Real–world Data of In–hospital Administration of Alglucosidase Alfa in French Patients with Pompe Disease: Results from the National Claims Database

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Abstract

Introduction: Pompe disease, caused by a rare biallelic mutation in the GAA gene resulting in acid α-glucosidase deficiency and glycogen accumulation.

Aim: We analyzed hospital admissions associated with the administration of Myozyme®, utilizing the French hospital discharge database, known in France as the *Programme de Médicalisation des Systèmes d'Information* (PMSI), which comprehensively captures all hospital activity within the country.

Methods: In this observational study, we examined hospitalization records from April 4, 2012, to December 31, 2019, within the PMSI database, focusing on admissions where Myozyme® was administered. We particularly investigated the incidence of critical care admissions and adverse events (AEs) related to Myozyme®.

Results: From 2012 to 2019, approximately 26,714 hospital stays involving Myozyme® administration were recorded for 239 patients. Most (96.6%) of these were outpatient stays, with only 3.2% requiring critical care. Furthermore, hospitalizations without critical care needs increased from 96% in 2012 to 99% in 2019. Of the patients receiving at least one infusion, 997 critical care admissions were recorded, with 781 (78.3%) occurring concurrent with or the day after the Myozyme® treatment without directly correlating to adverse effects of enzyme therapy.

Conclusions: The analysis of the French hospital discharge database indicated that Myozyme® was associated with a low incidence of AEs and complications in a hospital context, supporting the consideration of its safe use in home-infusion settings.

Introduction

Acid α–glucosidase (GAA) deficiency or Pompe disease is an autosomal recessive rare lysosomal storage disorder, leading to the accumulation of glycogen, especially in skeletal, cardiac, and smooth muscles [1]. Based on the residual GAA activity and age of onset of symptoms, Pompe disease can be classified into two major forms, i.e., classic infantile–onset Pompe disease (IOPD; GAA activity: <1%) usually present in the first months of life, and late–onset Pompe disease (LOPD; GAA activity: 2–40%), in which appearance of symptoms can range from infancy to late adulthood [1, 2].

The incidence of the diseases varies by geographic origin, diagnostic criteria, and methods. However, the LOPD is the most commonly diagnosed and represents more than 90% of cases reported in France [3]. One of the French cohort studies estimated the frequency of LOPD to be 1 in 69,927 newborns [4]. In contrast, data is very limited for IOPD, with only one retrospective study reporting the incidence of IOPD in the French Guiana population to be 1 in 4528 births. The incidence of IOPD in French Guiana is much higher compared to the rest of the world [5].

Earlier, the prognosis of classical infantile Pompe disease was poor, with patients rarely surviving beyond 1 year, whereas patients with LOPD often live longer as disease progresses slowly. However, the approval of the first intravenous enzyme replacement therapy (ERT) using recombinant human GAA substantially improved the prospects for both IOPD and LOPD patients [1]. Alglucosidase alfa (Myozyme®) was first approved in 2006 in US and Europe for both IOPD and LOPD [6-8]. The safety and efficacy of alglucosidase alfa have been established in various clinical trials [9-14]. There are real world studies investigating the effectiveness of alglucosidase alfa, but the safety aspect has not been studied in much detail [3, 15, 16]. A French Pompe Registry study conducted during COVID-19 pandemic suggested that the interruption of ERT, worsened motor and respiratory function in patients with Pompe disease. Therefore, continuing ERT at home for risk-free LOPD patients has been encouraged [17-19]. Data from the Swiss Pompe Registry also suggested that long-term interruption of ERT in LOPD may lead to deterioration of clinically meaningful parameters and quality of life [20].

In France, the administration of alglucosidase alfa occurs exclusively within hospital settings, administered by healthcare professionals. Each patient's hospital stay is meticulously documented through a standardized electronic discharge summary outlining their medical treatment in detail. At the heart of France's healthcare reimbursement landscape is the *Programme National de Médicalisation des Systèmes d'Information* (PMSI), a cornerstone of the French Prospective Payment System. The PMSI's robust framework records an impressive breadth of data, encompassing full and partial hospitalizations in public and private facilities, amassing over 25 million records annually.

