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Safety and efficacy of alternative alglucosidase alfa regimens in Pompe disease

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Abstract

Emerging phenotypes in long-term survivors with Pompe disease on standard enzyme replacement therapy (ERT) (alglucosidase alfa 20 mg/kg/2 weeks) can include patients with worsening motor function. Whether higher doses of ERT improve skeletal function in these patients has not been systematically studied. This exploratory, randomized, open-label, 52-week study examined the safety and efficacy of 2 ERT regimens of alglucosidase alfa (20 mg/kg/week or 40 mg/kg/2 weeks) in 13 patients with Pompe disease and clinical decline or a lack of improvement on standard ERT: late-onset (n = 4), infantile-onset (n = 9). Cross-reactive immunologic material assay-negative patients were excluded. Eleven of 13 patients completed the study. Trends for improvement were seen in total gross motor function, but not mobility; however, 6 (late-onset, 2; infantile-onset, 4) of 11 patients (55%) who met the entry criteria of motor decline (late-onset, 4; infantile-onset, 7) showed improvement in motor and/or mobility skills. No between-regimen differences in efficacy emerged. Two case studies highlight the benefits of increased ERT dose in patients with Pompe disease experiencing clinical decline. Both alternative regimens were generally well tolerated. This study was limited by the small sample size, which is not uncommon for small clinical studies of rare diseases. Additionally, the study did not include direct assessment of muscle pathology, which may have identified potential causes of decreased response to ERT. Results were inconclusive but suggest that increased ERT dose may be beneficial in some patients with Pompe disease experiencing motor decline. Controlled studies are needed to clarify the benefits and risks of this strategy.

Keywords: Alglucosidase alfa; Enzyme replacement therapy; Infantile onset; Late onset; Pompe disease; Clinical decline; Dose

1. Introduction

Pompe disease, a rare autosomal recessive neuromuscular disorder caused by a deficiency of the lysosomal enzyme acid α-glucosidase (GAA), results in glycogen accumulation in various organs, primarily muscle tissue [1]. Infantile-onset Pompe disease represents the most severe form, with early death due to cardiorespiratory failure within the first year of life [2]. The main clinical manifestations of Pompe disease include profound hypotonia/generalized muscle weakness, respiratory distress, and marked hypertrophic cardiomyopathy [3]. The only available treatment for Pompe disease, alglucosidase alfa (Genzyme, a Sanofi company, Cambridge, MA), targets the underlying cause by replacing the deficient GAA enzyme; and the recommended dosage is 20 mg/kg/2 weeks [4].

In infants with Pompe disease, alglucosidase alfa treatment has been shown to extend overall survival and invasive

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ventilation-free survival, reverse cardiomyopathy, and permit children to achieve gross motor milestones, including independent walking, not observed in untreated cohorts where the median age of death was less than 9 months [3,5,6]. However, with increased long-term survival on alglucosidase alfa, an emerging phenotype characterized by progressive weakness and decreased motor function has been identified in patients with infantile-onset Pompe disease that initially responded well to enzyme replacement therapy (ERT) with alglucosidase alfa [7,8]. The emergence of this phenotype has raised the question of whether the currently approved ERT regimen (alglucosidase alfa 20 mg/kg/2 weeks) eventually may be insufficient in some patients, even in those who initially responded well to treatment.

We report on an open-label study (ClinicalTrials.gov, NCT00483379) including 2 detailed case reports that examine the efficacy and safety of alternative regimens of alglucosidase alfa in patients with late-onset and infantile-onset Pompe disease who experienced clinical decline or a lack of improvement despite continuation of ERT at the dose recommended in the package insert of 20 mg/kg/2 weeks. Together, these results suggest that controlled studies are warranted to establish the effects of alternative ERT regimens of alglucosidase alfa in Pompe disease and the development of new treatment approaches to allow for a continued clinical benefit.

2. Patients and methods

We first report on an open-label study of 13 cases that evaluated the safety and efficacy of alternative regimens of alglucosidase alfa (20 mg/kg/week or 40 mg/kg/2 weeks) in patients with late-onset or infantile-onset Pompe disease who experienced clinical decline or lack of improvement while receiving the recommended ERT dose of 20 mg/kg/2 weeks for ≥6 months. Patients <18 years of age who were cross-reactive immunologic material (CRIM) - negative were excluded. After reviewing results from this cohort, we subsequently selected 2 patients in the infantile-onset group (<18 years of age) for further review to elucidate examples in which patients who exhibited suboptimal treatment response with standard ERT may benefit from dose adjustments of alglucosidase alfa.

2.1. Open-label study design

This open-label, randomized, exploratory, 52-week study was conducted at 11 centers (9 in the United States, 1 in Australia, and 1 in Canada) with experience in treating Pompe disease. The primary objectives were to evaluate the safety and efficacy of 2 alternate alglucosidase alfa regimens and to evaluate differences in efficacy between the 2 dosing arms. The study protocol and informed consent forms were approved by an Institutional Review Board or Independent Ethics Committee at each individual study site, and the study complied with the Declaration of Helsinki. Written informed consent was provided by all patients or parents/legal guardians.

2.2. Study participants

Eligible patients were clinically diagnosed with Pompe disease, defined by documented endogenous GAA deficiency in skin fibroblasts or blood; were compliant in receiving the standard regimen of alglucosidase alfa (20 mg/kg/2 weeks) for ≥6 months immediately prior to study entry; and experienced clinical decline or a lack of improvement in ≥1 of the following parameters compared with their condition prior to beginning alglucosidase alfa treatment:

- Motor skills
  - For patients ≤2 years of age at study entry, failure to acquire ≥2 new gross motor milestones (e.g. turning head side to side [supine], grasping small objects with hands, transferring objects from hand to hand, holding head upright with body supported, rolling [supine to prone or prone to supine], sitting [supported or unsupported], walking [with support, i.e. cruising or independently], and walking upstairs [with assistance or independently])
  - For patients previously ambulatory, progression to the use of an assistive device for ambulation because of worsening of proximal lower extremity muscle weakness.
- Respiratory
  - New development of respiratory failure requiring the use of ventilatory assistance (invasive or noninvasive) for ≥4 weeks prior to study enrollment

Among other potential inclusion criteria were cardiac left ventricular mass (LVM) Z-score of ≥6 or LVM index of ≥150 g/m^2; or for patients >2 years of age at study entry, worsening of proximal UE muscle weakness through the loss of functional use of the UEs; or for patients >8 years of age at study entry, worsening of proximal UE muscle weakness through longitudinal assessments of manual muscle testing (MMT).

Exclusion criteria were CRIM-negative status and patients who used any investigational product other than alglucosidase alfa ≤30 days prior to study enrollment.

2.3. Treatment

Eligible patients were randomized 1:1 to a high-frequency group (alglucosidase alfa 20 mg/kg/week) or a high-dose group (alglucosidase alfa 40 mg/kg/2 weeks). Alglucosidase alfa was supplied by Genzyme, a Sanofi company. Randomization to the 2 treatment groups was stratified by age (<18 years of age and ≥18 years of age), which for the patients enrolled corresponded with the patients being randomized by phenotype (infantile-onset and late-onset, respectively). Randomization by age was done to achieve an even distribution of pediatric and adult patients in each dosing arm.

2.4. Efficacy assessments

Efficacy was evaluated at scheduled visits and included gross motor function as measured by the Gross Motor Function Measure 66 (GMFM-66) [9]; functional status as measured by the Pompe Pediatric Evaluation of Disability Index (Pompe PEDI) [10]; proximal and distal muscle strength as measured by MMT [11] in patients ≥8 years of age; respiratory function as