely affected patients. However, potential discontinuation of ERT in severely affected patients during long-term treatment is not addressed. To implement this re-evaluation, we propose to consider to stop ERT in a patient who has insufficient residual skeletal and respiratory function left to be functionally relevant.

Our multidisciplinary approach in decision making on starting and stopping ERT has several advantages. Since the majority of these experts do not have a direct relationship with the patient regarding the prescription of ERT, this allows an objective process of treatment decision making. The multidisciplinary basis of the team ensures careful consideration of all relevant clinical, pharmacological, biological and ethical aspects in decision making in every patient and justifies the handling of this costly therapy to society.

The strength of our study is the standardized follow up of a large cohort of patients over a long period of time. Moreover, our population encompasses all known adults with a confirmed diagnosis of Pompe disease in the Netherlands. The most important limitation is the small number of patients of whom long term follow up data after discontinuation of ERT were available.

Our study evaluates our long-standing experience in treating adults with Pompe disease, focusing on decision making in stopping ERT. In three patients, who discontinued ERT in accordance with the stop criteria, we did not observe a more rapid decline after treatment discontinuation, which is often a concern of both patients and physicians. However, as the number of patients with long-term follow-up data after discontinuation of ERT was small, additional studies are needed. In general, the current EPOC guidelines work well in decision making on stopping ERT. However, (re)evaluation of the rationale for continuation of ERT in (far) advanced disease stage is not addressed in the current criteria. We recommend to handle treatment decisions in a multidisciplinary expert team, to ensure objective and careful consideration of all relevant medical and non-medical aspects of the disease and its treatment, including quality of life, in every single patient.

Erasmus MC Pompe expert committee

W.L. van der Pol (Chair), E. Brusse, I.A.M. Ditters, L. Harlaar, M.J. Hoogendijk-Boon, H.H. Huidekoper, E.J.O. Kompanje, A. Oskam, W.W.M. Pijnappel, B.J. Sibbles, J.J.A. van den Dorpel, N.A.M.E. van der Beek, J.M.P. van der Hout, H. van der Kuy, A.T. van der Ploeg, P.A. van Doorn, H.A. van Kooten, A.G. Vulto, M.A.E.M. Wagenmakers.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.11.007.

References

[1] van der Ploeg AT, Reuser AJ. Pompe's disease. Lancet 2008;372(9646):1342–53.
[2] van den Hout HM, Hop W, van Diggelen OP, Smeitink JA, Smit GP, Poll-The BT, et al. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. Pediatrics 2003;112(2):332–40.
[3] van Capelle CI, van der Meijden JC, van den Hout JM, Jaeken J, Baethmann M, Voit T, et al. Childhood Pompe disease: clinical spectrum and genotype in 31 patients. Orphanet J Rare Dis 2016;11(1):65.
[4] Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, Corzo D, et al. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. J Pediatr 2006;148(5):671–6.
[5] Muller-Felber W, Horvath R, Gempel K, Podskarbi T, Shin Y, Pongratz D, et al. Late onset Pompe disease: clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. Neuromuscul Disord 2007;17(9–10):698–706.
[6] van Capelle CI, van der Beek NA, Hagemans ML, Arts WF, Hop WC, Lee P, et al. Effect of enzyme therapy in juvenile patients with Pompe disease: a three-year open-label study. Neuromuscul Disord 2010;20(12):775–82.
[7] Strothotte S, Strigl-Pill N, Grunert B, Kornblum C, Eger K, Wessig C, et al. Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial. J Neurol 2010;257(1):91–7.

