



Home-Based Infusion of Alglucosidase Alfa Can Safely be Implemented in Adults with Late-Onset Pompe Disease: Lessons Learned from 18,380 Infusions

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Abstract

Background Enzyme replacement therapy (ERT) with alglucosidase alfa is the treatment for patients with Pompe disease, a hereditary metabolic myopathy. Home-based ERT is unavailable in many countries because of the boxed warning alglucosidase alfa received due to the risk of infusion-associated reactions (IARs). Since 2008, home infusions have been provided in The Netherlands.

Objectives This study aimed to provide an overview of our experience with home-based infusions with alglucosidase alfa in adult Pompe patients, focusing on safety, including management of IARs.

Method We analysed infusion data and IARs from adult patients starting ERT between 1999 and 2018. ERT was initially given in the hospital during the first year. Patients were eligible for home treatment if they were without IARs for multiple consecutive infusions and if a trained home nurse, with on-call back-up by a doctor, was available. The healthcare providers graded IARs.

Results We analysed data on 18,380 infusions with alglucosidase alfa in 121 adult patients; 4961 infusions (27.0%) were given in hospital and 13,419 (73.0%) were given at home. IARs occurred in 144 (2.9%) hospital infusions and 113 (0.8%) home infusions; 115 (79.9% of 144) IARs in hospital and 104 (92.0% of 113) IARs at home were mild, 25 IARs (17.4%) in hospital and 8 IARs (7.1%) at home were moderate, and very few severe IARs occurred (4 IARs in hospital [2.8%] and 1 IAR at home [0.9%]). Only one IAR in the home situation required immediate clinical evaluation in the hospital.

Conclusion Given the small numbers of IARs that occurred with the home infusions, of which only one was severe, we conclude that alglucosidase alfa can be administered safely in the home situation, provided the appropriate infrastructure is present.

Key Points

Alglucosidase alfa can be administered safely in the home situation in adults with late-onset Pompe disease, since very few infusion-associated reactions (IARs) occur and the majority of IARs are mild.

Enzyme replacement therapy can be safely provided at home if a patient is without IARs for multiple consecutive infusions, if a home-infusion protocol describing infusion and IAR management is in place, and if a trained home nurse with on-call back-up by a doctor is available.

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1 Introduction

Enzyme replacement therapy (ERT) with intravenously administered alglucosidase alfa (recombinant human alfa-glucosidase [rhGAA]) is the treatment for patients with Pompe disease (OMIM #232300), a metabolic myopathy due to the deficiency of the lysosomal enzyme alfa-glucosidase (GAA; EC 3.2.1.20) [1]. The clinical spectrum of Pompe disease is broad and continuous. A differentiation is made between the classic infantile form of the disease and late-onset Pompe disease (LOPD) or non-classic Pompe disease. Classic infantile Pompe patients have a severe enzyme deficiency with virtually no residual activity of alfa-glucosidase, leading to severe hypotonia and a hypertrophic cardiomyopathy with a fast progressive course of disease [2]. Patients with LOPD have a higher residual enzyme activity than those with classic infantile patients, leading to axial and limb girdle as well as respiratory muscle weakness. LOPD patients can have a disease onset at any age and do not have a hypertrophic cardiomyopathy. ERT has positively altered the disease course for most Pompe patients, improving both motor and pulmonary function [1, 3]. Nevertheless, patients' quality of life is negatively impacted by the time-consuming biweekly infusions [4] taking several hours. Home infusions provide more autonomy and flexibility for the patient [5] and are therefore a more patient-centred approach to ERT. However, when rhGAA was approved for the treatment of Pompe disease in 2006, home infusions were not included in the summary of product characteristics (SmPC), and the drug received a boxed warning from the US FDA due to the risk of anaphylaxis, severe allergic and immune-mediated reactions, and risk of cardiorespiratory failure [6]. A similar risk of severe IARs was included in the European SmPC [7]. These warnings have hampered the introduction of home infusion therapy with alglucosidase alfa worldwide.

The coronavirus disease 2019 (COVID-19) pandemic has prompted the need for home-based ERT. Patients have missed their alglucosidase alfa infusions in the hospital due to the downscaling of regular healthcare, resulting in deterioration of clinical status, as reported in some patients [8, 9]. Even when hospital-based infusions were offered, 60% of patients with lysosomal storage disorders (LSDs) refused to come to the hospital due to fear of acquiring COVID-19 [10]. In addition, fear of infection and reorganisation of infusion centres have led to patients missing infusions with ERT [10, 11]. Of patients with an inborn error of metabolism who reported a change to their treatment during the COVID-19 pandemic, 50% switched to home therapy [12]. Reliance on hospital infusion may increase the risk of contracting COVID-19, and switching

to home therapy may mitigate this risk [13]. Thus, the pandemic has only made the need for home-based therapy for Pompe patients more urgent.

Since 1999, ERT with alglucosidase alfa has been provided at the Center for Lysosomal and Metabolic Diseases, Erasmus MC, the national referral centre for Pompe disease in The Netherlands. The Netherlands was the first country to implement home infusion with alglucosidase alfa. Since 2008, Pompe patients can receive their infusions at home after 1 year of uncomplicated treatment in the hospital. In this paper, we describe our experience with home-based infusions with alglucosidase alfa in adult Pompe patients, focusing on safety, including management of infusion-associated reactions (IARs). This work may help implement home-based ERT for Pompe disease in other countries.

2 Methods

This study was conducted and reported in line with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement [14]. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

2.1 Patient Population

All adult patients with LOPD who started treatment with alglucosidase alfa between 1999 and 2018 at the Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands, were included. Infusions with alglucosidase alfa from Chinese hamster ovary (CHO) cells between 2002 and 2019 were included for analysis in this study. We used observational routinely collected infusion data, collected per our standardised protocol. All patients had a confirmed diagnosis of Pompe disease, as demonstrated by a deficiency of alfa-glucosidase (EC 3.2.1.20) in leucocytes, fibroblasts, and/or two disease-causing GAA variants in trans. All patients received their first infusion after the age of 18 years and provided informed consent. They were followed up within a standardised protocol approved by our Institutional Review Board (IRB; METC 2007-103). Twenty patients were initially included in the randomised, double-blind, multicentre, placebo-controlled study on the effects of alglucosidase alfa in late-onset Pompe patients (Late-Onset Treatment Study [LOTS/AGLU02704], NCT00158600) [1] and the subsequent open-label study (AGLU03206, NCT00455195) [15].

2.2 Organisation of Alglucosidase Alfa Infusions

Alglucosidase alfa infusions were initially given in the hospital for a year to monitor patients and assess the safety of

infusions. Patients were eligible for home treatment if they were without IARs for multiple consecutive infusions in the hospital setting and if a home nurse trained by the Erasmus MC was available to administer infusions at home (or at a regional hospital if preferred by the patient). The nurse stays at home for the entire duration of the infusion. The infusion line is then flushed with at least 20 mL NaCl 0.9%, after which the nurse stays with the patient for an additional 15 min, or longer on indication. Logistics for infusions provided in a regional hospital were similar to those in the home situation.

All infusions were prepared centrally at our hospital's pharmacy and were then transported to the regional pharmacy of the patient under strict conditions with continuous temperature monitoring. A standard operating procedure (SOP) was in place, describing the administration of

alglucosidase alfa and the management of IARs and other emergencies (e.g. extravasation). Infusions were administered stepwise according to a standard infusion schedule, 0.2, 0.8, and 3.5 mg/kg/h with steps of 30 min for the first three infusion steps and 10 mg/kg/h for the remainder of the infusion (see Online Resource 6, Table 1). Infusion rates might be adapted if needed to treat or prevent IARs (see Online Resource 6, Table 2 for our slow infusion schedule). Premedication was not given as standard prior to infusion but could be considered after the occurrence of IARs. Patients were monitored in line with the SOP using on-site charts with preset checklists. For each infusion, an infusion form was filled out, containing information on the vital parameters (before, during, and right after infusion), the dosage and volume administered, (pre)medication (if any), applied infusion schedule, start and stop time of the infusion,

