Molecular Genetics and Metabolism Reports 11 (2017) 31–35

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Albuterol as an adjunctive treatment to enzyme replacement therapy in infantile-onset Pompe disease☆

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ARTICLE INFO

Keywords:
Pompe disease
Enzyme replacement therapy
Albuterol
Creatine kinase
6-Min walk test
4-Stair climb test

ABSTRACT

Background: Early initiation of enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase is an effective treatment for patients with infantile-onset Pompe disease (IOPD) but cannot prevent a slow progression of myopathy. Albuterol has been shown to be helpful in adult patients with Pompe disease, and therefore, we administered an open-label adjunctive therapy with albuterol in IOPD patients undergoing ERT.
Methods: Fourteen patients, aged 2 to 12 years, were enrolled in this study; all of them had a disease onset before 12 months of life, and 13 of them were ambulatory because of early initiation of ERT. All patients received albuterol (also referred to as salbutamol) 12 mg daily for 26 weeks. The outcome measurements included a 6-minute walk test, four-stair climb test (SCT), the standing/walking/running/jumping domains of Gross Motor Function Measure-88, speech quality, serum creatine kinase, and urinary glucose tetrasaccharide. Outcome and safety measurements were evaluated at baseline, and at 1, 3, and 6 months (26 weeks) after entering the trial.
Results: After a period of 26 weeks, among the 12 patients who were able to complete the SCT, the median time needed decreased by 22% ($p = 0.034$). Other parameters inconsistently improved in a variety of individuals. Eleven adverse events, including nausea, urinary frequency, and tachycardia, were potentially related to the study drug, but all were mild and disappeared after a brief drug withdrawal. One patient was actively withdrawn from the trial because of poor compliance.
Conclusions: The results of our study suggest that albuterol showed a good safety profile as an adjunctive treatment in our IOPD cohort, although the benefits are limited.

1. Introduction

Pompe disease, also known as glycogen storage disease type II or acid maltase deficiency, is a lysosomal disorder in which a deficiency of acid alpha-glucosidase (GAA, EC 3.2.1.20) leads to the intralysosomal accumulation of glycogen in all tissues, most notably in the skeletal muscles [1]. Classic infantile-onset Pompe disease (IOPD) typically presents with hypertrophic cardiomyopathy before 6 months of age, whereas late-onset Pompe disease (LOPD) presents with muscular weakness during early childhood to late adulthood. Currently, enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA) [2,3] is the only treatment for Pompe disease. However, the initial experiences of rhGAA in IOPD shows that approximately 50% of patients still require respiratory support, probably due to late initiation of treatment [4].

To facilitate the early treatment of IOPD, we performed newborn

Abbreviations: 6MWT, 6-minute walk test; AE, adverse event; CI-MPR, cation-independent mannose-6-phosphate receptor; CK, creatine kinase; CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy; GAA, acid alpha-glucosidase; Glc4, glucose tetrasaccharide; GMFM, Gross Motor Function Measure; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; MRI, magnetic resonance imaging; NBS, newborn screening; rhGAA, recombinant human GAA; SCT, 4-stair climb test

☆ Clinicaltrials.gov: NCT02405598.

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http://dx.doi.org/10.1016/j.ymgmr.2017.04.004
Received 9 April 2017; Accepted 9 April 2017