The PMSI stands out for its unparalleled exhaustiveness compared to other health registries, which often suffer from incomplete data capture and representativeness issues. This comprehensive recording process ensures that every hospitalization is accounted for, offering a complete picture of the healthcare provided. In contrast, other registries may be selective or incomplete, missing critical information that can affect the quality and reliability of research findings.

Utilizing the thorough PMSI database, the current study aims to deliver real-world insights by reviewing hospital admissions related to Myozyme® administration. It scrutinizes instances where patients transition to critical care post-administration and documents any adverse events or complications that may be associated with Myozyme®. This approach provides a more accurate and complete dataset than traditional registries, enabling a deeper understanding of the drug's impact in a real-world healthcare setting.

Methods

Study design and participants

This retrospective, observational, longitudinal study analyzed all hospital stays of French patients with Pompe disease receiving at least one injection of Myozyme® between April 4, 2012 and December 31, 2019. Hospital stays of incident patients who received at least one infusion of alglucosidase alfa were included, as identified by the common dispensing unit code (UCD 7/UCD 13) corresponding to Myozyme® 50mg PERF FL. Patients were followed from the index date defined as the first administration of Myozyme® occurring within the inclusion period (January 1, 2012 to December 31, 2019). Hospital stays occurring prior to the first administration of Myozyme® or stays with GHM coding (homogenous group of patients) in major diagnostic category CMD 90 (Errors and other unclassifiable stays) were excluded. The study was conducted following all relevant regulatory requirements, and the scope of the analysis was to mobilise PMSI data for the purposes of research, study, or evaluation within the meaning of Article L.1461–3 of the Public Health Code. Use of the PMSI database was regulated by the Health Data Hub (HDH). The study was reported on the HDH on November 12, 2020 in compliance with the Reference Methodology for Drug Manufacturers (MR 006) process.

Data source: PMSI

Hospital stays in the Medicine–Surgery–Obstetrics sector in France is always associated with standardized discharge summary providing description about patient's sociodemographics (age, gender, geographical location), and reasons for hospitalization (main pathology and associated conditions) as classified and coded by International Classification of Diseases 10th Revision (ICD–10). This data was obtained from the PMSI national databases, provided by *Agence Technique de l'Information Hospitalière* (ATIH) and made available through secure remote data access centre. The pseudo anonymization of the data was maintained by ATIH. In the data used, an anonymous number for each patient was used and allow to follow the patient across the study period.

Data validation

The robustness of patient merging step was validated by two approaches: statistical and analytical. The statistical approach assumed that the distribution of patients is homogeneous according to their geographical location, gender, and age, and thus the probability of merging different patients was found to be 0.067% using the formula:

Number of patients identified (271) / Number of geographic codes (5710) × number of genders (2) × number of ages (35).

The analytical approach identified 32 patients (n=5, invalid codes) to merge out of the initially identified 271 anonymous patients' identification codes. These 32 patients represented 932 stays between 2012–2019 period

(mean: 29 stays per patient). A screening of patients to be merged by year and month confirmed the appropriateness of this approach.

Study outcomes

The main objective of the study was achieved by three steps. Firstly, hospital stays with Myozyme® administration were identified, with a particular attention to the stays comprised of a step in critical care. The term 'critical care' is used to define stays in Intensive care unit (ICU) or emergency life support unit. Secondly, hospital stays including a passage in critical care within 1 day (Day 0 and Day 1) following Myozyme® injection. Lastly, complications or AEs associated with enzymes administration and possibly related to Myozyme® injection that were reported as described by the Significant Associated Diagnosis (DAS) code Y436, that is, adverse reactions to enzymes not otherwise classified in therapeutic use.