Table 1 Characteristics of patients receiving ERT

Sex [<i>n</i> (% of total)]	
Male	59 (48.8)
Female	62 (51.2)
Genotype [<i>n</i> (% of total)]	
IVS1 (c.-32-13T>G) + other GAA disease-causing variant	117 (96.7)
Two GAA disease-causing variants other than IVS1	4 (3.3)
Age at symptom onset, years [median (range)]	33.5 (1.4–67.4)
Age at diagnosis, years [median (range)]	42.9 (1.4–72.2)
Age at start of ERT, years [median (range)]	52.2 (19.9–76.3)
Disease duration at the start of ERT from symptom onset, years [median (range)]	13.7 (0.2–55.7)
Disease duration at the start of ERT from diagnosis, years [median (range)]	3.3 (0.2–31.1)
Number of patients ever treated at home [<i>n</i> (% of total)] ^a	95 (78.5)
Duration of ERT per patient, years [median (range)]	9.4 (0.2–16.2)

GAA alfa-glucosidase, ERT enzyme replacement therapy, COVID-19 coronavirus disease 2019

^aAn additional four patients (3.3%) were temporarily treated at home due to the COVID-19 pandemic

Table 2 Infusion data

	Total	Hospital ^a	Home
Patients ever receiving ERT	121	120 ^b	95
Patient ERT at the end of the study	85	5	80 ^c
Number of infusions [<i>n</i> (% of the total number of infusions)]	18,380 (100)	4961 (27.0)	13,419 (73.0)
Number of infusions per patient [median (IQR, range)]	148 (62.0–241.5, 6–330)	29 (18.5–52.5, 0–241)	110 (0.0–207.0, 0–281)
Infusion schedule [<i>n</i> (% of total per category)]			
Standard	16,243 (88.4)	4265 (86.0)	11,978 (89.3)
Adapted ^d	1617 (8.8)	540 (10.9)	1077 (8.0)
Not available at the time of analysis	520 (2.8)	156 (3.1)	364 (2.7)

ERT enzyme replacement therapy, IQR interquartile range

^aErasmus MC

^bIn one patient, treatment was started in a nursing home

^cThis includes nine patients treated at a regional hospital at study data cap. The logistics of these infusions are similar to those at home

^dAdapted infusion schedules were defined as all non-standard infusion schedules, i.e. infusions with adapted infusion rates or extra infusion steps

and possible adverse effects of ERT during infusion (if present). A specialised education programme for home nurses was developed at the Erasmus MC to ensure safe administration of ERT at home, including training by our specialised nurses on how to manage IARs in the home situation. An on-call service from the Erasmus MC run by nurses and doctors with experience with ERT in Pompe disease was available for consultation on questions and emergencies related to alglucosidase alfa administration.

2.3 Management of Infusion-Associated Reactions (IARs)

We defined an IAR as a disorder characterised by an adverse reaction related to the infusion of pharmacological or biological substances [16]. Nurses and doctors from our centre with experience treating Pompe disease, and trained home-care nurses, graded the IARs based on the classification described in Online Resource 1. If the severity of the IARs had not been graded, the researchers retrospectively graded the infusions (ID, HvdH, HH) according to the Common Terminology Criteria for Adverse Events (CTCAE) classification version 5.0 to avoid classification bias [16]. CTCAE Grade 1 corresponds with mild, CTCAE Grade 2 with moderate, and CTCAE Grades 3, 4, and 5 correspond with severe in the classification in Online Resource 1 [1]. We defined IARs as a serious adverse event (SAE) when an undesired medical event occurred that was fatal, and/or threatened the life of the subject, and/or made hospital admission or an extension of the admission necessary, and/or caused persistent or significant invalidity or work disability [17]. If an IAR occurred in the home situation, patients received subsequent infusions in the hospital if indicated based on the severity of the IAR (see Fig. 2). Patients were transferred back to the home when hospital infusions were assessed to be safe on a case-by-case basis.

2.4 Data Collection

Data on general descriptives (sex, genotype, age at symptom onset, age at diagnosis, age at start of ERT, disease duration at start of ERT from symptom onset, disease duration at start of ERT from diagnosis, duration of ERT) were collected. Based on the data on the infusion forms, the following information was collected: data on infusions (number of infusions in hospital and at home, number of infusions per patient, infusion schedule) and data on IARs (number of IARs, fever prior to infusion, sick/ill prior to infusions, severity of IAR, type of IAR, most severe intervention needed, action taken next infusion, premedication next infusion).

For interventions taken in response to IARs, the most severe intervention needed was reported, with the severity ranging from mild to severe in order: none taken, set

infusion back to the previous step, paused infusion and restarted infusion later, antihistamine was given, other medication was given, corticosteroid was given, antihistamine and corticosteroid were given, stopped infusion completely, and the patient required immediate clinical evaluation in hospital. For the action taken the next infusion after an IAR occurred, the most severe intervention needed was reported, with the severity ranging from mild to severe in order: none taken, the patient received premedication, infusion schedule was adapted, and the subsequent infusion was given in hospital. Only IARs clinically judged to have a probable or definite relationship with the infusion were included. To evaluate whether we missed any IARs based on the infusion forms, we checked the adverse event forms that were submitted to the pharmacovigilance department of Sanofi. Three researchers (ID, HvdH, and HH) had access to the database population used to create the study population. Data were cleaned by checking all data in duplicate, checking for missing values, and checking for numerical outliers. This study does not include data linkage across databases.

2.5 Statistical Analysis

Statistical analysis was executed using SPSS 25.0 (IBM Corporation, Armonk, NY, USA). Data were cleaned by checking for outliers. Descriptive analyses were performed, tabulating demographic and clinical information of patients, an overview of administered infusions, types of IARs, and actions taken to resolve these. Descriptive data (numbers, median, ranges, and percentages) were reported. We did not perform any statistical tests. If data were missing, it was reported as such.

3 Results

3.1 Study Population and Patient Characteristics

A total of 121 adult Pompe patients treated with alglucosidase alfa in The Netherlands were included in this study. All adult Pompe patients who met the inclusion criteria and for whom data were available were included. We did not filter participants based on data quality or linkage. Of these 121 patients, 95 (78.5%) received home infusions at some point. In February 2019 (data cap of the study), 85 of the 121 patients (70.2%) were receiving treatment with ERT (71 [58.7%] at home, 9 [7.4%] at a regional hospital, and 5 [4.1%] in the Erasmus MC). Reasons for receiving infusions at the Erasmus MC other than starting treatment with ERT were IARs, comorbidities, or a patient preference to receive their infusions at the Erasmus MC. Thirty-six patients were not receiving treatment with ERT as of February 2019. Twenty patients died while receiving treatment. ERT was

stopped in 16 patients; 8 of these patients were alive at study end and 8 patients had passed away. The reasons to abort treatment are discussed later. In total, 28 patients (23.1%) had passed away due to respiratory problems ($n=8$, 28.6% of deaths), malignancy ($n=6$, 21.4%), cardiovascular problems ($n=3$, 10.7%), cardiorespiratory failure ($n=2$, 7.1%), an infection ($n=2$, 7.1%), respiratory insufficiency and decubitus ($n=1$, 3.6%), aortic dissection ($n=1$, 3.6%), an infection and cardiovascular problems ($n=1$, 3.6%), and an autoimmune disorder ($n=1$, 3.6%). In three patients (10.7% of deaths), the cause of death was not recorded. None of the deaths were related to IARs.