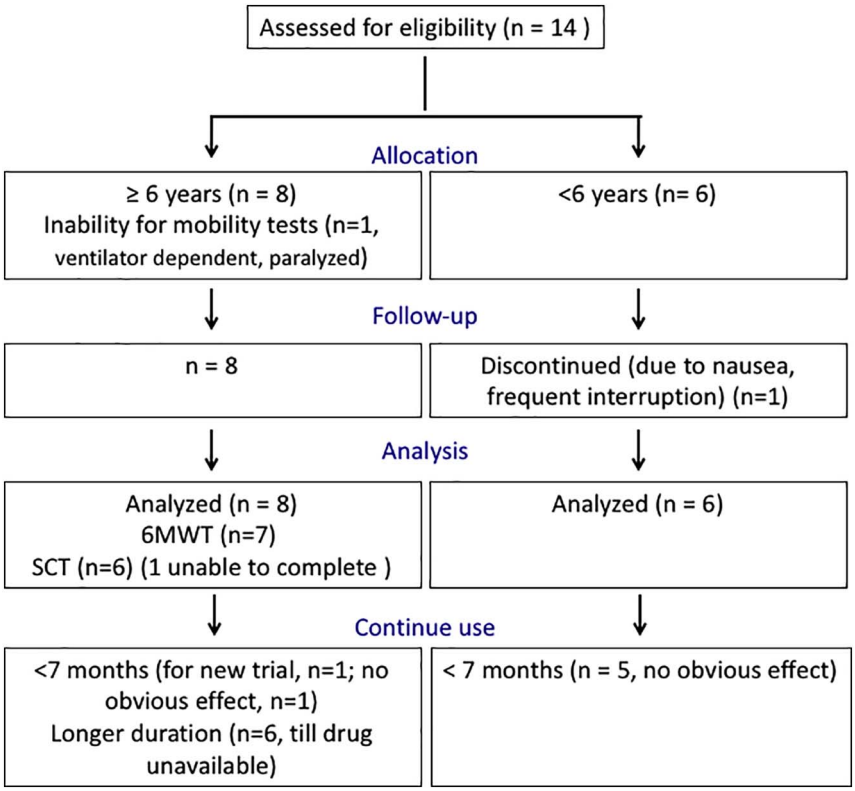

Fig. 1. The workflow and outcomes of the participants throughout the study.

screening (NBS) for Pompe disease since 2005 [5], and we demonstrated that early initiation of ERT improves ventilation-free survival [6]. However, the long-term prognosis of IOPD patients who were diagnosed by the NBS program and treated since birth was not perfect. After a median treatment time with an ERT of 63 months (range 28–90 months), all patients were able to walk independently, and no patients required mechanical ventilation. Nevertheless, muscle weakness, ptosis, and speech disorders still occurred in these early-treated IOPD patients [7], and changes in muscle magnetic resonance imaging suggested a progression of myopathy [8].

Beta-2 adrenergic agonists, most notably albuterol, have been used to increase muscle mass and strength in normal individuals and in patients with muscular dystrophy [9,10]. Beta-2 agonists were demonstrated to increase the expression of cation-independent mannose-6-phosphate receptor (CI-MPR) and CI-MPR-mediated uptake of rhGAA in murine Pompe disease [11], and beta-blockers decreased the efficacy of rhGAA therapy [12]. A pilot clinical trial also showed improvement in muscle power in a 6-minute walk test (6MWT) in adult patients with LOPD [13]. Therefore, we investigated whether an adjuvant therapy with albuterol could also be effective in IOPD patients.

2. Patients and methods

Fourteen IOPD patients older than 2 years of age were enrolled in the trial (Supplement Table 1). All patients exhibited severe GAA deficiency and two pathologic GAA mutations *in trans* and were cross-reactive immunological material positive [7,14–16]. All patients had presented symptoms before 12 months of age and were treated with rhGAA with dosages of 20–40 mg/kg/2 weeks (or 20 mg/kg every week), and none of them exhibited sustained high levels of anti-rhGAA antibodies. Patients were under regular diet and rehabilitation. The exclusion criteria included changes in rhGAA dosage in 3 months, symptomatic cardiac arrhythmia, and concurrent cardiac medications such as diuretics, digoxin, and beta-blockers. rhGAA dosage could not be changed during the study period.

During the 26-week study period, all patients received albuterol (also referred to as salbutamol) treatment in the form of tablets (for patients older than 6 years of age) or syrup (for patients younger than 6 years of age). The target dosage was 24 mg/day divided into three doses for patients older than 12 years, 12 mg/day for patients aged 6–11 years, and 0.6 mg/kg/day for patients aged less than 6 years. The dosage for patients aged less than 6 years was calculated according to the equivalent dosage of a 6-year-old boy with the 50th percentile body weight (20 kg). The dosages in all age groups were within the usual range of dosage of albuterol for asthma. Albuterol was administered at half the target dose for the first 2 weeks to minimize drug-associated adverse events (AEs). Drug compliance and adverse effects were enquired when patients come to the hospital for ERT, every 1–2 weeks. Parents were instructed to withhold albuterol if the patient was prescribed medications for common cold or if patients experienced tremor, tachycardia, or excitability after albuterol. If albuterol was on hold because of an AE, patients could resume a half dose of albuterol 2 days after that AE resolved, and to the full dose 3 days later. Outcomes and safety were evaluated at baseline and at 1, 3, and 6 months (26 weeks) after entering the trial. The outcome measurements included a 6-minute walk test (6MWT), a 4-stair climb test (SCT), the D dimension (standing) and E dimension (walking, running, jumping) percent score of Gross Motor Function Measure-88 (GMFM-88), serum creatine kinase (CK), and urinary glucose tetrasaccharide (Glc4) levels. Speech quality was evaluated by a speech-language pathologist for articulation (21 points for the correct production of the 21 Mandarin Consonants), resonance (7 points), hoarseness (2 points), and speech intelligibility (5 points), with a final sum score of 35, representing the best score [17]. The safety measurements included heart rate and heart rhythm measured by 12-lead electrocardiogram (ECG), resting blood glucose, and electrolytes. AEs were recorded throughout the study period. The differences in the parameters evaluated between baseline and 6 months after the start of albuterol treatment were analyzed using the Wilcoxon signed rank test, and a p-value less than 0.05 was considered statistically significant. This study

