

Hypersensitivity infusion-associated reactions induced by enzyme replacement therapy in a cohort of patients with late-onset Pompe disease: An experience from the French Pompe Registry

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ABSTRACT

Background and objectives: Pompe disease is a rare hereditary glycogen storage disorder due to lysosomal acid alpha-glucosidase deficiency. Enzyme replacement therapy (ERT) is the only available treatment. Infusion-associated reactions (IAR) are challenging since there are no guidelines for ERT rechallenge after a drug hypersensitivity reaction (DHR) in Pompe disease. The objective of the present study was to describe IAR and their management in late-onset Pompe disease (LOPD) patients in France, and to discuss the various possibilities of ERT rechallenge.

Methods: An exhaustive screening of LOPD patients receiving ERT between 2006 and 2020 from the 31-participating hospital-based or reference centers was performed. The patients who had presented at least one hypersensitivity IAR (=DHR) episode were included. Demographic characteristics of the patients, IAR onset and timing, were retrospectively collected from the French Pompe Registry.

Results: Fifteen patients among 115 treated LOPD patients in France presented at least 1 IAR; 80.0% were women. Twenty-nine IAR were reported; 18 (62.1%) IAR were Grade I reactions, 10 (34.5%) IAR were Grade II, and 1 (3.4%) IAR was Grade III. IgE-mediated hypersensitivity was found in 2/15 patients (13.3%). The median [IQR] time from ERT introduction to the first IAR was 15.0 months [11.0–24.0]. ERT was safely and effectively re-introduced either with premedication alone, or in combination with either modified regimen or desensitization

Abbreviations: AntiHis, antihistamine; ATB, antibiotics; CRP, cardiopulmonary resuscitation; CS, corticosteroids; DP, desensitization protocol; DHR, drug hypersensitivity reaction; ERT, enzyme replacement therapy; F, female; FDA, Food and Drug Administration; GAA, alglucosidase alfa; HBP, high blood pressure (> 180 mmHg); IAR, infusion-associated reaction; ICU/EU, intensive care unit/emergency unit; IDR, intradermal reaction; IQR, interquartile range; IV, intravenous; LOPD, Late-onset Pompe disease; M, male; mAbs, monoclonal antibodies; MR, modified regimen; N/A, not available; NM, neuromuscular; NSAID, non-steroidal anti-inflammatory drug; Premed, premedication; PT, prick test; SD, standard deviation; SWORD, Start With One Regular Drop desensitization protocol.

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protocol, in all 9 rechallenged patients; including in patients with IgE-mediated hypersensitivity, in the patient with the Grade III reaction, as well as in patients with very high anti-GAA titer.

Discussion: Based on the results herein and previous reports, we discuss premedication and modified regimen for Grade I reactions, and desensitization in Grade II and III reactions. In conclusion, ERT-induced IAR can be safely and effectively managed with a modified regimen or desensitization protocol in LOPD patients.

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1. Introduction

1.1. Pompe disease

Pompe disease is a rare autosomal recessive glycogen storage disorder due to lysosomal acid alpha-glucosidase deficiency (OMIM: 232300, EC 3.2.1.20). This deficiency induces excessive glycogen overload in the skeletal muscle tissue and progressive skeletal muscle dysfunction [1]. Pompe disease can both present as infantile or late-onset myopathy. Late-onset Pompe disease (LOPD) patients typically present with limb girdle and axial muscle weakness or, rarely, myalgia and exercise intolerance, ultimately leading to respiratory support and wheelchair use [1]. To date, alglucosidase alfa or avalglucosidase alfa (GAA) enzyme replacement therapy (ERT) is the only Food and Drug Administration (FDA)-approved therapy in Pompe disease. Infusions are given every two weeks and last approximately four to five hours. ERT has been reported to lead to motor and respiratory function improvement or stabilization, and a nearly five-fold lower mortality in LOPD patients [2,3]. In France, 115 patients have been treated with alglucosidase alfa (Myozyme®, Genzyme Europe B.V., Amsterdam, The Netherlands) [4].

1.2. Infusion-associated reactions

Infusion-associated reactions (IAR) are defined as signs or symptoms occurring during a drug infusion or during the hours following a drug infusion [5]. Four cohort studies reported ERT-induced IAR in LOPD patients but they were not specifically dedicated to IAR characterization. IAR were reported in three different studies in 18, 28 and 38% of the patients treated with alglucosidase alfa and in 26, 29 and 40% of the patients treated with avalglucosidase alfa (the modified form of alglucosidase alfa for enhanced uptake) [6–9]. The most frequently reported IAR signs or symptoms were urticaria, pruritus, nausea, high blood pressure, flushing, chills, hyperthermia, and headache; each sign or symptom individually was reported in 6.1 to 20.0% of the patients receiving alglucosidase or avalglucosidase alfa [6–9] suggesting that a significant part of LOPD patients with IAR had in fact drug hypersensitivity reactions (DHR). IAR can either be due to hypersensitivity mechanisms (DHR, as described above) or not due to hypersensitivity (such as administration site conditions and symptoms also experienced by placebo-treated patients: headaches, dizziness), but in these studies, clear distinction between IAR and DHR was not made and DHR were not systematically characterized; overall, IAR were described as mostly mild-to-moderate, and anaphylaxis was reported in 0.0% to 5.0% of the treated patients depending on the studies. The phenotype of the DHR (immediate or delayed), its severity grading, as well as its biological mechanisms (IgE hypersensitivity [allergic] and non-IgE hypersensitivity [mostly non-allergic reactions]) [10,11] are key information to consider drug rechallenge, however very few information was provided regarding DHR biological mechanisms in these studies. Immediate DHR of various biological mechanisms have similar clinical presentations, mostly due to mast cell activation, common to both IgE- and non-IgE-mediated hypersensitivity (Fig. 1); dedicated workup is thus necessary in most cases [11,12]. The four cohort studies provided very few details about reintroduction modalities after IAR: either “modified regimen” [6], or administration of antihistamines and/or corticosteroids

and infusion rate slowing [7]. The response to a drug reintroduction depends on DHR severity and its biological mechanisms, as well as predictive factors of DHR, which were unfortunately not systematically studied in these studies. Finally, there are currently no established guidelines concerning ERT discontinuation or reintroduction after hypersensitivity IAR (or DHR) in Pompe disease. The European consensus for starting and stopping ERT in LOPD patients states that “stopping treatment should be considered (...) [if] the patient suffers from severe IAR that cannot be managed properly”, without statement about mild and moderate IAR [3]. IAR management is not stated by the American guidelines [13]. The objective of the present study was to provide exhaustive analysis of hypersensitivity IAR and their management in LOPD patients in France, and to discuss the various possibilities of ERT rechallenge.