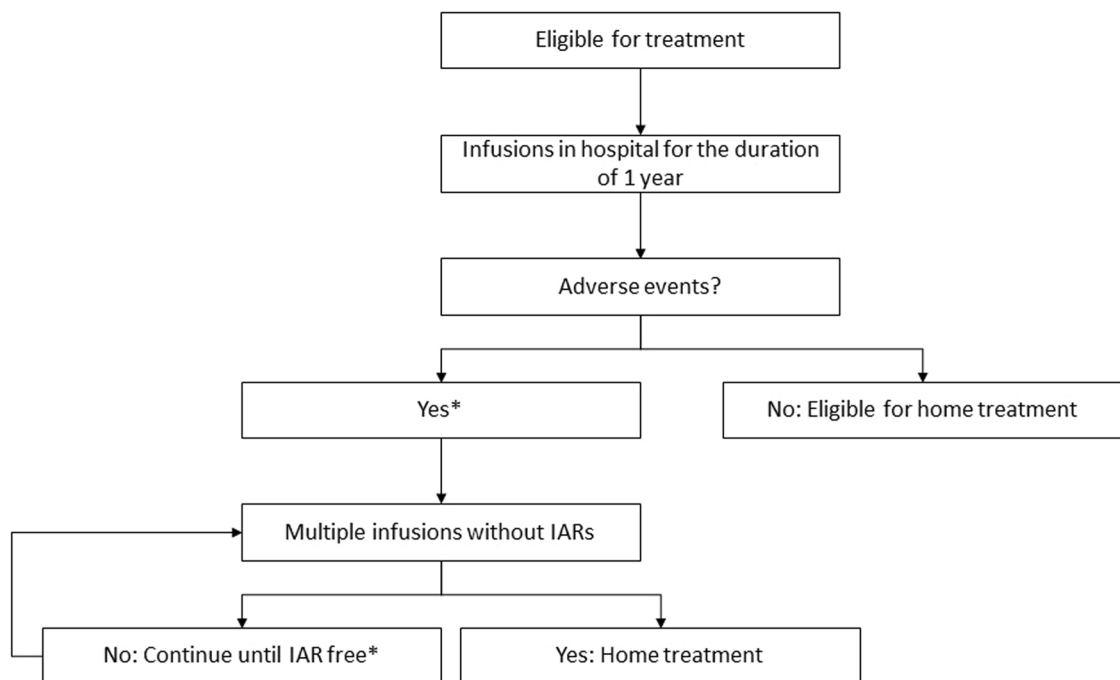
Patient characteristics are described in Table 1. The median age at symptom onset was 33.5 years (range 1.4–67.4) and the median age at diagnosis was 42.9 years (range 1.4–72.2). Patient age at the start of treatment ranged from 19.9 to 76.3 years (median 52.2 years). The time between symptom onset and the start of ERT ranged from 0.2 to 55.7 years (median 13.7 years). The time between diagnosis and start of ERT ranged from 0.2 to 31.1 years (median 3.3 years), which was partly explained by the fact that no treatment was available at the time of diagnosis for a proportion of patients. ERT duration per patient ranged from 0.2 to 16.2 years (median 9.4 years). Most patients ($n=117$, 96.7%) carried the IVS1 variant (c.-32-13T>G) plus another

disease-associated variant in the GAA gene. Only 3.3% of patients ($n=4$) carried two disease-associated variants other than IVS1.

3.2 Infusion Characteristics

Infusion characteristics of 18,380 infusions provided to patients since 2002 are described in Table 2. Of these infusions, 27.0% ($n=4961$) were given in hospital and 73.0% ($n=13,419$) were given at home. The median number of infusions per patient was 148 (range 6–330). In all but one patient, treatment with ERT was initially started in the hospital (for an overview of when to start home treatment, see Fig. 1). This patient started treatment with ERT in a nursing home due to colonisation by highly resistant microorganisms. During this patient's first infusions, a physician and an additional nurse were present, similar to the situation in the hospital. The median duration until the start of home infusion was 17.4 months (interquartile range [IQR] 12.4–25.8, range 0.0–121.4). This value was partly explained by the fact that some patients experienced IARs during the first year of treatment or because the home treatment only became available in 2008, with a proportion of patients having received treatment several years prior during a trial. At the end of the study, 83.5% of alglucosidase alfa infusions in

When to start ERT in the home situation:



*See appendix 2 for suggested interventions

Fig. 1 Flow chart depicting when to start with enzyme replacement therapy in the home situation. IAR infusion-associated reaction

adults with Pompe disease were provided in the home situation. Of all infusions, 88.4% ($n = 16,243$) were administered using the standard infusion schedule, and 8.8% were administered using an adapted infusion schedule (Table 2). Ninety-three patients always received infusions as per the standard schedule, and 28 patients received infusions using

an adapted infusion schedule at some point during treatment. The median duration for an infusion administered using the standard infusion was 205 min (IQR 195–210, range 125–518), and the median duration of an adapted infusion was 255 min (IQR 240–300, range 140–615).

3.3 IARs

IARs occurred in 257 (1.4%) of 18,380 infusions, of which 144 occurred in the hospital (2.9% of 4961 hospital infusions) and 113 in the home situation (0.8% of 13,419 home infusions). Most IARs were mild (79.9% of IARs in hospital; 92.0% of home-based IARs) (Table 3). Only five severe IARs were reported, one of which occurred at home (Table 3, Online Resource 5). The most prevalent symptoms were chills, itching, trembling, urticaria, localised exanthema, chest discomfort, and headaches (Table 4). An overview of all reported symptoms is presented in Online Resource 3. The median time between the start of treatment with ERT and the first IAR was 7.6 months (IQR 2.3–28.1). The median time between the start of an infusion and the occurrence of an IAR was 180 min (IQR 105.0–255.0) for IARs that occurred during hospital infusions ($n = 107$) and 150 min (IQR 117.5–192.5) for IARs that occurred in the home situation ($n = 61$), typically corresponding to step 4 of the infusion schedule. For the remaining IARs, these data were not available.

In total, 32 patients (26.4%) experienced IARs, of whom 21 (65.6% of patients with IARs) experienced their first IAR during the first year of ERT. Most patients with IARs ($n = 22$, 68.8%) experienced their first IAR in the hospital.

Table 3 Infusion-associated reactions (IARs)^a

	Hospital ^b	Home
Number of infusions [n (%)]	4961 (100)	13,419 (100)
With IAR ^a	144 (2.9)	113 (0.8)
No IAR ^a	4817 (97.1)	13,306 (99.2)
The severity of IARs [n (% of the total number of IARs ^c)]		
Mild	115 (79.9) ^e	104 (92.0)
Moderate	25 (17.4) ^e	8 (7.1)
Severe	4 (2.8) ^e	1 (0.9)
Infusion schedule infusions with IARs, n (% of total per category)		
Standard	43 (29.9)	91 (80.5)
Adapted ^d	100 (69.4)	22 (19.5)
Not available at the time of analysis	1 (0.7)	0 (0)

IAR infusion-associated reaction

^aWe defined an IAR as a disorder characterised by an adverse reaction to the infusion of pharmacological or biological substances [16]

^bErasmus MC

^cIn the hospital or at home

^dAdapted infusion schedules were defined as all non-standard infusion schedules (e.g. infusions with adapted infusion rates or extra infusion steps)

^eDue to rounding, the data add up to 100.1% for hospital infusions

Table 4 Number of patients with IARs and their symptoms

	Total
Number of patients with IARs [n (% of total)]	32 (26.4)
> 10 IARs	6 (5.0)
5–10 IARs	4 (3.3)
2–4 IARs	14 (11.6)
1 IAR	8 (6.6)
Reported IAR symptoms ^{a,b} [n (%)]	494 (100)
Very common ($\geq 10\%$): Chills	74 (15.0)
Common ($\geq 1\%$ and $< 10\%$): Itching, trembling, urticaria, localised exanthema, chest discomfort, headache, hypertension, subfebrile temperature, generalised exanthema, localised angioedema, flushing, tachycardia, nausea, dyspnoea, pallor, hyperthermia or fever, malaise, coughing, dizziness, musculoskeletal pain, desaturation, fatigue ^c	408 (82.6)
Uncommon ($\geq 0.1\%$ and $< 1\%$): Vomiting, palpitations, excess sweating, agitation, bradycardia, oedema, paraesthesia	12 (2.4)

IAR infusion-associated reaction, ADR adverse drug reaction, CIOMS Council for International Organizations of Medical Sciences

^aPatients may have had more than one symptom per IAR, percentages of the total number of symptoms (Online Resource 3)

^bADR frequency, CIOMS [18]

^cOther symptoms reported include itchy throat, localised erythema, tingling/squeezing sensation throat, tingling sensation mouth, strange feeling in the oesophagus, stomach ache, feeling warm/hot, drowsy, increased mucus production, tingling sensation cheek, sensitive palate, hypotension; dry mouth, hyperglycaemia, heartburn, gagging, cyanosis, cold hands; nose, brain fog, atrial fibrillation, weird feeling, swollen throat, feeling warm; atrial fibrillation, hypotension and light-headedness; uncomfortable feeling in the gastric region and dirty flavour in the mouth

Of these, 18 IARs (81.5%) were mild, 3 IARs (13.6%) were moderate, and 1 IAR (4.5%) was severe. Ten patients (31.3% of patients with IARs) experienced their first IAR at home; 6 of these IARs (60.0%) were mild, and 4 (40.0%) were moderate. Twenty-four patients (75.0% of patients with IARs) experienced repetitive IARs. Only 6 patients (5.0% of the total) experienced more than 10 IARs (Table 4). These patients accounted for 181 (70.4%) of all IARs. At study end, 11 of 24 patients with repetitive IARs (45.8%) were treated at home and 2 (8.3%) were treated in a regional hospital. The remaining 11 patients (45.8%) were not under treatment with alglucosidase alfa at the study end.