The PMSI coding methods were unable to determine whether an AE was directly linked to the Myozyme® injection. However, they do identify an AE that occurred in the proximity of the infusion. As a result, the complications associated with the hospital stays during Myozyme® injection, or within 24 hours after the injection were studied in 2 groups: Group 1 included complications were coded with Y436 related to enzyme reaction and considered directly linked to Myozyme®; Group 2 included complications comprised of all codes enumerated in Supplementary Table 1 in addition to Y436. As these codes are not specific to enzyme reaction, therefore AEs in group 2 were assumed as probably linked to Myozyme®. For establishments not using the Y code systematically, an additional list of selected AE codes for recording complications during hospital stay was used. (Table 1).

Statistical analysis

The study was purely descriptive, and no statistical hypotheses were tested. Continuous variables are described by mean (SD), whereas categorical variables are presented as frequency counts and percentage.

Results

Overall hospital stays with Myozyme® injection including a part stay in critical care

Overall, 26714 hospital stays with Myozyme® injection were identified in 239 patients (males, n=113; female, n=126; mean age, 39.8 [SD 24.2], median age 45 [Q1: 20; Q3: 59] between 2012 and 2019. The majority of hospital stays i.e., 25818 (96.6%) were carried out as outpatients since the duration of stay was found to be less than 1 day (Table 2).

Critical care hospital stays during or near Myozyme® injection

During the study period, patients treated with Myozyme® had 997 critical care hospital stays. While 852 (85.5%) of the 997 occurred during a stay with Myozyme® injection, 145 (14.5%) additional critical care stays were identified and may have occurred near a Myozyme® injection. The critical care transitions considered for this analysis may occur at any time during the stay, and possibly at a different timepoint from the Myozyme® injection. Besides, the proportion of hospitalizations not associated with critical care increased from 96% in 2012 to 99% in 2019 **(Figure 1).** Therefore, the stays in critical care should be assessed separately. After an assessment of the time between the stay in critical care and the infusion of Myozyme®, 781 (78.3%) from 997

stays in critical care were identified on the D0 or D1 after a Myozyme® injection. A year–wise breakdown of these 781 stays indicated a clear decrease in critical care admissions after 2016 **(Figure 2)**. Most importantly, none of these admissions were found to be associated with Myozyme®. Moreover, about 709 (90.8%) of 781 stays pertained to 11 patients only who were identified as hospitalized more than 9 times in critical care during the study period.

Nearly 90% of admissions to critical care immediately after a Myozyme® injection were mainly treated as outpatients, and for 75% cases the next Myozyme® injection was not delayed (administered within 15 days of previous admission). Four (0.5%) patients discontinued their treatment **(Table 3)**. However, no deaths were reported in patients receiving regular ERT treatment in critical care.

Complications and adverse events of Myozyme®

Of the 26714 stays, only 10 (0.04%) had an associated diagnosis code Y436, among which no patient was transferred to critical care, and 6 of them were treated on an outpatient basis. Following the stay with complication, Myozyme® was rapidly resumed with the administration of next injection within 17.4 days on average. In addition, 25 stays with others AE were identified to be probably linked with Myozyme® infusion (**Table 4**).

Discussion

This real–world study assessed the hospital admissions related to Myozyme® administration for more than 7.5 years beginning from April 2012 to December 2019, particularly those hospital stays involving admission to critical care. The study was aimed at describing hospitalizations with alglucosidase alfa, as there is limited knowledge on long-term courses with Myozyme® infusion. Moreover, adverse events that were directly or probably linked with Myozyme® were also reported.

The present analysis found out an increase in the number of hospital stays every year since 2012 (Table 1). This may be due to improvement in diagnostic methods [21], and use of an increased dose of ERT, especially for IOPD patients [22]. Moreover, the French National Authority for Health (*Haute Autorité de santé* or HAS) granted reimbursement to Myozyme® on April 4, 2012.

Myozyme® is administered as an intravenous infusion and should be supervised by a physician experienced in managing patients with Pompe disease or other inherited metabolic or neuromuscular diseases [8]. Therefore, Myozyme® is mostly administered in a hospital setting in France. The recent COVID–19 pandemic necessitated Pompe patients to receive ERT at home.