was approved by the Institutional Review Board, and written consent was obtained from the parent at study entry. After the 26-week trial period, patients could choose to stay on albuterol.

3. Results

The 14 IOPD patients were between 2 and 12 years of age when they entered the trial (Fig. 1). Five patients received rhGAA at a dosage of 20 mg/kg every 2 weeks, and the other nine patients received 40 mg/kg every 2 weeks or 20 mg/kg every week (Supplement Table 1) and there was no change in rhGAA dosage 6 months before entering the study and throughout the study period [7]. One patient (no. 3) stopped albuterol at the fourth month of the trial; thus, only her 3-month data were analyzed. All the other patients continued albuterol after the completion of the study: seven for an additional 4 to 8 months and six for an additional 20 to 27 months until the drug was unavailable. Patients who were not able to complete a specific test because of a physical factor or noncooperation were excluded from the data analysis of that test.

Among the 12 patients who were able to complete the SCT at the 6 months of treatment, the median time needed decreased by 22% over the study period ($p = 0.034$; Fig. 2). The distance of 6MWT decreased by 2% (n = 12; $p = 0.859$), speech quality improved by 4.2% (n = 12; $p = 0.092$), GMFM-88 standing (D domain) increased by 5.4% (n = 11; $p = 0.357$), and GMFM-88 movement (E domain) increased by 7.8% (n = 11; $p = 0.050$). CK levels decreased by 0.5% (n = 14; $p = 0.433$), and urinary Glc4 levels decreased by 4.3% (n = 13; $p = 0.600$). Baseline and 6-month data are also presented in Fig. 3. Patient no. 13 had a more than 200% increase in urinary Glc4 (from 153 to 478 μmol/g creatinine) during the 6 months. He deteriorated slightly before entering the study period, and his ERT dosage was increased from 20 mg/kg every 2 weeks to 20 mg/kg every week after the 26-week albuterol treatment period. However, during this trial period, his motor performances, including 6MWT, SCT, pulmonary function, and GMFM-88, improved. Patient no. 10 had a more than 100% increase in SCT time, but the time of the SCT increased only from 2.38 to 5.51 s (Fig. 3).

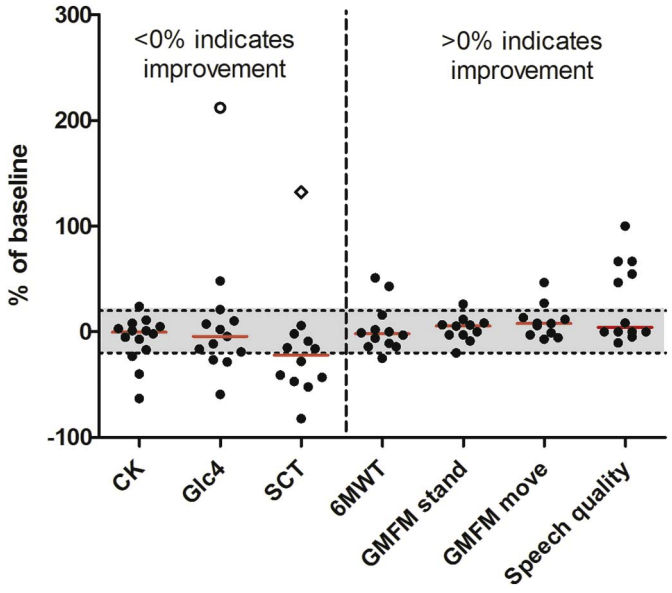

Fig. 2. Summary of the changes in each measurement at the end of the study compared with baseline. Changes are expressed as percent of the baseline values, and the solid lines indicate the medians. A decrease in values indicates improvements in CK, Glc4, and SCT, whereas an increase in values indicates improvements in 6MWT, GMFM, and speech quality. CK: creatine kinase; Glc4: glucose tetrasaccharide; SCT: 4-stair climb test; 6MWT: 6-minute walk test; GMFM: Gross Motor Function Measure-88, sum of domain D (stand) and domain E (move). The open circle of Glc4 indicates the data of patient no. 13, and the open diamond of SCT indicates the data of patient no. 10.