During our study, 16 patients (13.2%) had stopped treatment with alglucosidase alfa. Eight of these patients have passed away and eight were still alive at study end. In the eight patients who were still alive at study end, treatment was stopped due to IARs ($n=5$), burden of ERT ($n=1$) non-compliance with therapy ($n=1$), and IARs and high antibody titres ($n=1$). In the eight patients who had passed away during the study, treatment was stopped due to IARs ($n=1$), being terminally ill ($n=4$), poor clinical condition, i.e. fully invasive ventilation-dependent and wheelchair bound ($n=1$), no effect of ERT ($n=1$), and both the burden of ERT and IARs ($n=1$).

3.4 Management of IARs

In 22.9% ($n=33$) of IARs occurring in hospital and 72.6% ($n=82$) occurring at home, no intervention was needed (Online Resource 4). In 18.1% ($n=26$) of hospital-based IARs, pausing the infusion and restarting it after symptoms subsided without needing medication was sufficient. This was also the most frequent intervention for home-based IARs, with 12.4% ($n=14$) of IARs subsiding without needing medication. Administration of antihistamines 8.0% ($n=9$) was the second most prevalent intervention at home. In the hospital, the most severe interventions needed were the administration of corticosteroids (5.6%, $n=8$), antihistamines (18.1%, $n=26$), or both (2.8%, $n=4$). In 18.1% ($n=26$), other medication (such as a beta-blocker or codeine) was needed. Only 16 (0.3%) of the 4961 hospital infusions and 6 (<0.1%) of the 13,419 home infusions were not restarted (on the same day) after the IAR occurred. Only one IAR in the home situation, during which atrial fibrillation occurred, required immediate clinical evaluation in the hospital. Premedication was only given to patients who had experienced IARs in the past or had a high risk of developing them (e.g. allergic reactions to medication in medical history). In 18.6% of IARs at home ($n=21$ of 113) and 66.0% of IARs in hospital ($n=95$ of 144), the patient received premedication before the infusion during which an IAR occurred. The most common premedication to prevent IARs in the hospital were an antihistamine and a corticosteroid

(22.2%, $n=32$) or only an antihistamine (20.8%, $n=30$). In contrast, an antipyretic was the most common premedication in the home situation, at 12.4% ($n=14$). For an overview of our protocol regarding the management of IARs and subsequent infusions, see Fig. 2; for an overview of medication to be administered during an IAR and actions and premedication to be considered for the subsequent infusion(s), see Online Resource 2.

3.5 Subsequent Infusions After the Occurrence of an IAR

After the occurrence of an IAR, no intervention was needed for the subsequent infusion in 16.0% ($n=23$) of hospital and 69.9% ($n=79$) of home infusions. Administration of premedication was the most prevalent intervention for the infusion after an IAR had occurred, with premedication administered the next infusion after 56.9% of IARs ($n=82$) in the hospital and 18.6% of IARs ($n=21$) at home. Adaptation of the infusion schedule was the second most prevalent intervention after 18.1% ($n=26$) of the IARs in the hospital and 7.1% ($n=8$) of IARs at home. In the hospital, an antihistamine and a corticosteroid (27.1%, $n=39$) or an antihistamine alone (20.8%, $n=30$) were most commonly prescribed. In contrast, an antipyretic drug (11.5%, $n=13$) and an antihistamine (9.7%, $n=11$) were the most commonly prescribed premedication after an IAR in the home situation (Online Resource 4).

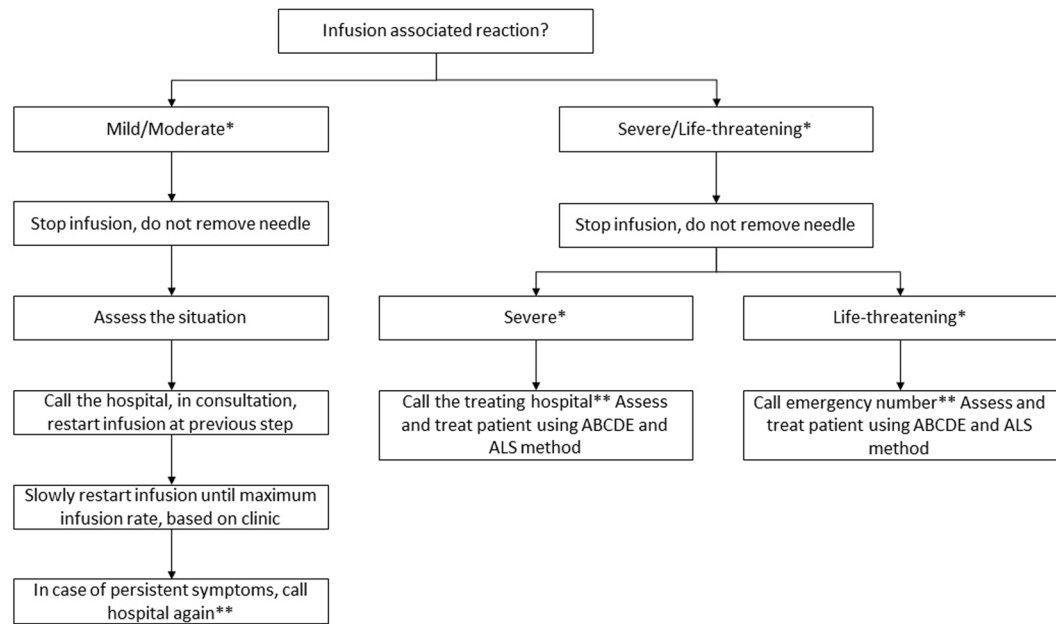
3.6 Severe IARs

A total of five severe IARs were reported in three different patients, two of whom had two severe IARs each. The first patient experienced the first severe IAR in the home situation after 9 years of ERT and the second in the hospital immediately after. In this patient, the first severe IAR was also an SAE. Before this severe IAR, the patient had previously experienced 30 mild IARs. A second patient experienced two severe IARs in the hospital; she had experienced two previous IARs, a mild IAR a year ago and a moderate IAR during the infusion prior to the severe IAR. The third patient in whom a severe IAR occurred in the hospital had a history of allergic reactions to other medications and was still in the first year of treatment (see Table 5 and Online Resource 5 for a more detailed overview).

4 Discussion

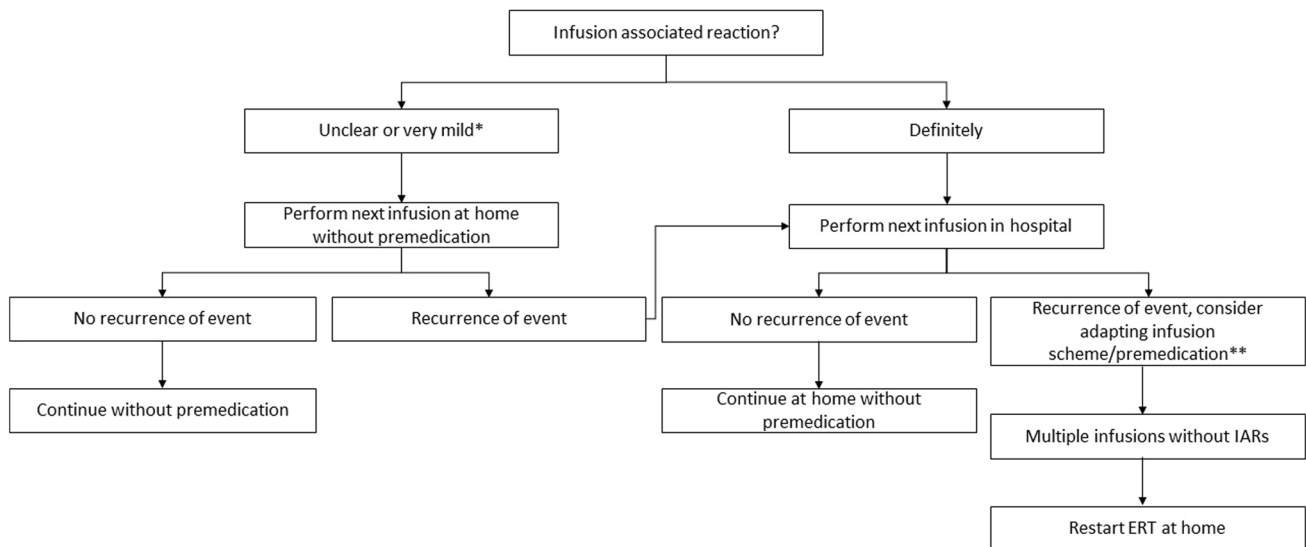
Based on the analyses of 18,380 alglucosidase alfa infusions administered to 121 adult patients with Pompe disease between 2002 and 2019, we concluded that alglucosidase alfa can be provided safely at home in adult patients with

A. Course of action after an IAR → acute situation



*According to CTCAE classification **Emergency medication as indicated, see appendix 2a 'medication during an IAR'. Clear IV line prior to giving intravenous medication.