2. Material and methods

2.1. Patients

Exhaustive screening of LOPD patients receiving ERT between 2006 and 2020 and followed in the 31-participating hospital-based or reference centers were performed by each local referent neurologist. No home-therapy is currently available in France, thus there are no patients treated with ERT outside of the French reference network. The patients who had presented at least one hypersensitivity IAR (=DHR) episode were included. Demographic characteristics of the patients, IAR onset and timing, as well as functional assessment parameters (6 min walk test, motor function measurement, and forced vital capacity) were retrospectively collected from the French Pompe Registry.

2.2. IAR characteristics

In the present study, included DHR were hypersensitivity IAR defined as signs and symptoms occurring within the first 24 h from the start of ERT administration and resembling drug allergy [10]. The severity of each DHR was defined according to the Ring and Messmer classification; pure (muco-)cutaneous involvement was classified as Grade I reaction, measurable extra-cutaneous involvement without life-threatening signs as Grade II, life-threatening signs were defined as Grade III, and cardiac and/or respiratory arrest as Grade IV [14]. The time from ERT introduction to DHR was defined as the number of months between the first ERT infusion (first introduction of the treatment) and the day of the first IAR. The time from intravenous (IV) ERT onset to DHR was defined as the number of minutes between the beginning of the ERT infusion and the first signs/symptoms of DHR.

2.3. Diagnostic allergy work-up

Diagnostic tests performed after the first and/or the following DHR episodes, and before ERT reintroduction were collected retrospectively from medical records: anti-GAA IgE, tryptase level, skin prick tests, intra-dermal reactions, and complement activation. Anti-GAA IgG titers were collected retrospectively from medical records at any time point available: before the first DHR, in-between episodes, and/or after the last DHR before ERT reintroduction. Anti-GAA IgG titers were classified

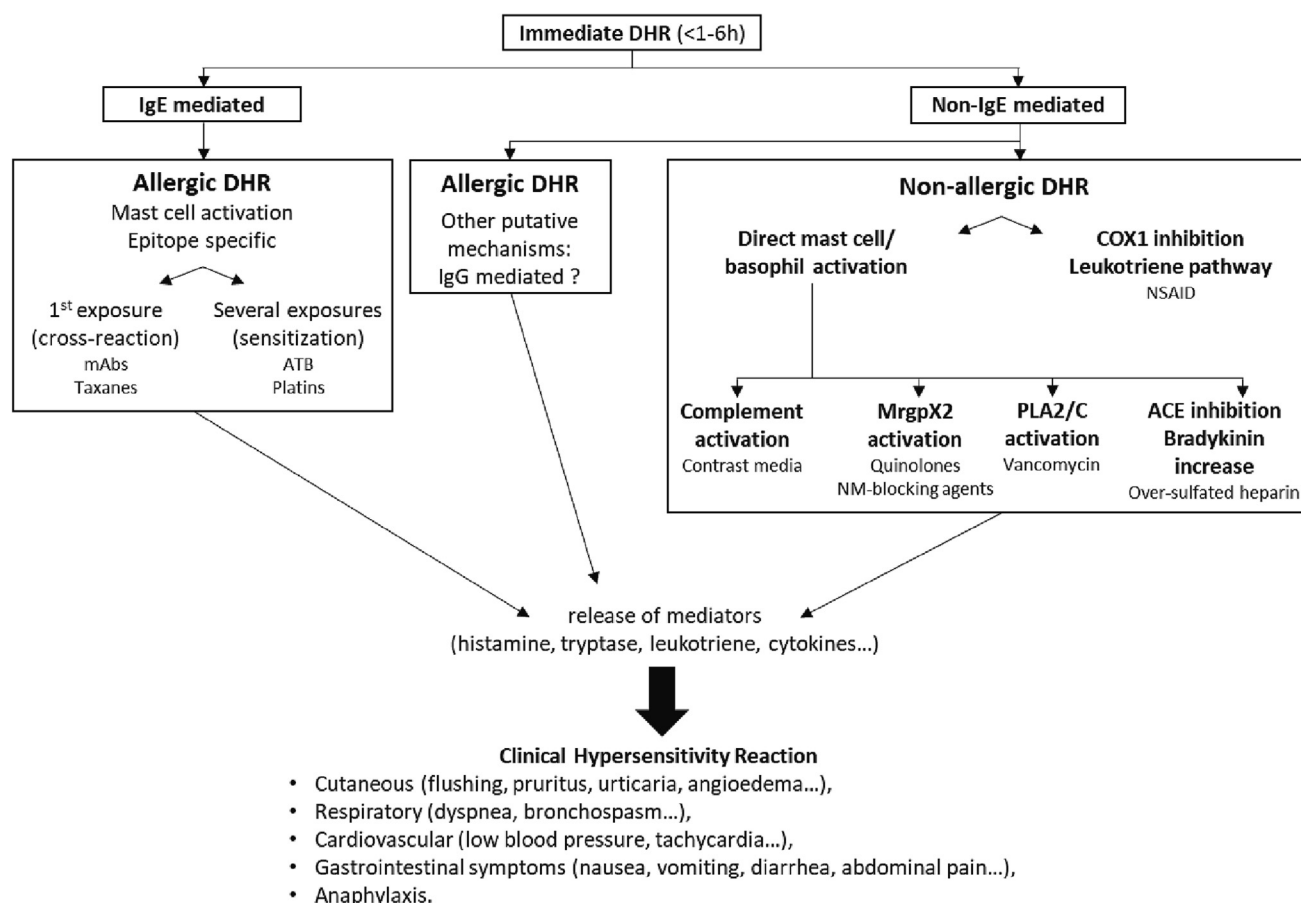


Fig. 1. Immune mechanisms involved in immediate drug hypersensitivity reactions.

Immediate DHR can be divided into IgE-mediated (allergic reactions) and non-IgE mediated reactions (mostly non allergic). Allergic reactions involve the adaptive immune system while non-allergic reactions involve the innate immune system and a direct activation of mast cells/basophils or specific metabolic pathway alterations without specific IgE production or T-cell activation.