Further age subgroup analysis revealed that only patients under 5 years of age have significant improvement in SCT ($p = 0.027$). The treatment duration analysis revealed that the improvement of SCT was only demonstrated at 6 months (26 weeks) ($p = 0.041$) of treatment but not at 1 month ($p = 0.069$) or at 3 months ($p = 0.069$) of treatment. In addition, the significant improvement at 6 months of treatment was only seen in patients under 5 years of age ($p = 0.042$). The best five patients in SCT were no. 1, 8, 9, 11, and 14. They also presented improvement in 6MWT (2 patients out of a total of 4 patients completion), GMFM-88 movement (4/4), and urinary Glc4 (3/5).

The patients' median heart rate increased slightly from 97 bpm (range, 61–126 bpm) to 102 bpm (range, 75–132 bpm) at 3 months and to 103 bpm (range, 67–116 bpm) at 6 months of therapy. Fifty-seven AEs were reported. Eleven AEs, all mild, were possibly related to the study drug: three tachycardia events were reported in two patients (no. 2 twice, no. 6 once); three sinus tachycardia events were recorded on ECG in three patients; one patient (no. 5) presented with a slight increase in blood pressure and facial flushing; and one patient (no. 9) reported an episode of increase in urinary frequency. These events were resolved by temporarily decreasing the dose or stopping the test drug, and all these patients resumed the test drug. Patient no. 3 frequently refused drug with nausea (three episodes), probably due to not accept the taste of the drug or coexisting minor respiratory or gastroenteral infections. We dropped this patient at the fourth month of the trial. No tremor was reported or observed throughout the study period.

4. Discussion

In the current study, we administered albuterol for a period of up to 2.5 years to 14 IOPD patients, 2 to 12 years of age, who were undergoing rhGAA treatment starting early in their lives, and most of them were still ambulatory. IOPD is the most rapidly progressing form of Pompe disease. Previously, when IOPD patients were diagnosed by clinical manifestations, many had already suffered from extensive muscle damage and failed to respond to either rhGAA or other adjuvant therapies. In contrast, in our cohort of IOPD patients, who were primarily diagnosed by NBS, the motor functions were better preserved than those of clinically diagnosed patients. After a 26-week adjunctive treatment with albuterol, patients had faster climb stairs especially in patients under 5 years of age. Improvements were also demonstrated in other parameters in individual patients, including the 6MWT (4 patients out of a total of 11 patients completion), GMFM-88 movement (6/10), speech quality (6/11), serum CK levels (6/12), and urinary Glc4 levels (5/11), but none of these reached statistical significance. Although the risk of arrhythmia in IOPD is high [18], we did not observe any significant cardiac arrhythmia except tachycardia. Therefore, more than half of the patients continued to use albuterol after the study period.

The improvement in the SCT performance by albuterol may be explained by the increased uptake of rhGAA after enhancing CI-MPR expression or by the directly stimulation of muscle strength. Beta-2 agonists have been reported to increase the amount of CI-MPR and CI-MPR-mediated uptake of rhGAA in mice and patients with Pompe disease [11,13]. In the current study, we did not perform muscle biopsies to measure CI-MPR or glycogen content. Alternatively, we measured urinary Glc4 levels, which decreased in half of the patients, suggesting a decrease in glycogen accumulation. However, albuterol has been known to increase skeletal muscle strength in men [19], and in a recently study, inhalation of beta-2 agonists within the range specified in anti-doping regulations increased muscle strength, sprint performance, and respiratory muscle strength in elite swimmers [20]. In the current study, we did not test for muscle strength due to the lack of reliable measurements in our target population. Therefore, we cannot confirm if the improvement in the SCT performance in IOPD patients was due to a direct muscle-strengthening effect of the beta-2 agonist. In addition, the positive effects in our study after 6 months were equal to

