55

Characterization of Response to Enzyme Replacement Therapy in Patients With Late-Onset Pompe Disease: A Retrospective Chart Review

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INTRODUCTION

- Pompe Disease (PD) is a rare autosomal recessive disorder caused by pathogenic variants in the gene encoding acid α-glucosidase (GAA) that result in complete or partial loss of endogenous GAA activity, which is responsible for lysosomal glycogen degradation[1]
- Pompe disease may be categorized into 2 classes: infantile-onset Pompe disease (classic and non-classic) and late-onset Pompe disease (LOPD)[2]
- LOPD may manifest from early childhood to adulthood and is characterized by progressive weakness, primarily in the limb-girdle and respiratory muscles, leading to motor and respiratory difficulties[1]
- The only approved treatment for PD is enzyme replacement therapy (ERT) with alglucosidase alfa, and further characterization of patient response to this treatment is warranted[3]

OBJECTIVE

- To characterize disease progression in patients with LOPD receiving ERT in a clinical setting using retrospective chart review

METHODS

Study Design

- This was a retrospective, noninterventional, multicenter study conducted via medical chart review of patients with LOPD
  - 6 study sites in the United States, United Kingdom, and Spain participated in the study
- All available prespecified variables, including demographics, Pompe disease history, history of ERT, motor and respiratory functional status and laboratory test results were collected from baseline (the start of ERT) up to the last visit or to when ERT was permanently discontinued

Patient Population

- Study included male and female patients aged 3-75 years who provided or whose legal representative provided informed consent/assent for the data collection
- Patients met the following criteria
  - Had a diagnosis of Pompe disease based on GAA activity deficiency and/or documented *GAA* gene variants
  - Had received ≥2 years of standard-of-care ERT without interruption and were still receiving treatment
  - Did not require invasive ventilator support at the initiation of ERT
  - Did not require use of a wheelchair or meet any other definition of nonambulatory status at the initiation of ERT

Analyses

- The last patient chart review was completed on September 12, 2018
- The primary endpoint was 6-minute walk distance (6MWD, in meters) measured using the 6-minute walk test (6MWT)
- Secondary endpoints include:
  - Sitting forced vital capacity (FVC; % predicted)
  - Supine FVC (% predicted)
  - Maximum inspiratory pressure (MIP)
  - Maximum expiratory pressure (MEP)
- For this report, only patients who had a baseline and at least 1 postbaseline assessment of 6MWD and/or FVC were included in the efficacy analysis (the Efficacy Population)
  - Baseline value was defined as the last available measurement on or prior to the initiation of ERT
- Statistical analysis was carried out using SAS software version 9.4
- Safety was evaluated for all enrolled patients (the Safety Population)

RESULTS

Patient Characteristics

- 98 ERT-treated patients were enrolled; 44 had both a baseline and ≥1 postbaseline assessment of 6MWD and/or sitting FVC and were included in the Efficacy Population
- Patients demographics, baseline characteristics, and Pompe disease history are summarized in **Table 1**
  - In the Efficacy Population, mean age of PD diagnosis was 42.7 (±13.7) years and mean time from diagnosis to ERT initiation was 1.9 ±2.6 (range 0.1-10.6) years
  - Mean duration of recorded ERT treatment was 6.7 ± 2.9 (range: 2.1 to 12.3) years
- The median (range) of duration of the observation period for the efficacy population was 6.1 (0.9-14.4) years

Table 1. Patient Characteristics at Baseline

Variable	Safety Population N=98	Efficacy Population n=44
Age at enrollment, years		
Mean (SD)	50.6 (12.3)	51.0 (12.8)
Median (range)	52.5 (17-74)	53.0 (17-73)
Sex, n (%)		
Male	48 (49.0)	21 (47.7)
Female	50 (51.0)	23 (52.3)
Age at Pompe disease diagnosis, years		
Mean (SD)	41.3 (13.1)	42.7 (13.7)
Median (range)	42.0 (2-68)	44.5 (8-68)
Age at ERT initiation, years		
Mean (SD)	43.5 (12.9)	44.7 (13.7)
Median (range)	45.0 (9-69)	46.0 (9-69)
Time from Pompe diagnosis to ERT initiation, years		
Mean (SD)	2.1 (3.0)[a]	1.9 (2.6)[b]
Median (range)	0.8 (0-15.5)	0.8 (0.1-10.6)
Method of Pompe diagnosis, n (%)[c]		
Muscle biopsy	54 (55.1)	23 (52.3)
GAA enzyme	79 (80.6)	34 (77.3)
Genotyping	72 (73.5)	31 (70.5)
Other	1 (1.0)	0 (0)
Age at 1st respiratory decline, years		
Mean (SD)	41.5 (13.9)[d]	41.3 (13.7)[e]
Median (range)	42.0 (35-51)	42.0 (5-62)
Age at 1st muscle strength decline, years		
Mean (SD)	31.6 (13.0)[f]	33.8 (13.8)[g]
Median (range)	34.0 (1-62)	38.0 (1-62)
Patients requiring ambulatory support, n (%)	44 (44.9)	20 (45.5)
Patients requiring ventilator support, n (%)	55 (56.1)	27 (61.4)

GAA=acid α-glucosidase; SD=standard deviation. [a]n=92; [b]n=41; [c]For some subjects, multiple methods may be used in the diagnosis of Pompe disease so the sum of percentages may exceed 100;[d]n=80; [e]n=39; [f]n=97;[g]n=43.