Abbreviations: ATB: antibiotics; DHR: drug hypersensitivity reaction; mAbs: monoclonal antibodies; NM: neuromuscular; NSAID: non-steroidal anti-inflammatory drug.

according to a previous report: very high ($>1:100,000$), high ($\geq 1:31,250$), intermediate ($1:1250$ – $1:31,250$), and no-to-low titer (0 – $1:1250$) [7].

2.4. ERT reintroduction

After DHR, the timeline of ERT discontinuation (or not), premedication addition (or not), and ERT rechallenge (or not) was collected for each patient. ERT rechallenge was defined as any modality of ERT administration for the first time after a DHR: either without discontinuation after the DHR, or after a period of drug discontinuation, with or without changes to the usual protocol.

2.5. Statistical analyses

Descriptive statistics were performed using GraphPad Prism version 7.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com. Characteristics were provided as number and percentages for nominal variables. Continuous variables which followed normal distribution were presented as mean, standard deviation (SD) and range; others as median and interquartile range [IQR].

2.6. Standard protocol approvals, registrations, and patient consents

All procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2013. All data were collected

from the French Pompe Registry for which all patients had given written informed consent.

3. Results

3.1. Demographic and clinical characteristics

Data were collected from 15 LOPD patients treated with ERT in 7 French reference centers who had presented at least one DHR episode (Table 1). Twelve (80.0%) patients were women. No personal history of additional auto-immune or inflammatory disease was reported in any of the patients; auto-antibody titer(s) apart from anti-GAA IgE and IgG were not collected. The mean age at reaction was 52.0 years (SD: 16.5; range: 26.0–76.0 years). Six (40.0%) patients presented more than one DHR. Twenty-eight DHR were fully described in the 15 patients; among these, 18 (64.3%) DHR were Grade I reactions, 9 (32.1%) DHR were Grade II, and one (3.6%) DHR was Grade III. No transfer to intensive care unit was required. Urticaria or erythema was reported in 16 (57.1%) DHR, chest and/or throat tightness in 8 (28.6%), dyspnea in 4 (14.3%), chills and/or cold sweats in 4 (14.3%), facial edema in 4 (14.3%), oxygen desaturation in 3 (10.7%), and high blood pressure in 2 (7.1%; Table 2). Patient 1 also experienced severe low back pain during each DHR, resolving when the infusion was stopped. The median [IQR] time from ERT introduction to the first DHR was 15.0 months [11.0–24.0]; this was 14.0 months [11.0–33.0] for those with Grade I, 21.0 months [13.0–24.0] for Grade II, and 1.5 months for

Table 1

Demographic, clinical, and laboratory characteristics of the 15 patients reported with hypersensitivity infusion-associated reaction (DHR).

Case no.	Sex/ Age, years	DHR, number	Time from ERT introduction to DHR, months	First DHR Grade	Last DHR Grade	Anti-GAA IgE	Tryptase	Skin test	Comp-lement activation	ERT re-challenge	Delay, months	Follow-up, months
1	F/60	†	24	II	II [‡]	—	—	N/A	—	—	N/A	[§] 28
2	F/37	1	11	I	I	—	—	PT - IDR +	—	Modified regimen	29	29
3	F/34	1	36	I	I	—	—	N/A	N/A	Modified regimen	31	33
4	F/44	1	1.5	III	III	—	—	PT + IDR +	—	SWORD DP	2	62
5	F/26	1	144	II	II	—	—	N/A	+	SWORD DP	16	121
6	F/70	2	13	II	I [‡]	—	—	N/A	N/A	DP	0	61
7	F/76	†	13	I	I [‡]	—	—	N/A	N/A	Premed.	0	73
8	M/58	6	1.5	I	II [‡]	+	N/A	PT + IDR +	N/A	SWORD DP	78	41
9	F/27	5	18	I	I	+	—	IDR +	—	DP	7	38
10	M/76	1	21	II	II	—	N/A	N/A	N/A	—	N/A	25
11	M/61	1	1	I	I	—	N/A	N/A	N/A	—	N/A	196
12	F/63	1	33	I	I	—	N/A	N/A	N/A	—	N/A	116
13	F/45	1	24	I	I	—	N/A	N/A	N/A	—	N/A	38
14	F/46	1	15	II	II	—	N/A	N/A	N/A	—	N/A	40
15	F/57	1	14	I	I	—	—	PT —	N/A	DP	15	9

Abbreviations: DHR: drug hypersensitivity reaction; DP: desensitization protocol; F: female; GAA: αglucosidase α; HBP: high blood pressure (> 180 mmHg); IDR: intradermal reaction; M: male; MR: modified regimen; N/A: not available; Premed: premedication; PT: prick test.

† Numerous DHR; §: the second and following DHR occurred despite premedication.

‡ The second and following DHR episodes occurred despite premedication.

§ Death of unknown cause three years after ERT discontinuation.

the patient with Grade III reaction. Overall, 11/15 (73.3%) patients experienced the first DHR after the first year of treatment, and 3/15 (20.0%) after >2 years of treatment. One patient experienced DHR 144 months after ERT introduction. Sixteen (88.9%) Grade I reactions and 8 (88.9%) Grade II reactions occurred 60 min or later after the beginning of the IV injection. The Grade III reaction occurred 20 min after the beginning of the infusion. Among the 5 patients with multiple DHR, the interval between infusion start and the first symptoms progressively decreased at each new episode in two of them (patients 1 and 9; Fig. 2). Of note, no changes in medication, or infection, or other concurrent condition prior to DHR were reported.

The acute management of the episode as well as the DHR work-up was performed differently in each reference center, left to the discretion of the clinician in charge of the patient. Then, the risk assessment of ERT rechallenge considered the severity of the DHR, the number of episodes, the putative biological mechanisms, and the general physical condition of the patient. The discussion with the patient included the explanation of the risk of breakthrough reaction, the risk of ERT interruption on motor and respiratory function, and the impact of the rechallenge modalities on the patient's quality of life. The final decision of ERT pursuit or definitive discontinuation was made after national collegiate discussions of French experts based on previous literature, but was

implemented with different protocols according to the local facilities and the local practices of allergy specialists in each reference centers.

3.2. Laboratory and skin tests

3.2.1. DHR work-up

Anti-GAA IgE were performed in 10/15 patients and skin tests in 5/15 patients. Anti-GAA IgE and skin test positivity was found in two patients (last DHR: one Grade I and one Grade II). Prick tests were negative in the three anti-GAA IgE-negative patients (last DHR: two Grade I and one Grade III). Tryptase level was normal in all 9 tested patients (last DHR: five Grade I, three Grade II, one Grade III). Complement activation was observed in 1/5 tested patients (last DHR: Grade II). The exact timing between DHR and these tests was not available.