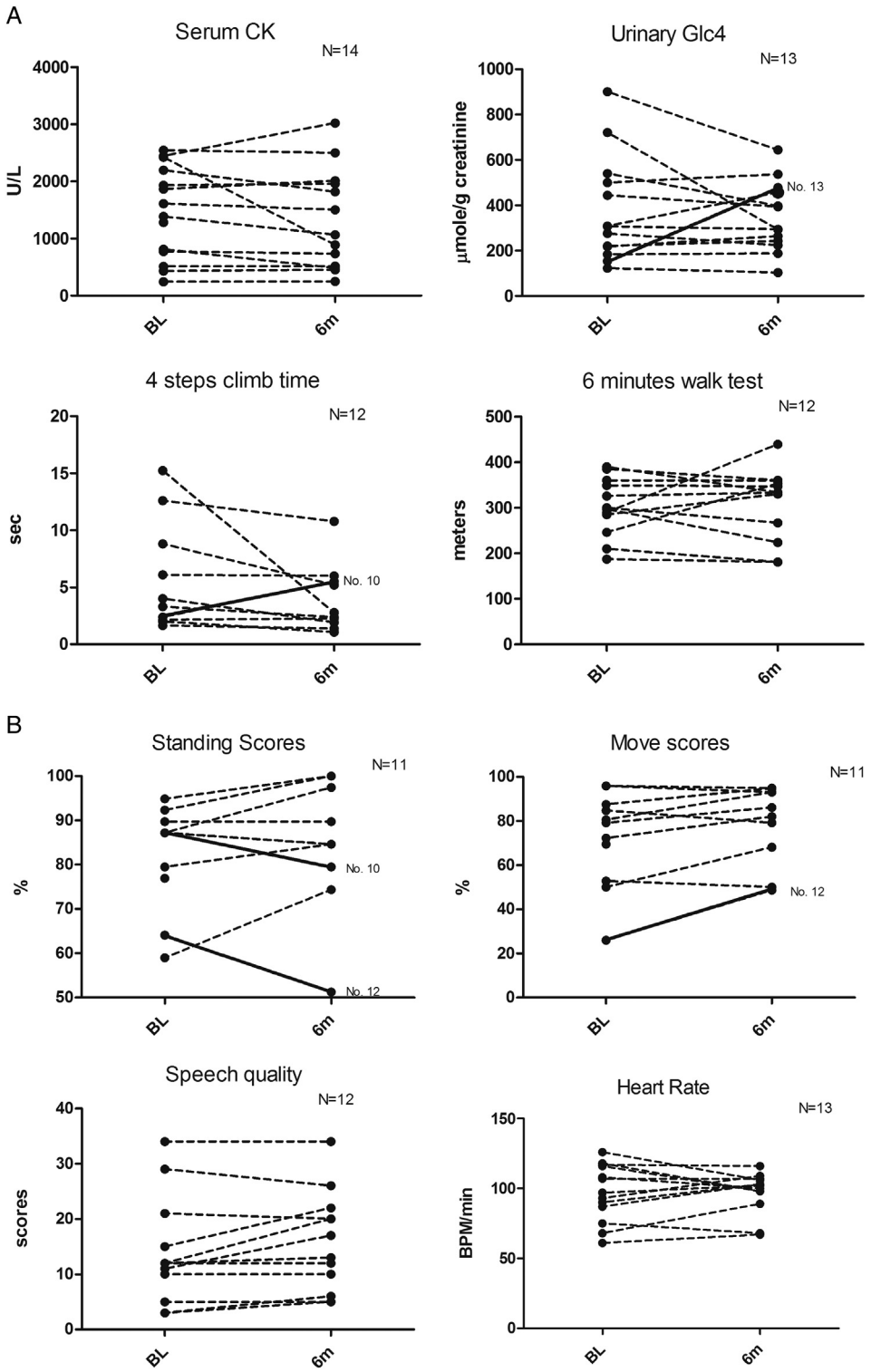

Fig. 3. Measurements of tests at baseline and at the end of the study. The lines link data from the same patients. The solid line of Glc4 indicates patient no. 13. The solid line of 4-stair climb test indicates patient no. 10. The solid line of Standing and Move scores indicate patient no. 10 and no. 12. CK: creatine kinase; Glc4: glucose tetrasaccharide; Standing scores: D dimension percent score of Gross Motor Function Measure (GMFM)-88; Move scores: E dimension (walking, running, jumping) of GMFM-88.

or less obvious than those in month 6 (data not shown), suggesting the desensitization of beta-2 receptors, one of the G protein-coupled receptors, after sustained activation [21] or down regulation of the receptor.