B. Course of action after an IAR → next infusions



* No vital sign abnormalities, very mild symptoms, no higher than CTCAE classification grade 1

** See appendix 2b 'premedication'

Fig. 2 Protocol regarding IARs and subsequent infusions. **a** The course of action after an IAR in the acute situation. **b** Course of action the next infusion after a (possible) IAR has occurred. *IAR* infusion-associated reaction, *ALS* advanced life support, *CTCAE* Common Terminology Criteria for Adverse Events, *ERT* enzyme replacement therapy

important to start ERT in the hospital initially. Most IARs were mild (85.2%), and only five severe IARs were reported, of which only one occurred in the home situation. This demonstrates that the current organisation of infusion therapy in The Netherlands ensures that ERT can be administered

Pompe disease in the presence of trained home care nurses and protocols describing infusion and IAR management. In 1.4% of infusions, an IAR occurred in 2.9% of hospital infusions and only 0.8% of home infusions. Most first IARs (68.8%) occurred in the hospital, illustrating that it is

important to start ERT in the hospital initially. Most IARs were mild (85.2%), and only five severe IARs were reported, of which only one occurred in the home situation. This demonstrates that the current organisation of infusion therapy in The Netherlands ensures that ERT can be administered

Table 5 Severe IARs

	Patient 1, severe IAR 1	Patient 1, severe IAR 2	Patient 2, severe IAR 1	Patient 2, severe IAR 2	Patient 3, severe IAR 1
Location of the IAR	Home	Hospital	Hospital	Hospital	Hospital
Duration of ERT prior to the IAR	9 years	9 years and 1 month	1 year and 3 months	1 year and 4 months	One month
Duration of home therapy prior to the IAR	8 years and 2 months	8 years and 2 months	NA	NA	NA
Previous IARs	Yes, 30 mild IARs	Yes, 30 mild IARs, one severe IAR	Yes, one mild, one moderate	Yes, one mild IAR, one moderate IAR, one severe IAR	No
Infusion schedule	Standard	Standard	Adapted	Adapted	Standard
Duration infusion up to IAR	45 min	Unknown	195 min	90 min	120 min
Alglucosidase alfa administered prior to the IAR	29 mg	Unknown	924 mg	42 mg	682 mg
Premedication prior to the IAR	No medication	No medication	Antihistamine	Antihistamine, corticosteroid	Antihistamine
Symptoms	Stabbing chest pain, coughing, redness in the face, blisters	Coughing, redness of the face, strange sensation in the chest, generalised exanthema, urticaria, and tight sensation in the throat	Subcutaneous infusion, generalised exanthema, nausea	Localised exanthema, itching, nausea	Itching, generalised exanthema, urticaria, increased blood pressure and temperature
Intervention during IAR	Paused infusion, administered clemastine, ondansetron, and fentanyl, stopped infusion completely	Paused infusion, administered clemastine, hydrocortisone, and salbutamol, stopped infusion completely	Paused infusion, administered clemastine and hydrocortisone, stopped infusion completely	Paused infusion, clemastine and hydrocortisone were given, stopped infusion completely	Paused infusion, clemastine and hydrocortisone were administered, stopped infusion completely
Intervention next infusion	The next infusion was given in the hospital	Premedication with clemastine, adjusting infusion schedule	Adjusted infusion schedule, premedication with clemastine and hydrocortisone	Treatment with alglucosidase alfa permanently discontinued (patient request)	Premedication with hydrocortisone, adjusted infusion schedule
Anti-rhGAA antibody titre around the time of the IAR	10 months before and 2 months after IAR 1:31,250	10.5 months before and 1.5 months after IAR 1:31,250	1 month prior to IAR 1:250, 4.5 months after 1:1250	2.5 months prior to IAR 1:250, 3 months after 1:1250	Two weeks post IAR 1:250
Anti-rhGAA antibody titre over time	Varying between 1:31,250 and 1:156,250	Varying between 1:31,250 and 1:156,250	Varying between 1:250 and 1:6250	Varying between 1:250 and 1:6250	Varying between 1:250 to 1:31,250
Persistent high titres	Yes	Yes	No	No	Yes
IgE [kU/L]	Not available	34 (< 100)	Not available	163	Not available
Tryptase [μ g/L]	Not available	2.8 (< 11.4)	Not available	6.4 (0–11.4)	Not available
Complement [g/L]	Not available	Not available	Not available	C3 1.17 (0.9–1.8) C4 0.23 (0.1–0.4) C1Q 0.17 (0.05–0.25)	Not available

IARs infusion-associated reactions, ERT enzyme replacement therapy, NA not applicable, rhGAA recombinant human alpha-glucosidase, IgE immunoglobulin E

safely in the home setting. A period of 12 months is sufficient for a safe transfer to home treatment since the median time from starting treatment with ERT until the first IAR occurred was 7.6 months. This duration is in line with our previous publication [19]. The three patients who experienced severe IARs did so after first having milder IARs, except for one patient who had a history of autoimmune disease and allergies. In case of (recurrent) IARs, patients should thus return to treatment in the hospital, as they may be at risk of developing a severe IAR. Eventually, in our population, 78.5% of patients ($n=95$) could be transferred home after 1 year.

The safe implementation of home-based ERT after an initial start-up phase has been demonstrated in other LSDs, such as Gaucher, Fabry, and mucopolysaccharidosis (MPS) I, II, and VI [20–24]. One of the main factors initially preventing home infusions from being implemented on a larger scale was that alglucosidase alfa received a boxed warning from the FDA due to a risk of anaphylactic, severe allergic, and immune-mediated reactions [6]. This risk was also mentioned in the European Medicines Agency (EMA) SmPC [7]. The higher risk of severe IARs in response to rhGAA compared with other enzyme replacement therapies may be explained by the higher dosages of ERT needed in Pompe disease to sufficiently reach the target tissues [25–27]. In other LSDs, such as Fabry and MPS I, II, and VI, patients are treated with doses of 0.2–4 mg/kg [21, 24, 28]. In adults with LOPD, 20 mg/kg is needed to adequately target skeletal muscle tissue, as a large fraction of ERT is taken up in the liver and spleen [29, 30].

Drug hypersensitivities can be immunoglobulin (Ig) E-mediated or non-IgE-mediated [31]. IgE-mediated reactions are mostly immediate [32, 33], while non-IgE-mediated reactions can be both immediate and delayed [34]. Symptoms at clinical presentation also show overlap, with both IgE- and non-IgE-mediated reactions causing cutaneous reactions as well as systemic symptoms [31–33]. Diagnostic testing with validated biomarkers to differentiate the two reactions is limited, with mast cell and basophil activation occurring in both IgE- and non-IgE-mediated reactions through MRGPRX2, cytokine release and IgG-mediated mast cell activation through FcγRIII [31, 34, 35]. Overall, there is considerable overlap between IgE-mediated and non-IgE-mediated reactions. The exact mechanism of infusion-associated reactions to biologic agents, such as recombinant alfa-glucosidase, remains poorly understood.