3.2.2. Anti-GAA IgG titer and DHR

Anti-GAA IgG titer before DHR was available in 6/15 patients; four had no-to-low IgG titers, and two had intermediate titers, and this was repeated after DHR in 2/6 patients. For one of these patients the titer had increased from no-to-low to intermediate, and for the other from intermediate to very high; the interval between the two tests was not available. After the last DHR, anti-GAA IgG titer was available in 10/15 patients. Three (30.0%) patients had very high anti-GAA IgG titer, none had high titer, two (20.0%) had intermediate titers, and four (40.0%) had no-to-low titer. The anti-GAA IgG were positive in the patient with Grade III reaction (no exact titer available). No clear trend was found between DHR severity grading and anti-GAA IgG titer.

3.3. ERT rechallenge

3.3.1. ERT pursuit or discontinuation

After the first DHR, ERT was stopped in 10/15 (66.7%) patients and continued under premedication in 5/15 (33.3%, patients 1, 6, 7, 8, and 9, Fig. 2). Patient 1 received antihistamines and corticosteroids, and further presented 2 Grade I reactions and one Grade 2 reaction before ERT was stopped. Patient 6 received antihistamines, corticosteroids, and antileukotrienes, she further presented a Grade I reaction before ERT was stopped. Patient 7 received antihistamines and corticosteroids and has since been presenting very discrete facial erythema after each ERT infusion, Patient 8 received antihistamines and corticosteroids

Table 2

Clinical characteristics of the 28 drug hypersensitivity reactions (DHR).

	DHR, N = 28
Urticaria and/or erythema, n (%)	16 (57.1)
Chest and/or throat tightness, n (%)	8 (28.6)
Dyspnea, n (%)	4 (14.3)
Chills and/or cold sweats, n (%)	4 (14.3)
Facial edema, n (%)	4 (14.3)
Oxygen desaturation, n (%)	3 (10.7)
High blood pressure, n (%)	2 (7.1)
Cyanosis, n (%)	2 (7.1)
Hot flush, n (%)	1 (3.6)
Cough, n (%)	1 (3.6)
Paresthesia, n (%)	1 (3.6)
Confusion, n (%)	1 (3.6)
Severe fatigue, n (%)	1 (3.6)
Low back pain, n (%)	1 (3.6)
Anaphylaxis, n (%)	1 (3.6)

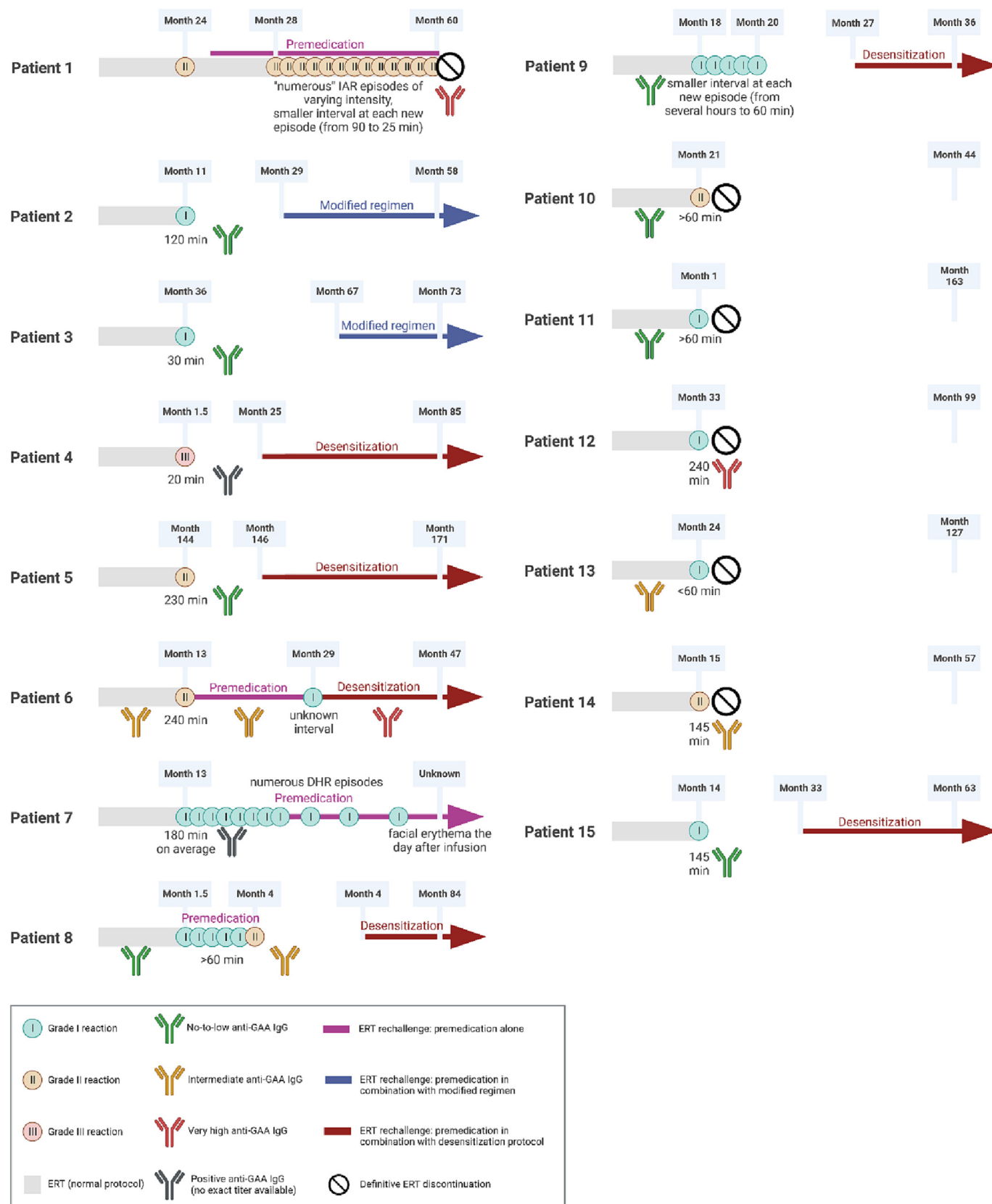


Fig. 2. Timeline of drug hypersensitivity reactions (DHR) and enzyme replacement therapy (ERT) management in the total population.