Research on alglucosidase alfa has primarily focused on its effectiveness and safety, with few studies delving into its long-term benefits [24,25]. The STIG study has been pivotal in evaluating the extended safety of alglucosidase alfa in individuals with Pompe disease, corroborating that its safety profile aligns with the established data of Myozyme® [12]. Furthermore, a comprehensive Japanese post-marketing surveillance report, which collated data over a nine-year period, has revealed that alglucosidase alfa is generally well-tolerated and effectively mitigates disease progression in Pompe disease patients [14].

Keeping all this in view, the present study was an attempt to add to the existing evidence by gathering the hospitalization data in real–world settings for the patients receiving Myozyme® regularly in France. Also, to understand how many patients with hospitalizations had outpatient stays, or were associated with a complication, or moved to critical care. It was also interesting to note that hospitalizations related to Myozyme® administration between 2012 and 2019 were mainly outpatient stays (96.6%), with only 3.2% of patients transitioning to critical care. However, further analysis revealed that for about 89.7% of stays, critical care was the first hospitalization unit. Thus, it can be hypothesized from this finding that most patients managed in critical care were at an advanced stage of the disease that required systematic management in critical care to prevent any medical complications occurring during their hospital stay. Also, this could be related to varied management practices among hospitals, certain institutions prefer to directly manage the patients in critical care even in the absence of any complication.

Concerning admission in critical care during or near Myozyme® injection, there was a clear decrease in critical care admissions from 2016 to 2019 [23]. This decrease may be attributed to general changes in management practices for patients treated with Myozyme® (i.e. Myozyme less administered in critical care services over time). Notably, none of these admissions were reported to be associated with Y436 code. Moreover, only 10 stays were associated with adverse reactions of Myozyme® and majority (60%) of them were treated as outpatients. Complications that may be associated with Myozyme® injection appeared non-interfering with patient management as the next dose was resumed within 14.3 days (mean) following any AE. These findings sync with the real–world safety data [12, 13].

Furthermore, the PMSI coding methods identified an AE that occurred in the proximity of Myozyme® injection during the same hospital stay or that necessitate re-hospitalization. PMSI studies are also subject to potential risk of errors during the coding process.

Few other limitations of this analysis can be acknowledged. Firstly, some institutions might face difficulty in sending the complete data at the end of the year, leading to slight under–reporting. Secondly, the quality of coding has improved significantly over the past decade. However, there is a large scope for improvement of coding of adverse events. This can be achieved by providing training courses within institutions.

In the nutshell, it can be concluded that the present analysis provided evidence that the administration of Myozyme® over a long period in the hospital setting was mainly as an outpatient and rarely associated with adverse reactions and complications. These findings do encourage the use of Myozyme® infusion mainly as an outpatient or as home–based treatment. Further studies are definitely warranted to support these findings.

Data availability statement

Data are available upon reasonable request.

Ethics statements (Patient consent for publication)

Not applicable.

Contributors

Conception and design of the study: Marion Afonso and Pierre Karam; statistical analysis: Pierre Karam; Interpretation of the data: Marion Afonso and Pierre Karam; drafting or revising the manuscript for intellectual content: all authors.

Competing interests

No competing interests

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Table 1: List of ICD 10 adverse drug reaction/complication Codes used in the analysis in addition to the Y436 code

ICD 10 code	Description	ICD 10 category
D590	Autoimmune hemolytic anemia, due to drugs	Acquired hemolytic anemia
D611	Medication–induced bone marrow aplasia	Other bone marrow aplasia
L270	Generalized rash due to medications	Dermatitis due to substances taken internally
L271	Localized rash due to medications	Dermatitis due to substances taken internally
R502	Fever due to medication	Fever of other and unknown origin
T802	Infections following therapeutic injection, infusion, and transfusion	Complications following therapeutic injection, infusion, and transfusion
T806	Other serum reactions	Complications following therapeutic injection, infusion, and transfusion
T808	Other complications following therapeutic injection, infusion, and transfusion	Complications following therapeutic injection, infusion, and transfusion
T809	Complication following therapeutic injection, infusion, and transfusion, unspecified	Complications following therapeutic injection, infusion, and transfusion
T811	Shock during or after a diagnostic and therapeutic procedure, not elsewhere classified	Complications of diagnostic and therapeutic procedures, not elsewhere classified
T886	Anaphylactic shock due to adverse effects of an appropriate and properly administered drug substance	Other complications of surgical and medical care, not elsewhere classified
T887	Unspecified adverse drug reaction	Other complications of surgical and medical care, not elsewhere classified
T888	Other specified complications of medical and surgical care, not elsewhere classified	Other complications of surgical and medical care, not elsewhere classified
T889	Complication of surgical and medical care, unspecified	Other complications of surgical and medical care, not elsewhere classified
Y578	Adverse effects of other substances and drugs during their therapeutic use	Adverse drug reactions, other and unspecified