The prevalence of IARs and high IgG antibody titres are known to be disease and medication-dependent, with some ERTs being more immunogenic than others [36]. Especially in classic infantile Pompe disease, the effect of anti-rhGAA IgG antibodies has been demonstrated [36–40]. These patients may be more prone to develop antibodies because patients with classic infantile Pompe disease have < 1%

residual alfa-glucosidase activity; one-third do not express any GAA protein. In contrast, patients with the late-onset form of the disease have more residual activity, albeit usually no more than 20–30% of normal average activity [2]. In our cohort, 96.7% of patients carried the IVS1 variant, consistent with the literature, where 90% of Caucasian patients have been reported to carry this variant [41–52]. Patients with this common splicing variant produce wild-type GAA protein, although only approximately 10–15% of transcripts are spliced normally [53, 54]. The presence of wild-type GAA may partially explain why we saw relatively few IARs in this cohort.

Although the relation between antibody titres and IARs has been less clearly demonstrated in LOPD than in classic-infantile Pompe disease [55], it has been shown that most adults receiving alglucosidase alfa develop anti-rhGAA antibodies [1, 19]. The IgG antibody titre level seems to positively correlate with the occurrence and number of IARs in adults with Pompe disease in a study with 3 years of follow-up in 73 patients, who are also included in this study. Only 1/28 (4%) patients in the no- to low-titre group, 5/29 (17%) in the intermediate-titre group, and 7/16 (44%) in the high-titre group experienced IARs ($p=0.001$). Furthermore, the total number of IARs that patients experienced during this study increased with higher antibody titres ($\rho=0.46$, $p<0.001$). No correlation between antibody titres and treatment efficacy was found [19]. It should be noted that not all patients with high titres developed IARs, while some patients with low to intermediate titres did experience IARs. In the current study, only one of the three patients with severe IARs had a high IgG antibody titre around the time of the IARs (with persistent high titre during the whole treatment period). One patient had a low to intermediate titre around the time of IARs, and one patient had a low titre around the time of the IAR.

The differences between patients with regard to the consequence of anti-rhGAA antibodies, such as a decline in the clinical effects of ERT or the development of IARs, may be explained by the different IgG subclasses produced in response to ERT. The IgG1 and IgG4 subclasses in particular have been shown to be elevated in a subset of LOPD subjects who received long-term ERT, however these antibodies tend to be non-inhibitory antibodies with no evident effect on enzyme activity or uptake [55].

Very few papers report on IgE in Pompe patients [1, 56–60]. In the initial phase I/II study in classic-infantile Pompe patients, IgE levels did not rise above background levels [60]. One paper describes a patient with a grade III anaphylactic reaction, with negative IgE, normal tryptase and complement C3/C4/CH50 [58]. Two other papers also measured complement and tryptase, with one describing two classic-infantile patients who tested positive for complement, with normal to elevated tryptase but negative for

IgE [59], and one describing a patient testing negative for complement with normal tryptase and positive IgE [56]. In two patients in our study, IgE and tryptase were measured at the time of a severe IAR. IgE and tryptase were normal in one patient, while IgE was slightly elevated in the other patient with normal tryptase, complement C3, C4 and C1q. These data suggest that IARs in Pompe disease are usually IgG-mediated or anaphylactoid reactions, with IgE-mediated or anaphylactic reactions making up < 1% of IARs [61].

Studies on effective management of IARs in biologicals in general and in ERT more specifically are scarce. Empirical experience has learned that in case of an IAR, the infusion must be stopped, after which the symptoms mostly resolve [31, 62]. Reoccurrence of IARs in future infusions can be prevented by reducing the infusion rate [62]. The fact that this is successful in most patients is also an indication that the IgE pathway is not involved [31]. In IgG-mediated IARs, sufficiently large amounts of antigen are needed to induce an IAR [34]. Potentially, the reduction of the infusion rate may decrease the concentration of the drug in the circulation, avoiding the induction of the cascade leading to an IAR. Finally, pretreatment with antihistamines, leukotriene-modifying agents and systemic steroids, as well as paracetamol in case of the occurrence of fever, can ameliorate the IARs. This is also our experience. When we performed the very first study on ERT in Pompe disease in 1999, we started with a constant infusion rate over 2 h. After four to six infusions, patients started to develop IARS. Trial and error learned that (1) IAR symptoms resolved after stopping the infusion; and (2) subsequent IARs could be managed by slowing down the infusion rate in the beginning.

IARs typically occurred during step 4 of the infusion schedule, corresponding with an infusion rate of 10 mg/kg/h. The Dutch infusion schedule for adult patients has been adapted from the schedule recommended by the pharmaceutical company and starts slower to prevent IARs (see Online Resource 6, Table 1). This schedule has been used since the first trial with ERT in adult Pompe patients [1] and was applied in the Dutch patients ($n = 20$) participating in this multicentre, randomised, placebo-controlled trial with alglucosidase alfa. This slower build-up of infusion speed may be one of the reasons we see relatively few IARs in our population.

Home-based therapy has advantages over hospital therapy as it decreases the burden of ERT, which has been demonstrated in other LSDs [20–22]. It has less impact on daily life, is more convenient, is less stressful [63], and improves patients' self-perceived quality of life [64]. In addition, it might improve treatment compliance, as demonstrated in MPS, Fabry, and Gaucher [64–66], as well as reduce costs of ERT [21, 67] and thus release resources for alternative use and thereby improve the efficacy of healthcare [68]. One study in Gaucher patients comparing home therapy with

hospital infusion demonstrated a reduction of approximately 90% in therapy costs (excluding the cost of the enzyme) [20]. A Dutch study using bottom-up costing research estimates drug administration out of the hospital to be about 15% cheaper than in-hospital drug administration [69].

Based on our results and experience, we aim to provide guidance for transitioning to home therapy with ERT (Fig. 1) and for acute management of IARs, and actions to take to prevent subsequent IARs (Online Resource 2, which can be deviated from at the discretion of the treating physician), such as slowing down the infusion rate (see Online Resource 6, Table 2 for our slow infusion schedule) and/or prescribing premedication. Antipyretics, antihistamines and corticosteroids were the most commonly used medications for the managements of IARs in our study. This is in line with what has been described in the literature as the standard approach for the management of IARs [19, 48, 57, 61, 70]. To ensure safe administration of ERT in the home situation, it is necessary to monitor patients in the hospital during the first year of ERT, and if IARs occur, to take measures until these are well managed. Only when hospital infusions have been demonstrated to be safe can ERT be safely transferred to the home situation. In case of recurrent IARs, hospital treatment should be re-initiated until the IARs are under control.

Although a strict protocol was in place and trained nurses were present during the home infusions, the home infusions were not monitored with the rigour of a clinical trial. Clinical information was occasionally limited during the analysis of 18,380 infusions, making interpretation of some IARs more difficult. Therefore, it cannot be ruled out that there were underreported mild IARs or minor interventions during infusions. Nevertheless, we think our results and recommendations are sufficiently substantiated by the analysis of such a vast number of infusions.

5 Conclusion

Our data demonstrate that few IARs occur during ERT with alglucosidase alfa. The majority of IARs were mild and did not necessitate any clinical intervention. Five severe IARs occurred, of which only one was during a home infusion. This shows that ERT with alglucosidase alfa can safely be administered in the home situation, provided an appropriate protocol and infrastructure is in place.

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Declarations

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Consent to participate We received consent to participate from all participants and/or their caregivers.

Consent for publication We received consent for publication from all participants and/or their caregivers.

Data availability Deidentified data will be shared upon reasonable request to the corresponding author from any qualified investigator for the sole purpose of replicating procedures and results presented in this article, in agreement with EU legislation on the general data protection regulation.

Code availability Not applicable.