Timeline of drug hypersensitivity reaction (DHR) occurrence from the first month of DHR, to the last visit. The severity of the reaction (grade I, II or III; circles) as well as the interval from infusion start to the first signs or symptoms of DHR are indicated (when available) for each episode. Anti-GAA IgG titers were collected retrospectively from medical records at any time point available: before the first DHR, in-between episodes, and/or after the last DHR before ERT rechallenge. Anti-GAA IgG titers were classified as: very high ($>1:100,000$), high ($\geq 1:31,250$), intermediate ($1:1250$ – $1:31,250$), and no-to-low titer (0 – $1:1250$).

Abbreviations: DHR: drug hypersensitivity reaction; ERT: enzyme replacement therapy; GAA: α -glucosidase alfa.

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and further presented a Grade II reaction before ERT was stopped. Patient 9 did not receive additional premedication, she presented 5 Grade I reactions before ERT was stopped. Among all patients, regarding the severity of the last DHR before ERT rechallenge or discontinuation, 7/15 (46.7%) were Grade I, 7/15 (46.7%) were Grade II, and 1/15 (6.7%) was Grade III.

3.3.2. ERT rechallenge modalities

ERT was reintroduced in 9/15 patients: the last DHR before ERT rechallenge was Grade I in 5/9 (55.6%) patients, Grade II in 4/9 (44.4%), and Grade III in 1/9 (11.1%) patient (Fig. 3). The median time from treatment discontinuation to rechallenge was 15.1 months [1.2; 30.0]. ERT rechallenge involved: premedication alone in 1/9 patient; premedication combined with a modified regimen (MR) in 2/9 patients (MR was characterized by a “simplified” protocol, consisting in a decreased starting dose ($>1/1000$), decreased total dose, and moderately decreased flow rate for the three first infusions; Supp. Table 1); or premedication combined with a desensitization protocol (DP) in 6/9 patients. DP was characterized by the induction of a temporary tolerance state by incremental escalation of sub-optimal doses of ERT until the cumulative therapeutic dose is reached and tolerated (very low starting dose $<1/10,000$, very slow infusion rate, increased number of steps, increased total duration, Supp. Tables 2 to 4) as reported by Muraro et al [15]

Regarding ERT rechallenge modalities, premedication consisted most frequently of antihistamines (9/9 patients), followed by corticosteroids (6/9), and antileukotriene (2/9; Fig. 3). Among the patients who received DP, 3/6 received a simplified DP, the Start With One Regular Drop (SWORD) protocol (Supplemental Table 2) [16]; the other three patients treated in two different reference centers received a DP defined locally and based on previous publications (Supplemental Table 3 and 4) [17–19]. ERT re-introduction was safe in all rechallenged

patients, in case of putative IgE-mediated drug allergy (22.2%) as well as in non-IgE hypersensitivity (77.8%).

The median [IQR] follow-up after ERT rechallenge was 41 months [31.0; 67.5]. Among the 6 patients concerned, after the initial infusion with DP, premedication was used in all patients, a return to standard flow rates was achieved in two patients, and DP with extended infusion (24 h-long) was used in one patient. Patient 5 was progressively switched from alglucosidase alfa to avalglucosidase alfa 4 years after ERT reintroduction, she has not been presenting any DHR under the novel ERT after several months of standard flow rates infusions. Functional monitoring of rechallenged patients showed mild decrease or stability of the locomotor and respiratory functions during ERT discontinuation and after ERT rechallenge (Supplemental Fig. 1). Patient 6 died 61 months after ERT rechallenge (aged 73); Patient 15 died 6 months after ERT rechallenge from an unrelated cause (accident).

3.3.3. ERT definitive discontinuation

General physical condition of the patient and precautionary principles were the two main reasons for definitive ERT discontinuation in the 6/15 remaining patients: the last DHR before definitive ERT discontinuation was Grade I in 2/6 and Grade II in 4/6 patients. Overall, the locomotor and respiratory functions worsened after ERT definitive discontinuation. Patient 1 was lost to follow-up after ERT definitive discontinuation and died 2 years later (aged 66), patient 10 died 2 years after ERT discontinuation (aged 77), patient 11 died 16 years after ERT discontinuation (aged 62), and patient 14 died 3 years after ERT discontinuation (aged 45, respiratory failure). Patient 12 experienced disease progression over the 10 years following ERT discontinuation, her 6 min walk test (6MWT) decreased from 216 m without help (aged 63) to total incapacity (aged 73). The 6MWT of patient 13 was stable (between 238 and 251 m using a walking frame) during the 3 years after ERT discontinuation (aged 45 to 48, Supplemental Fig. 1).