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[8] van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med 2010;362(15):1396–406.
[9] Gungor D, Kruijshaar ME, Plug I, Rizopoulos D, Kanters TA, Wens SC, 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. J Inherit Metab Dis 2016;39(2):253–60.
[10] Kuperus E, Kruijshaar ME, Wens SCA, de Vries JM, Favejee MM, van der Meijden JC, et al. Long-term benefit of enzyme replacement therapy in Pompe disease: a 5-year prospective study. Neurology 2017;89(23):2365–73.
[11] Gungor D, Kruijshaar ME, Plug I, D'Agostino RB, Hagemans ML, van Doorn PA, et al. Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study. Orphanet J Rare Dis 2013;8:49.
[12] Toscano A, Schoser B. Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review. J Neurol 2013;260(4):951–9.
[13] Schoser B, Stewart A, Kanters S, Hamed A, Jansen J, Chan K, et al. Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis. J Neurol 2017;264(4):621–30.
[14] van der Ploeg AT, Kruijshaar ME, Toscano A, Laforet P, Angelini C, Lachmann RH, et al. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. Eur J Neurol 2017;24(6):768–e31.
[15] Vill K, Schessl J, Teusch V, Schroeder S, Blaschek A, Schoser B, et al. Muscle ultrasound in classic infantile and adult Pompe disease: a useful screening tool in adults but not in infants. Neuromuscul Disord 2015;25(2):120–6.
[16] van der Ploeg RJ, Oosterhuis HJ, Reuvekamp J. Measuring muscle strength. J Neurol 1984;231(4):200–3.
[17] van der Ploeg RJ, Fidler V, Oosterhuis HJ. Hand-held myometry: reference values. J Neurol Neurosurg Psychiatry 1991;54(3):244–7.
[18] van Capelle CI, van der Beek NA, de Vries JM, van Doorn PA, Duivenvoorden HJ, Leshner RT, et al. The quick motor function test: a new tool to rate clinical severity and motor function in Pompe patients. J Inherit Metab Dis 2012;35(2):317–23.
[19] de Vries JM, van der Beek NA, Hop WC, Karstens FP, Wokke JH, de Visser M, et al. Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: an open-label single-center study. Orphanet J Rare Dis 2012;7:73.
[20] Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40(6):1324–43.
[21] de Vries JM, van der Beek NA, Kroos MA, Ozkan L, van Doorn PA, Richards SM, et al. High antibody titer in an adult with Pompe disease affects treatment with alglucosidase alfa. Mol Genet Metab 2010;101(4):338–45.
[22] van der Beek NA, de Vries JM, Hagemans ML, Hop WC, Kroos MA, Wokke JH, et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. Orphanet J Rare Dis 2012;7:88.
[23] El-Gharbawy AH, Bhat G, Murillo JE, Thurberg BL, Kampmann C, Mengel KE, et al. Expanding the clinical spectrum of late-onset Pompe disease: dilated arteriopathy involving the thoracic aorta, a novel vascular phenotype uncovered. Mol Genet Metab 2011;103(4):362–6.
[24] Hundsberger T, Rosler KM, Findling O. Cessation and resuming of alglucosidase alfa in Pompe disease: a retrospective analysis. J Neurol 2014;261(9):1684–90.
[25] Scheidegger O, Leupold D, Sauter R, Findling O, Rosler KM, Hundsberger T. 36-Months follow-up assessment after cessation and resuming of enzyme replacement therapy in late onset Pompe disease: data from the Swiss Pompe Registry. J Neurol 2018;265(12):2783–8.
[26] Stepien KM, Hendriksz CJ, Roberts M, Sharma R. Observational clinical study of 22 adult-onset Pompe disease patients undergoing enzyme replacement therapy over 5years. Mol Genet Metab 2016;117(4):413–18.
[27] Papadopoulos C, Orlikowski D, Prigent H, Lacour A, Tard C, Furby A, et al. Effect of enzyme replacement therapy with alglucosidase alfa (Myozyme(R)) in 12 patients with advanced late-onset Pompe disease. Mol Genet Metab 2017.
[28] Orlikowski D, Pellegrini N, Prigent H, Laforet P, Carlier R, Carlier P, et al. Recombinant human acid alpha-glucosidase (rhGAA) in adult patients with severe respiratory failure due to Pompe disease. Neuromuscul Disord 2011;21(7):477–82.

Please cite this article as: H.A. van Kooten, L. Harlaar and N.A.M.E. van der Beek et al., Discontinuation of enzyme replacement therapy in adults with Pompe disease: Evaluating the European POmpe Consortium stop criteria, Neuromuscular Disorders, https://doi.org/10.1016/j.nmd.2019.11.007