ICD–10, International classification of disease version 10.

Table 2: Descriptive analysis of overall hospitalizations with a Myozyme® infusion

Year	Number of patients	Number of hospitalizations (n=26,714)
2012	123	1901 (7.1%)
2013	139	2955 (11.1%)
2014	155	3143 (11.8%)
2015	152	3446 (12.9%)
2016	156	3670 (13.7%)
2017	158	3817 (14.3%)
2018	154	3853 (14.4%)
2019	163	3929 (14.7%)
Duration of stay (Days)	**Number of hospital stays (n=26,714)**	
0	25818 (96.6%)	
1	456 (1.7%)	
2	159 (0.6%)	
3–5	106 (0.4%)	
6–10	80 (0.3%)	
>10 days	95 (0.4%)	

Table 3: Length of hospital stay in critical care and duration for resuming Myozyme®

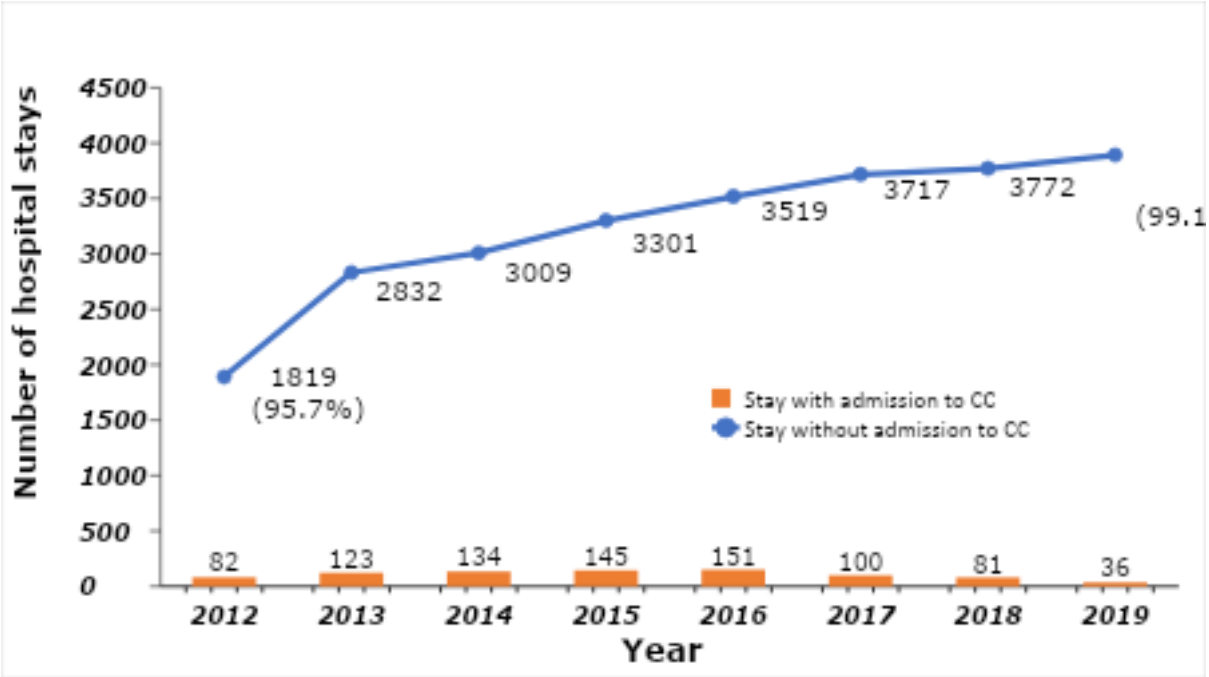
Duration (days) of admission to critical care	**Number of stays, n (%)** **N=781**
0	698 (89.4%)
1	39 (5.0%)
2	14 (1.8%)
3–5	8 (1.0%)
6 to 10	10 (1.3%)
>10 days	12 (1.5%)
Duration (days) before resuming Myozyme® injections, n=781	
Treatment discontinued	4 (0.5%)
1 to 12	42 (5.4%)
13 to 15	545 (69.8%)
16 to 30	124 (15.9%)
31 to 60	45 (5.8%)
>60	21 (2.7%)