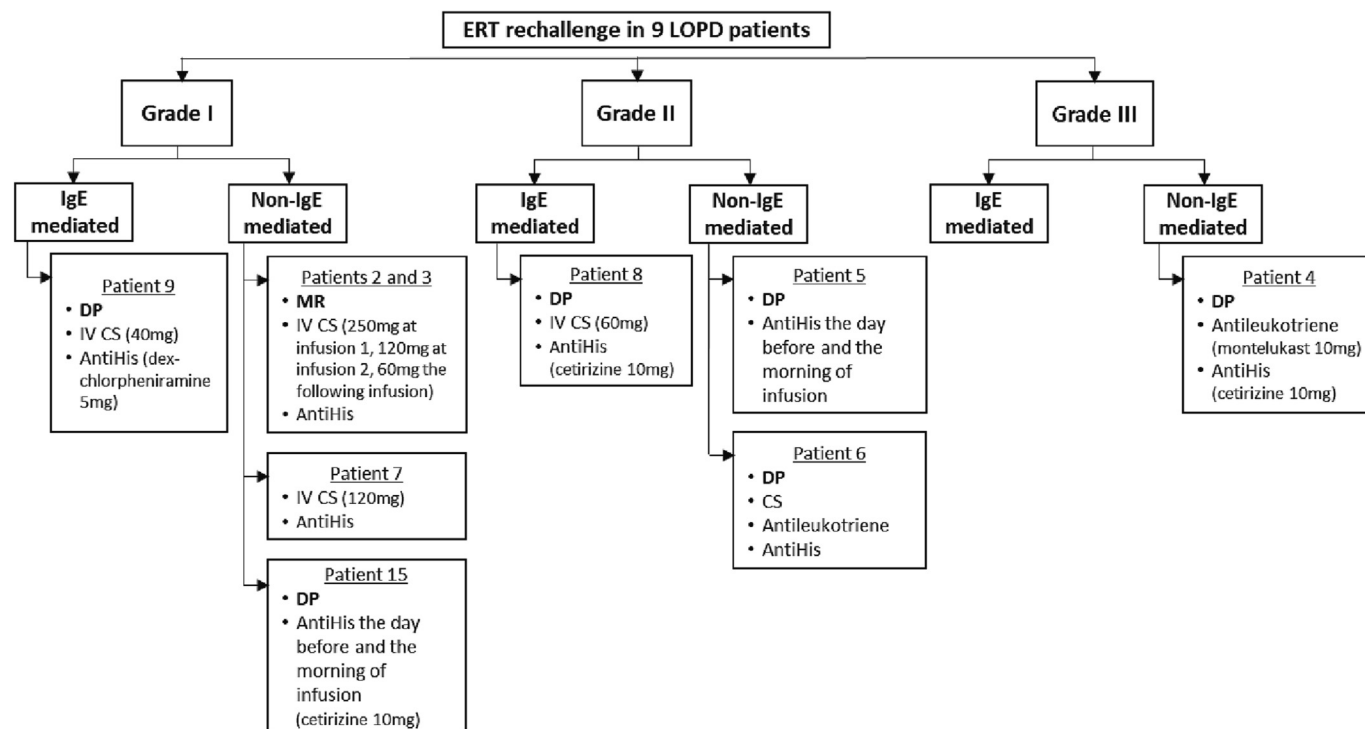


Fig. 3. Enzyme replacement therapy (ERT) rechallenge.

Enzyme replacement therapy (ERT) was successfully rechallenged in all 9 patients. Rechallenge consisted in premedication combined with either modified regimen (MR) or desensitization protocol (DP). MR was characterized by a “simplified” protocol, consisting in a decreased starting dose ($>1/1000$), decreased total dose, and moderately decreased flow rate for the three first infusions. DP was characterized by the induction of a temporary tolerance state by incremental escalation of sub-optimal doses of ERT until the cumulative therapeutic dose is reached and tolerated (very low starting dose $<1/10,000$, very slow infusion rate, increased number of steps, increased total duration).

Abbreviations: AntiHis: antihistamine; CS: corticosteroids; DP: desensitization protocol; ERT: enzyme replacement therapy; IV: intravenous; LOPD: late-onset Pompe disease; MR: modified regimen.

4. Discussion

The present study provides additional characterization of ERT-induced DHR and ERT reintroduction in LOPD patients. Most DHR occurred in female patients; DHR were most frequently due to non-IgE mediated hypersensitivity, most were Grade I reactions, and nearly half of patients experienced multiple DHR. The interval between ERT introduction to first DHR was variable, and ERT re-introduction was safe and effective in all rechallenged patients, involving either premedication alone or in combination with MR or DP.

DHR characterization is crucial to investigate their potential predictive factors in LOPD patients. Although the sex ratio of LOPD patients in the source population studied herein was not collected, it is expected to be around one in Pompe disease [20] and therefore the present study suggests that female LOPD patients are more prone to suffer from a DHR. This has been reported by De Vries et al. (92.3% of patients with an IAR were female) in a LOPD population that had a sex ratio of 1 [7]. This is consistent with that reported more generally for DHR, regardless of the type of drug, in American and European populations [21]. In an epidemiological study among 2.7 million patients, 377,474 (13.8%) reported drug-induced hypersensitivity reactions, of which 70.3% were female [22], and in a Portuguese population specifically, the OR was 2.05 (95% confidence interval [1.04; 2.82]) [23]. Another point is that IAR occurred in patients with no-to-low, intermediate, or very high anti-GAA IgG titers herein, which is not in favor of a potential predictive role of this biomarker in adult patients. The peak anti-GAA IgG titer was also previously reported to correlate significantly with IAR occurrence [7], but this association remains controversial [6]. It may be of interest in future studies to investigate the kinetics of anti-GAA IgG titer rather than the peak anti-GAA IgG titer, as a predictive factor of DHR occurrence. Moreover, ERT was safely and effectively re-introduced in all rechallenged patients herein, in particular in patients with intermediate and very high anti-GAA IgG titer, suggesting that this titer should not *per se* contraindicate ERT rechallenge. It is of note that most previously reported IAR were mild-to-moderate [6–9], however the method used to assess reaction intensity was provided in only the most recent study reported by Diaz-Manera et al.: mild, moderate, and severe IAR were defined by the importance of discomfort and interference with everyday activities [9]. In the present study we used the Ring and Messmer classification that does not account for discomfort and limitations [14]; Grade I and II reactions could therefore either be classified as mild or moderate according to Diaz-Manera et al. [9], which limits comparison. However, Grade III reactions are life-threatening and thus would be classified as severe IAR in the study reported by Diaz-Manera et al. [9]; the present study found 6.7% of Grade III patients, and Diaz-Manera et al. [9] found 4.0% of patients with severe IAR. In addition, previous studies did report anaphylaxis; 6.7% of patients herein experienced anaphylaxis, while <5.0% did so elsewhere [6–9]. Taken together, these results suggest that severe IAR are infrequent in LOPD patients. This result is an argument for administering the treatment at home, which is not currently possible in France. It would be of interest for future studies to apply both classifications that explore different dimensions of adverse reactions and which would allow comparison. Another point is that the present study did not find a link between DHR severity and the interval from ERT introduction to first DHR. To our knowledge, this relationship has never been studied. It is of note that IAR (of any severity) occur mostly during the first year after ERT introduction [7,8,24], whereas in the present study these occurred later, even years after ERT introduction. Interestingly, similar “late” ERT-induced DHR were reported in adult patients suffering from other lysosomal storage disorders (LSD) such as Fabry and Gaucher diseases, and viral infection was reported as a potential trigger for the DHR in one case [25–29]. Concurrent conditions to DHR, such as infections, that could have favored these “late” DHR occurring after the first year of treatment were not reported in LOPD patients. This is of particular interest for future studies to evaluate predictive risk factors. Risk factors and pathomechanisms

underlying DHR in LOPD patients are incompletely characterized; the potential role of cellular processes other than dysimmune, such as autophagy, should be considered. Ripolone et al. all demonstrated the positive impact of ERT on the dysregulated autophagy processes in LOPD patients [30], future studies based on muscle biopsy histology and transcriptomic analyses from LOPD patients with DHR *versus* without DHR could provide very interesting insights regarding DHR biological mechanisms. The findings presented herein also did not support a link between DHR severity and its biological mechanism. Both IgE and non-IgE mediated IAR were previously reported in 6 LOPD patients [6,8,18]; DHR work-up was not available in the 62 other LOPD patients [6–9,24]. Herein, DHR occurred mostly after 60 min of ERT infusion, tryptase level were within normal range, and IgE/skin test were negative in all but two patients, suggesting that most IAR were probably due to non-IgE mediated hypersensitivity [31]; complement activation was also found in one patient as reported in [8]. Taken together, these observations suggest that IgE-mediated hypersensitivity accounts for a low proportion of DHR in LOPD patients.