RESULTS

- At baseline, ≥80% of patients in the Efficacy Population had difficulty in both respiratory and daily activities **(Table 2)**
- 46% of the patients in the Efficacy Population required ambulatory support and 61% required ventilator support

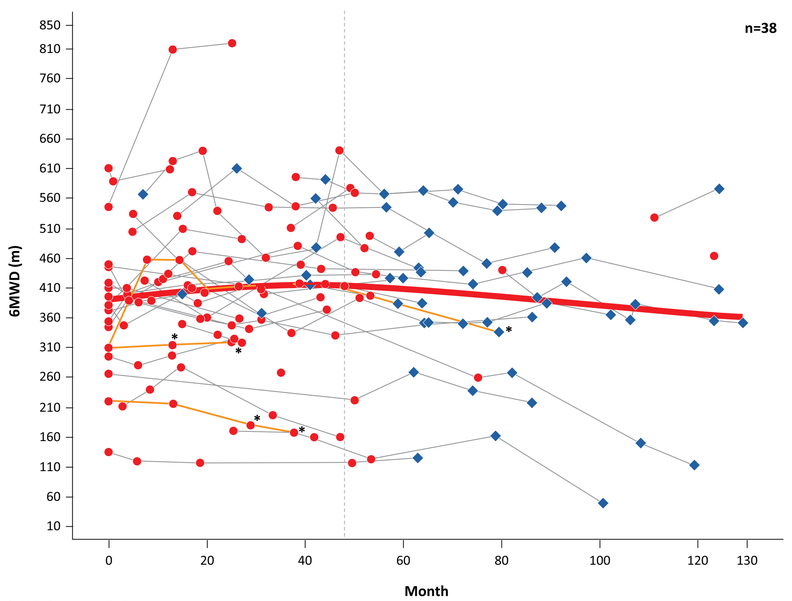
Table 2. Features of Respiratory Difficulties and Difficulties With Activities at Baseline (the Efficacy Population)

	Efficacy Population n=44
Number of patients with respiratory difficulty, n (%)	38 (86.4)
Features of respiratory difficulty, n (%)	
Shortness of breath on exercise	26 (59.1)
Current use of noninvasive ventilator assistance device	17 (38.6)
Inability to lie supine	9 (20.5)
Initial use of noninvasive ventilator assistive device	9 (20.5)
Morning headache	8 (18.2)
Shortness of breath at rest	6 (13.6)
Sleeping with head raised or on a chair	3 (6.8)
Excessive daytime sleepiness	2 (4.5)
Current use of invasive ventilator device	1 (2.3)
Other	4 (9.1)
Number of patients with activity difficulty, n (%)	43 (97.7)
Activities that cause difficulty, n (%)	
Climbing stairs	27 (61.4)
Rising from a chair	20 (45.5)
Initial use of cane/walking frame	16 (36.4)
Walking on plain ground	14 (31.8)
Participating in sports/athletics/dancing	11 (25.0)
Walking uphill	8 (18.2)
Running	7 (15.9)
Carrying weights (eg, groceries)	5 (11.4)
Initial use of wheelchair	4 (9.1)
Combing hair	1 (2.3)
Other	21 (47.7)

6-Minute Walk

- In the Efficacy Population, patients showed an initial improvement in 6MWD that reached a maximum at 2-3 years, followed by a secondary decline (**Figure 1**)
- Based on available patient data at each visit, the median (Q1, Q3) change from baseline in 6MWD was -15.0 (-22.0, 0.0) meters at 0.5 years (n=9), 54.0 (-18.0, 128.0) meters at 1.5 years (n=7), -10.0 (-40, 35) meters at 3 years (n=9), and -15.5 (-60, 24) meters at >3 years (n=10; median [range] follow-up duration: 45 [39-75] months)
- 3 patients who did not require ambulatory support for the 6MWT at baseline used assistive devices for the 6MWT during follow up, ranging from visits 3-7

Figure 1. Spaghetti Plots of 6MWD Over Time (the Efficacy Population)