Table 4: Hospitalization data related to adverse events of Myozyme®

Characteristics	**Direct link (Y436)**	**Probable link (Other AE codes)**
Number of stays	10	25
Average duration of stays	0.5 days	0.64 days
Outpatient stays	6	15
Number of admissions to critical care	0	0
Time (days) between 2 injections		
Mean (SD)	17.4 (10.1)	14.3 (11.6)
Median (Q1–Q3)	14 (13–15)	13 (7–14)

SD, standard deviation; Q1–Q3, lower and upper quartile range.

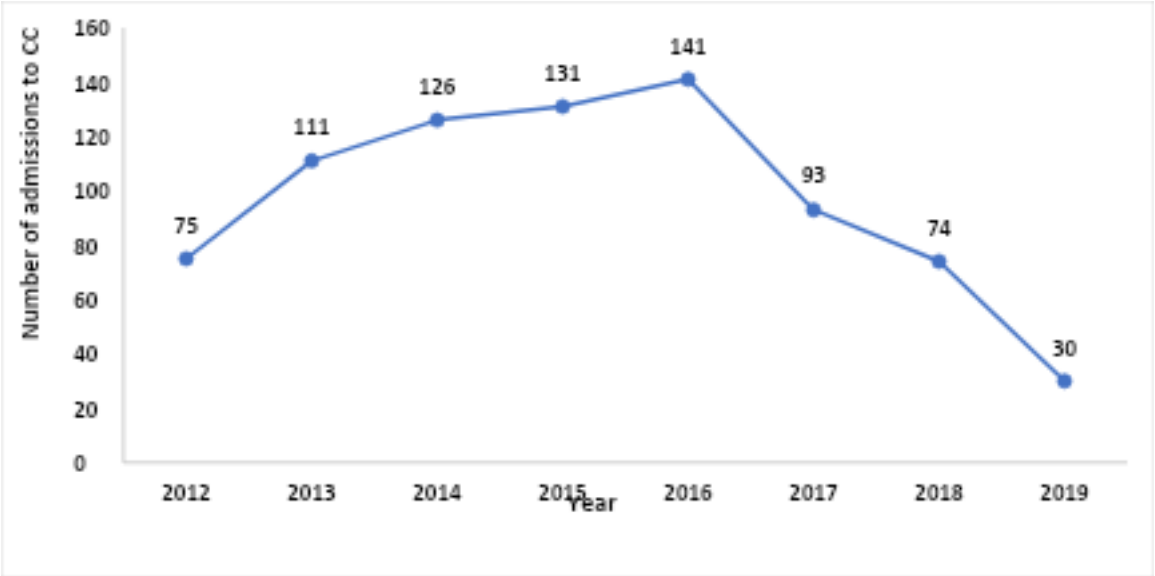
Figure 1: Number of hospital stays with or without admission to critical care



CC, critical care.

The blue line represents the proportion of hospitalisations without admission to critical care showed an increase from 2012 to 2019, while the orange bar graph represents year-wise breakdown of 852 hospital stays involving a passage through critical care.

Figure 2: Year–wise breakdown of the number of critical care admissions at D0 and D1



CC, critical care; D, day.

The blue line graph represents a year-wise breakdown of 781 hospital stays in critical care identified on the D0 or D1 after a Myozyme® injection.