For drug rechallenge, the risk assessment considered: the severity of the DHR, the putative biological mechanisms, and the general physical condition of the patient, as proposed in general DHR management [11,17]. European and American guidelines state that *in vivo* or *in vitro* testing for isolated acute urticaria is not mandatory but is recommended for other DHR [32,33]; LOPD patients with disabling and/or recurrent Grade I reactions, as well as those with Grade II and III reactions, should thus be referred to reference centers for *in vivo/in vitro* testing; these investigations were not performed in all 15 patients herein, and taken together with the lack of DHR work-up in previous studies, this highlights the need to standardize IAR workup in LOPD patients. DHR work-up should be performed 3–6 weeks after DHR, meaning at least 3 weeks of interruption of the ERT; this interruption should be kept to the minimum. In the present study, a dramatic worsening of the locomotor and respiratory functions was observed in non-rechallenged patients, while mild decrease to stability was observed in the rechallenged patients in which ERT discontinuation was the shorter. This proposal to keep ERT stop <6 weeks is further supported by recent literature, as a worsening of motor and respiratory function was reported in LOPD patients after 2.2 months of ERT interruption due to COVID-19 pandemic; interestingly, no severe IAR was observed at restart [34]. Of note, the present study found that MR as well as DP may drastically increase the infusion duration, thus highlighting that local human as well as technical resources may be potential limiting factors for ERT rechallenge. The patient should be actively consulted in the difficult decision of re-introducing vs discontinuing ERT; the evaluation of the risk of breakthrough reaction should be exposed, as well as the impact on the quality of life regarding the prolonged hospitalization duration required by DP, to be weight against the natural course of the untreated disease. Of note, ERT definitive discontinuation was associated with a disruption in the medical follow-up of one of the 6 non-rechallenged patients, this patient loss to follow-up after ERT discontinuation is frequently observed in clinical practice; medical compliance as well as medical follow-up in a reference center participate in the indirect efficacy of ERT.

Algorithms for DHR management in other LSD were previously published, but similar to Pompe disease, no international consensus is available. [26,35,36] Interestingly, IAR are also frequent in Fabry disease (57 to 59% of patients), while they are rarely reported in Gaucher disease (approximately 6% of patients) [37–39]. Future studies should consider comparing DHR in LSD patients, as it could increase our understanding of the pathomechanisms of ERT-induced DHR, as and DHR management algorithms in Pompe disease could have a broader applicability to other LSD. In LOPD patients there is no report of ERT reintroduction after Grade I reaction but reports of mild IAR effectively managed with premedication and MR, as were non-IgE-mediated Grade I reactions in the present study; the single case of IgE-mediated Grade I reaction herein was managed with DP. Taking into account the limitation of Grade I/mild IAR comparison, these results suggest that ERT may be