Author contributions Conceptualization: IAM Ditters, NAME van der Beek, ME Kruijshaar, AT van der Ploeg, JMP van den Hout and HH Huidekoper. Data curation: IAM Ditters. Formal analysis: IAM Ditters, JMP van den Hout and HHHuidekoper. Investigation: IAM Ditters, JMP van den Hout and HH Huidekoper. Methodology: IAM Ditters, ME Kruijshaar, AT van der Ploeg, JMP van den Hout and HH Huidekoper. Project administration: IAM Ditters, JMP van den Hout and HH Huidekoper. Resources: IAM Ditters, HA van Kooten, NAME vander Beek, JF Hardon, G Ismailova, E Brusse, AT van der Ploeg, JMP van den Hout and HH Huidekoper. Supervision: AT van der Ploeg, JMP van den Hout and HH Huidekoper. Validation: IAM Ditters, JMP vanden Hout and HH Huidekoper. Visualization: IAM Ditters, AT van der Ploeg, JMP van den Hout and HHHuidekoper. Writing original draft: IAM Ditters, AT van der Ploeg, JMP van den Hout and HH Huidekoper. Writing – review & editing: IAM Ditters, HA van Kooten, NAME van der Beek, JF Hardon, G Ismailova, E Brusse, ME Krui-

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References

- 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.
- van der Ploeg AT, Reuser AJ. Pompe's disease. *Lancet*. 2008;372(9646):1342–53.
- Harlaar L, Hogrel J-Y, Perniconi B, Kruijshaar ME, Rizopoulos D, Taouagh N, et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. *Neurology*. 2019;93(19):e1756–67.
- Güngör 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.
- Perraudin C, Bourdin A, Vicino A, Kuntzer T, Bugnon O, Berger J. Home-based subcutaneous immunoglobulin for chronic inflammatory demyelinating polyneuropathy patients: a Swiss cost-minimization analysis. *PLoS One*. 2020;15(11):e0242630.
- FDA. Highlights of prescribing information MYOZYME® (alglucosidase alfa) injectable for intravenous infusion: FDA [updated 05-2019]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125141s2191bl.pdf.
- Myozyme: EPAR—Product information: European Medicines Agency; 2022 [updated 25-08-2022]. https://www.ema.europa.eu/en/documents/product-information/myozyme-epar-product-information_en.pdf.
- Weninger S, Gutschmidt K, Wirner C, Einvag K, Montagnese F, Schoser B. The impact of interrupting enzyme replacement therapy in late-onset Pompe disease. *J Neurol*. 2021;268(8):2943–50.
- Tard C, Salort-Campana E, Michaud M, Spinazzi M, Nadjpakleza A, Durr H, et al. Motor and respiratory decline in patients with late onset Pompe disease after cessation of enzyme replacement therapy during COVID-19 pandemic. *Eur J Neurol*. 2022;29(4):1181–6.
- Fiumara A, Lanzafame G, Arena A, Sapuppo A, Raudino F, Praticò A, et al. COVID-19 pandemic outbreak and its psychological impact on patients with rare lysosomal diseases. *J Clin Med*. 2020;9(9):2716.
- Sechi A, Macor D, Valent S, Da Riolo RM, Zanatta M, Spinelli A, et al. Impact of COVID-19 related healthcare crisis on treatments for patients with lysosomal storage disorders, the first Italian experience. *Mol Genet Metab*. 2020;130(3):170–1.

12. Lampe C, Dionisi-Vici C, Bellettato CM, Paneghetti L, van Lingen C, Bond S, et al. The impact of COVID-19 on rare metabolic patients and healthcare providers: results from two MetabERN surveys. *Orphanet J Rare Dis.* 2020;15(1):341.
13. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology.* 2020;94(22):959–69.
14. Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med.* 2015;12(10): e1001885.
15. van der Ploeg AT, Barohn R, Carlson L, Charrow J, Clemens PR, Hopkin RJ, et al. Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa. *Mol Genet Metab.* 2012;107(3):456–61.
16. National Institutes of Health NCI. Common Terminology Criteria for Adverse Events, version 5.0: National Institutes of Health, National Cancer Institute; 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf [updated Nov 27].
17. Central Committee on Research Involving Human Subjects. L4. SAEs. <https://english.ccmo.nl/investigators/standard-research-file/l-safety-information/l4-saes>.
18. Council for International Organizations of Medical Sciences (CIOMS). Guidelines for preparing core clinical-safety information on drugs: Including new proposals for investigator's brochures. Switzerland: Council for International Organizations of Medical Sciences; 1999.
19. de Vries JM, Kuperus E, Hoogeveen-Westerveld M, Kroos MA, Wens SCA, Stok M, et al. Pompe disease in adulthood: effects of antibody formation on enzyme replacement therapy. *Genet Med.* 2017;19:90.
20. Zimran A, Hollak CE, Abrahamov A, van Oers MH, Kelly M, Beutler E. Home treatment with intravenous enzyme replacement therapy for Gaucher disease: an international collaborative study of 33 patients. *Blood.* 1993;82(4):1107–9.
21. Linthorst GE, Vedder AC, Ormel EE, Aerts JM, Hollak CE. Home treatment for Fabry disease: practice guidelines based on 3 years experience in The Netherlands. *Nephrol Dial Transplant.* 2006;21(2):355–60.
22. Cox-Brinkman J, Timmermans RG, Wijburg FA, Donker WE, van de Ploeg AT, Aerts JM, et al. Home treatment with enzyme replacement therapy for mucopolysaccharidosis type I is feasible and safe. *J Inherit Metab Dis.* 2007;30(6):984.
23. Burton BK, Guffon N, Roberts J, van der Ploeg AT, Jones SA, HOS Investigators. Home treatment with intravenous enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II—data from the Hunter Outcome Survey. *Mol Genet Metab.* 2010;101(2–3):123–9.
24. Bagewadi S, Roberts J, Mercer J, Jones S, Stephenson J, Wraith JE. Home treatment with Elaprased and Naglazyme is safe in patients with mucopolysaccharidoses types II and VI, respectively. *J Inherit Metab Dis.* 2008;31(6):733–7.
25. Joep HJ, Kamphoven LD, Kroos MA, van der Ploeg AT, Duncker DJ, Reuser AJJ. Both low and high uptake forms of acid a-glucosidase target to muscle of KO mice with Pompe's disease. In: Center EMUM, editor. Pompe's disease; the mouse model as model in the development of enzyme therapy; 2004. p. 90–104. https://repub.eur.nl/pub/15246/Kamphoven_Joep%20H%20J_18%20feb%202004.pdf.
26. Zhu Y, Li X, McVie-Wylie A, Jiang C, Thurberg BL, Raben N, et al. Carbohydrate-remodelled acid alpha-glucosidase with higher affinity for the cation-independent mannose 6-phosphate receptor demonstrates improved delivery to muscles of Pompe mice. *Biochem J.* 2005;389(Pt 3):619–28.
27. Winkel LPF, Kamphoven JHJ, van den Hout HJMP, Severijnen LA, van Doorn PA, Reuser AJJ, et al. Morphological changes in muscle tissue of patients with infantile Pompe's disease receiving enzyme replacement therapy. *Muscle Nerve.* 2003;27(6):743–51.
28. Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). *J Pediatr.* 2004;144(5):581–8.
29. Zhang XS, Brondyk W, Lydon JT, Thurberg BL, Piepenhagen PA. Biotherapeutic target or sink: analysis of the macrophage mannose receptor tissue distribution in murine models of lysosomal storage diseases. *J Inherit Metab Dis.* 2011;34(3):795–809.
30. Do HV, Khanna R, Gotschall R. Challenges in treating Pompe disease: an industry perspective. *Ann Transl Med.* 2019;7(13):291.
31. Cianferoni A. Non-IgE-mediated anaphylaxis. *J Allergy Clin Immunol.* 2021;147(4):1123–31.
32. Drain KL, Volcheck GW. Preventing and managing drug-induced anaphylaxis. *Drug Saf.* 2001;24(11):843–53.
33. van der Klauw MM, Wilson JH, Stricker BH. Drug-associated anaphylaxis: 20 years of reporting in The Netherlands (1974–1994) and review of the literature. *Clin Exp Allergy.* 1996;26(12):1355–63.
34. Joshi SR, Khan DA. Non-IgE-mediated drug hypersensitivity reactions. *Curr Allergy Asthma Rep.* 2021;21(7):41.
35. Khan AA, Case LE, Herbert M, DeArmy S, Jones H, Crisp K, et al. Higher dosing of alglucosidase alfa improves outcomes in children with Pompe disease: a clinical study and review of the literature. *Genet Med.* 2020;22(5):898–907. <https://doi.org/10.1038/s41436-019-0738-0>.
36. Broomfield A, Jones SA, Hughes SM, Bigger BW. The impact of the immune system on the safety and efficiency of enzyme replacement therapy in lysosomal storage disorders. *J Inherit Metab Dis.* 2016;39(4):499–512.
37. Kishnani PS, Goldenberg PC, DeArmy SL, Heller J, Benjamin D, Young S, et al. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. *Mol Genet Metab.* 2010;99(1):26–33.
38. Banugaria SG, Prater SN, Ng YK, Kobori JA, Finkel RS, Ladda RL, et al. The impact of antibodies on clinical outcomes in diseases treated with therapeutic protein: lessons learned from infantile Pompe disease. *Genet Med.* 2011;13(8):729–36.
39. van Gelder CM, Hoogeveen-Westerveld M, Kroos MA, Plug I, van der Ploeg AT, Reuser AJJ. Enzyme therapy and immune response in relation to CRIM status: the Dutch experience in classic infantile Pompe disease. *J Inherit Metab Dis.* 2015;38(2):305–14.
40. van Gelder CM, Poelman E, Plug I, Hoogeveen-Westerveld M, van der Beek N, Reuser AJJ, et al. Effects of a higher dose of alglucosidase alfa on ventilator-free survival and motor outcome in classic infantile Pompe disease: an open-label single-center study. *J Inherit Metab Dis.* 2016;39(3):383–90.
41. Angelini C, Semplicini C, Tonin P, Filosto M, Pegoraro E, Sorarù G, et al. Progress in enzyme replacement therapy in glycogen storage disease type II. *Ther Adv Neurol Disord.* 2009;2(3):143–53.
42. Figueroa-Bonaparte S, Llauger J, Segovia S, Belmonte I, Pedrosa I, Montiel E, et al. Quantitative muscle MRI to follow up late onset Pompe patients: a prospective study. *Sci Rep.* 2018;8(1): 10898.
43. 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.
44. Löscher WN, Huemer M, Stulnig TM, Simschitz P, Iglseder S, Eggers C, et al. Pompe disease in Austria: clinical, genetic and epidemiological aspects. *J Neurol.* 2018;265(1):159–64.
45. Montalvo AL, Bambi B, Donnarumma M, Filocamo M, Parenti G, Rossi M, et al. Mutation profile of the GAA gene in 40 Italian