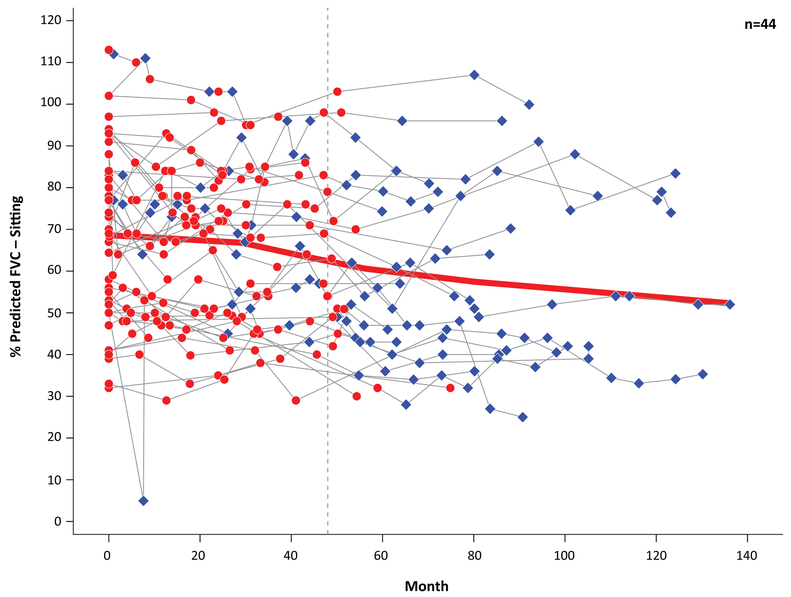


6MWD=6-minute walk distance.
The red solid curve is the estimated trendline obtained using a Loess regression with the smooth parameter at 0.8.
The vertical line indicates Month 48. Red dots indicate data points used for summary statistics based on the visit windows; blue dots indicate data points not used for summary statistics.
Orange lines indicate patients who did not require walking assistance devices during baseline 6MWT but required them during a follow-up test. The visits during which walking assistance devices were used were labeled with an asterisk (*).
The time (in months) on the X-axis was calculated from the actual assessment dates relative to the first dose of ERT.

Respiratory Function

- In the Efficacy Population, sitting FVC (% predicted) showed some initial stability followed by a slow progressive decline **(Figure 2)**
- Based on available data, median (Q1, Q3) changes from baseline in sitting FVC (% predicted) was -3.0 (-8.0, 3.0) at 0.5 years (n=17), -1.5 (-5.0, 0.0) meters at 1.5 years (n=18), -0.5 (-7.0, 5.0) at 3 years (n=30), and -0.5 (-10.0, 3.9) at >3 years (n=30; median [range] follow-up duration: 44 [39-75] months)

Figure 3. Spaghetti Plots of Sitting FVC Over Time (the Efficacy Population)



FVC=forced vital capacity.
The red solid curve is the estimated trendline obtained using a Loess regression with the smooth parameter at 0.8.
The vertical line indicates Month 48. Red dots indicate data points used for summary statistics based on the visit; blue dots indicate data points not used for summary statistics.
The time (in months) on the X-axis was calculated from the actual assessment dates relative to the first dose of ERT.

- MIP showed an initial improvement with a maximum effect at 2 years (median change from baseline [CFBL]: 11.0 cm of water, n=9), followed by a secondary decline (median CFBL: 5.0 cm of water at 3 years [n=8] and 1.5 cm of water at >3 years [n=10])
- MEP showed an initial improvement at 0.5 years (median CFBL: 5.0 cm of water [n=4]), followed by stabilization throughout the observation period (median CFBL: 4.0 cm of water at >3 years [n=6])

Safety

- Available safety data were reviewed for the whole enrolled population (N=98)
- Overall, 18 patients experienced 36 infusion-associated reactions (IARs), of which 14 occurred on the day of ERT initiation
  - 23 IARs completely resolved and 12 did not resolve; the outcome was not known for 1 IAR
- Two patients experienced IARs that lead to ERT interruption
  - One female patient experienced an anaphylactic reaction to ERT
  - One male patient presented with dystonia of moderate intensity
- No deaths were reported during the study

LIMITATIONS

- The retrospective and observational nature of the study and small number of patients at each time point are major limitations of the study
- Assessments were done in a real-world clinical setting and not in a research setting. There was no documentation on training or requirement of certification prior to use of ambulatory or pulmonary assessments. Because each institution would have employed its own guidelines to collect the data, the findings should be interpreted with caution
- The study was conducted at 6 sites in 3 countries and thus may not be representative of all centers that treat LOPD patients
- Furthermore, patient enrollment and signed informed consent requirement may introduce volunteer bias; as a result, non-ambulatory patients were less likely to be included in the study and patients who died before the study began were not included in the chart review

CONCLUSIONS

- Findings suggest that in this cohort, ERT was generally associated with initial improvement in motor function followed by a slow decline
- Assessment of FVC generally showed some initial stability followed by slow progressive decline
- These results are consistent with results from previous long-term studies of the current ERT[4-6] and suggest there are continued unmet needs in Pompe disease, which may be addressed by future treatment options

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Disclosures

Conflicts of interest

PSK served as consultant for Amicus Therapeutics, Sanofi Genzyme, Maze Therapeutics, JCR Therapeutics, and AskBio.
RM has nothing to declare.
AA served as consultant for Sanofi Genzyme and speaker for Biogen.
HT has nothing to declare.
TM served as consultant for Amicus Therapeutics, Sanofi Genzyme, Spark Therapeutics, and Audentes and as a speaker for Sanofi Genzyme, and his institution received grants from Sanofi Genzyme, Valerion, Spark Therapeutics, and Audentes for his participation in their clinical trials.
AS, SS, FH, and ZK are employees of and hold stock in Amicus Therapeutics.
JD-M has served as speaker for Sanofi Genzyme.

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