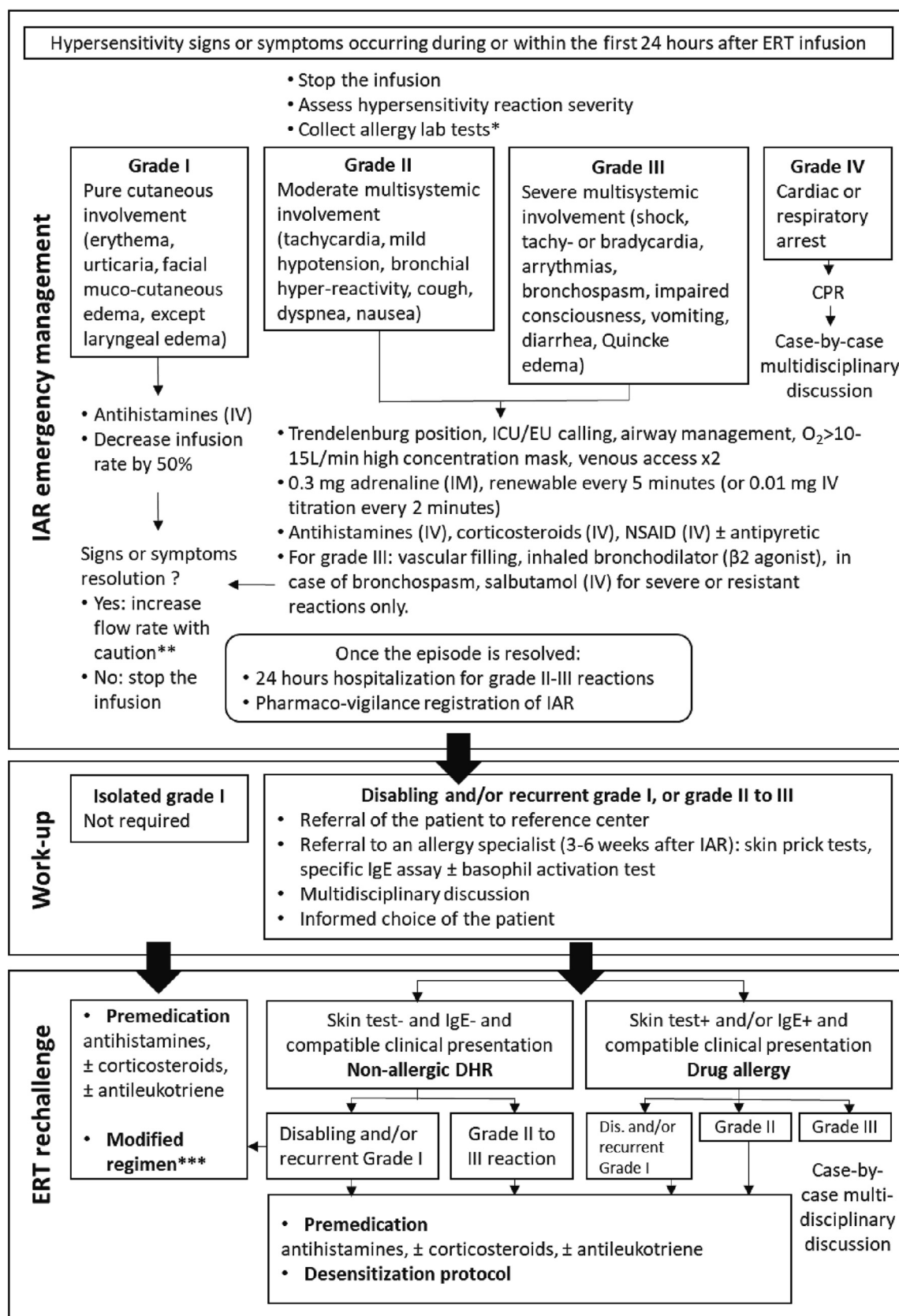


Fig. 4. Decision tree for enzyme replacement therapy (ERT)-induced drug hypersensitivity reaction (DHR) management and rechallenge in late-onset Pompe disease (LOPD) patients. Based on the results of the present study and the data from the literature, we established *a posteriori* a proposal of decision tree for the management of the future cases of DHR in LOPD patients. The present study did not detail the modalities of DHR emergency management, as it follows the general guidelines for DHR [15,33].

* Lab tests should not delay emergency management at any cost. Blood sample for tryptase should be collected as soon as possible and within the first 90 min; histamine and complement C3, C4, CH50 within one to three hours after a DHR. Anti-GAA IgE and IgG should be collected at least three days after a DHR and before the following enzyme replacement therapy (ERT) infusion. Basophil activation test detects the upregulation of basophil activation surface markers and represent an additional clue for the risk assessment of a reaction during desensitization.

** In case of signs and symptoms resolution after Grade I or II reactions, progressively increase the infusion flow rate by 50% during 15 to 30 min, and then return to initial flow rate.

*** MR is characterized by a "simplified" protocol, consisting in a decreased starting dose (>1/1000), decreased total dose, and moderately decreased flow rate for the three first infusions.

Abbreviations: CPR: cardiopulmonary resuscitation; DHR: drug hypersensitivity reaction; DP: desensitization protocol; ERT: enzyme replacement therapy; GAA: αglucosidase α; ICU/EU: intensive care unit/emergency unit; IV: intravenous; MR: modified regimen.

carefully reintroduced with premedication and MR after an isolated non-IgE mediated Grade I reaction. However, MR may be insufficient in disabling and/or recurrent Grade I reaction, and DP may be required. In the literature, patients with moderate DHR benefited from MR [6,7] and one patient with Grade II reaction from DP [18], as were all Grade II reactions in the present study; we thus propose DP rather than MR for Grade II reactions. In the literature, IgE-mediated Grade III reactions were managed with MR in two patients [6], and with DP in a third patient with Grade III IAR of unknown mechanism [24]; while we reported effective rechallenge with DP in a case of non-IgE mediated Grade III reaction. Based on the present study, DP can be considered in non-IgE mediated Grade III reaction; however, ERT rechallenge for IgE-mediated Grade III reactions should be carefully considered on a case-by-case basis, as the risk is higher in these patients. The French clinicians who participated in the present study collectively proposed a simple decision tree for future DHR management in LOPD patients, based on the retrospective assessment of the French Pompe Registry, and the data from the literature discussed here above (Fig. 4). This decision tree has been designed to homogenize the practices between the French reference centers, to improve our understanding of DHR mechanisms and future patient care. Of note, since no new DHR case was reported to the French Pompe Registry since, this protocol has not been implemented to a new LOPD patient yet. While ERT rechallenge modalities were managed locally according to local facilities and local clinical practice, the decision tree in Fig. 4 was established *a posteriori* by common concerted action after the French case review, and was designed for future DHR cases. Retrospectively, ERT was reintroduced according to this decision tree in all but 2 reported patients herein: the therapeutic approaches in Patient 7 (recurrent erythema under premedication alone) and Patient 15 (constraining DP for one isolated non-IgE grade I episode) were not considered optimal and were therefore not retained for the decision tree. Despite the decision tree proposal, the final decision to reintroduce or to definitively stop ERT in a LOPD patient is highly challenging, for the clinician as well as for the patient, who faces a very difficult dilemma and may refuse ERT reintroduction, balancing a life-threatening breakthrough reaction to a slowly-progressive disease.

The present study does have several limitations. The main one was the declarative design of the study; the 15 patients with IAR herein represented 13.0% of the total number of ERT-treated LOPD patients in France that is slightly lower than in other studies [6–9], suggesting that some Grade I DHR might not have been reported. However, it is unlikely that severe DHR were not reported, considering the limited number of ERT-treated LOPD patients per reference center, suggesting that the proportion of Grade I among all DHR might be slightly underestimated in the present study. Of note, the proportion of DHR versus non-DHR IAR has never been assessed; it thus not possible to compare the 13.0% observed herein with the proportion of non-DHR IAR in previous studies. In addition, only French patients were included, which limits the extrapolation of the results of the present study. More generally, missing data regarding DHR work-up was frequent; this was related to the retrospective design of the study but highlights the heterogeneity of IAR management in France.

5. Conclusion and perspectives

In conclusion, ERT-induced DHR can be safely and effectively managed with a MR or DP in LOPD patients. Further studies are required to investigate the biological mechanisms of DHR, to identify predictive factors, and to further define ERT rechallenge protocols.

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Ethics approval and patient consent

All procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2013. All data were collected from the French Pompe Registry for which all patients had given written informed consent.

CRediT authorship contribution statement

Lola E. R. Lessard: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Céline Tard:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Emmanuelle Salort-Campana:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Sabrina Sacconi:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Anthony Béhin:** Investigation, Writing – review & editing. **Guillaume Bassez:** Investigation, Writing – review & editing. **David Orlowski:** Investigation, Writing – review & editing. **Philippe Merle:** Investigation, Writing – review & editing. **Sylvain Nollet:** Investigation, Writing – review & editing. **Laure Gallay:** Investigation, Writing – review & editing. **Frédéric Bérard:** Writing – review & editing. **Philip Robinson:** Writing – review & editing. **Françoise Bouhour:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Pascal Laforêt:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator. This manuscript has data included as electronic Supplementary Material.

Declaration of Competing Interest

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Appendix A. Supplementary data

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