- patients with late onset glycogen storage disease type II. *Hum Mutat.* 2006;27(10):999–1006.
46. Mori M, Haskell G, Kazi Z, Zhu X, DeArmev SM, Goldstein JL, et al. Sensitivity of whole exome sequencing in detecting infantile- and late-onset Pompe disease. *Mol Genet Metab.* 2017;122(4):189–97.
 47. Papadimas GK, Terzis G, Methenitis S, Spengos K, Papadopoulos C, Vassilopoulou S, et al. Body composition analysis in late-onset Pompe disease. *Mol Genet Metab.* 2011;102(1):41–3.
 48. Regnery C, Kornblum C, Hanisch F, Vielhaber S, Strigl-Pill N, Grunert B, et al. 36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy. *J Inher Metab Dis.* 2012;35(5):837–45.
 49. Scheidegger O, Leupold D, Sauter R, Findling O, Rösler 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.
 50. Semplicini C, Letard P, De Antonio M, Taouagh N, Perniconi B, Bouhour F, et al. Late-onset Pompe disease in France: molecular features and epidemiology from a nationwide study. *J Inher Metab Dis.* 2018;41(6):937–46.
 51. van der Meijden JC, Kruijshaar ME, Harlaar L, Rizopoulos D, van der Beek N, van der Ploeg AT. Long-term follow-up of 17 patients with childhood Pompe disease treated with enzyme replacement therapy. *J Inher Metab Dis.* 2018;41(6):1205–14.
 52. Witkowski G, Konopko M, Rola R, Lugowska A, Ryglewicz D, Sienkiewicz-Jarosz H. Enzymatic replacement therapy in patients with late-onset Pompe disease—6-year follow up. *Neurol Neurochir Pol.* 2018;52(4):465–9.
 53. Kroos MA, Pomponio RJ, Hagemans ML, Keulemans JL, Phipps M, DeRiso M, et al. Broad spectrum of Pompe disease in patients with the same c.-32-13T->G haplotype. *Neurology.* 2007;68(2):110–5.
 54. van der Wal E, Bergsma AJ, Pijnenburg JM, van der Ploeg AT, Pijnappel W. Antisense oligonucleotides promote exon inclusion and correct the common c.-32-13T>G GAA splicing variant in Pompe disease. *Mol Ther Nucleic Acids.* 2017;7:90–100.
 55. Masat E, Laforêt P, De Antonio M, Corre G, Perniconi B, Taouagh N, et al. Long-term exposure to Myozyme results in a decrease of anti-drug antibodies in late-onset Pompe disease patients. *Sci Rep.* 2016;6: 36182.
 56. Lipinski SE, Lipinski MJ, Burnette A, Platts-Mills TA, Wilson WG. Desensitization of an adult patient with Pompe disease and a history of anaphylaxis to alglucosidase alfa. *Mol Genet Metab.* 2009;98(3):319–21.
 57. Capanoglu M, DibekMisirlioglu E, Azkur D, Vezir E, Guvenir H, Gunduz M, et al. IgE-mediated hypersensitivity and desensitisation with recombinant enzymes in Pompe disease and type I and type VI mucopolysaccharidosis. *Int Arch Allergy Immunol.* 2016;169(3):198–202.
 58. Gally L, Petiot P, Durieu I, Streichenberger N, Berard F. SWORD: a simplified desensitization protocol for enzyme replacement therapy in adult Pompe disease. *Neuromuscul Disord.* 2016;26(11):801–4.
 59. Kishnani PS, Corzo D, Leslie ND, Gruskin D, Van der Ploeg A, Clancy JP, et al. Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease. *Pediatr Res.* 2009;66(3):329–35.
 60. Van den Hout JMP, Kamphoven JHJ, Winkel LPF, Arts WFM, De Klerk JBC, Loonen MCB, et al. Long-term intravenous treatment of Pompe disease with recombinant human alpha-glucosidase from milk. *Pediatrics.* 2004;113(5):e448–57.
 61. Burrow TA, Hopkin RJ, Leslie ND, Tinkle BT, Grabowski GA. Enzyme reconstitution/replacement therapy for lysosomal storage diseases. *Curr Opin Pediatr.* 2007;19(6):628–35.
 62. Karimian Z, Whitley CB, Rudser KD, Utz JRJ. Delayed infusion reactions to enzyme replacement therapies. *JIMD Rep.* 2017;34:63–70.
 63. Milligan A, Hughes D, Goodwin S, Richfield L, Mehta A. Intravenous enzyme replacement therapy: better in home or hospital? *Br J Nurs.* 2006;15(6):330–3.
 64. Concolino D, Amico L, Cappellini MD, Cassinerio E, Conti M, Donati MA, et al. Home infusion program with enzyme replacement therapy for Fabry disease: the experience of a large Italian collaborative group. *Mol Genet Metab Rep.* 2017;12:85–91.
 65. Burton BK, Wiesman C, Paras A, Kim K, Katz R. Home infusion therapy is safe and enhances compliance in patients with mucopolysaccharidoses. *Mol Genet Metab.* 2009;97(3):234–6.
 66. Elstein D, Abrahamov A, Oz A, Arbel N, Baris H, Zimran A. 13,845 home therapy infusions with velaglucerase alfa exemplify safety of velaglucerase alfa and increased compliance to every-other-week intravenous enzyme replacement therapy for Gaucher disease. *Blood Cells Mol Dis.* 2015;55(4):415–8.
 67. Nalysnyk L, Sugarman R, Cele C, Uyei J, Ward A. Budget impact analysis of eliglustat for the treatment of gaucher disease type 1 in the United States. *J Manag Care Spec Pharm.* 2018;24(10):1002–8.
 68. Guest JF, Jenssen T, Houge G, Aaseboe W, Tøndel C, Svarstad E. Modelling the resource implications of managing adults with Fabry disease in Norway favours home infusion. *Eur J Clin Investig.* 2010;40(12):1104–12.
 69. Kanters TA, van der Ploeg AT, Kruijshaar ME, Rizopoulos D, Redekop WK, Rutten-van Mölken M, et al. Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in adult patients with Pompe disease. *Orphanet J Rare Dis.* 2017;12(1):179.
 70. El-Gharbawy AH, Mackey J, DeArmev S, Westby G, Grinnell SG, Malovrh P, et al. An individually, modified approach to desensitize infants and young children with Pompe disease, and significant reactions to alglucosidase alfa infusions. *Mol Genet Metab.* 2011;104(1–2):118–22.