The benefit of treatment in climb ability was more significant in younger patients, raising the possibility that the effect seen in these patients was due to the growth of the patients or the coordination/compliance of the patients. However, their improvement in GFMF-88 movement scores suggested that they had a better coordination. In addition, the better GMFM-88 movement scores were seen both in young patients (patient no. 8, 11, 14) and in older patients (patient no. 1), decreasing the role of the growing maturation for coordination. We suspect the benefit of albuterol in young children is more likely due to their relatively reversible muscle condition [8] that could be benefit

from albuterol or any other treatment. A further detailed prospective study is warranted to validate the albuterol effect.

Our results demonstrated less robust effectiveness of albuterol in patients with IOPD. In a previous study on the long-acting formulation of albuterol in adult LOPD patients, the 6MWT distance increased in all seven subjects at weeks 6, 12, and 24 (42 ± 37 m; $p = 0.02$) in comparison with that at baseline, and grip strength also improved significantly for both hands at week 12 [13]. Limitations of this study are the reliability of the 6MWT in young children and having no placebo control in this study; however, this is the largest cohort of early-treated IOPD patients. Another limitation is that the difference in the extent of muscle damage and residual GAA activity between these two cohorts may need to be considered. Furthermore, we selected the short-acting albuterol as in routine pediatric prescriptions for the flexibility and reversibility to adjust when encountering an AE. Although we used a higher equivalent albuterol dosage than in adults, the short-acting albuterol in our study might potentially decrease the effectiveness. In a previous preclinical study, a long-acting beta-2 agonist clenbuterol showed a stronger effect on Pompe disease in mice than the short-acting drug albuterol [11]; however, clenbuterol is currently not registered in our market.

Currently, there are significant unmet needs in the treatment of IOPD. Early initiation of rhGAA infusion after diagnosis through NBS improves the outcomes of IOPD, but muscle weakness, ptosis, and speech disorders still occurred [7,17]. An increase in the dosage or frequency of rhGAA infusion appears to provide some benefits to these patients but is not sufficient to prevent residual symptoms [7,22,23]. In the current study, we demonstrated that albuterol speeded the climb of patients and selectively improved muscle function and movement quality, but we could not prove its benefit in the 6MWT consistently nor its significant benefit in other measurements.

In conclusion, our data showed a potentially positive effect of albuterol as an adjuvant therapy in some IOPD patients without significant safety concerns. A further detailed prospective study in the treatment of IOPD and revision of the evaluation tools for treatment outcomes are required.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ymgmr.2017.04.004.

References

[1] R. Hirschhorn, A. Reuser, Glycogen storage disease type II: acid alpha-glucosidase (acid maltase) deficiency, in: C. Scriver, A. Beaudet, W. Sly, D. Valle (Eds.), The Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill, New York, 2001, pp. 3389–3420.

[2] H. Van den Hout, A.J. Reuser, A.G. Vulto, M.C. Loonen, A. Cromme-Dijkhuis, A.T. Van der Ploeg, Recombinant human alpha-glucosidase from rabbit milk in Pompe patients, Lancet 356 (2000) 397–398.

[3] A. Amalfitano, A.J. McVie-Wylie, H. Hu, T.L. Dawson, N. Raben, P. Plotz, Y.T. Chen, Systemic correction of the muscle disorder glycogen storage disease type II after hepatic targeting of a modified adenovirus vector encoding human acid-alpha-glucosidase, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 8861–8866.

[4] M. Nicolino, B. Byrne, J.E. Wraith, N. Leslie, H. Mandel, D.R. Freyer, G.L. Arnold, E.K. Pivnick, C.J. Ottinger, P.H. Robinson, J.C. Loo, M. Smitka, P. Jardine, L. Tato, B. Chabrol, S. McCandless, S. Kimura, L. Mehta, D. Bali, A. Skrinar, C. Morgan, L. Rangachari, D. Corzo, P.S. Kishnani, Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease, Genet. Med. 11 (2009) 210–219.

[5] Y.H. Chien, S.C. Chiang, X.K. Zhang, J. Keutzer, N.C. Lee, A.C. Huang, C.A. Chen, M.H. Wu, P.H. Huang, F.J. Tsai, Y.T. Chen, W.L. Hwu, Early detection of Pompe disease by newborn screening is feasible: results from the Taiwan screening program, Pediatrics 122 (2008) e39–e45.

[6] Y.H. Chien, N.C. Lee, B.L. Thurberg, S.C. Chiang, X.K. Zhang, J. Keutzer, A.C. Huang, M.H. Wu, P.H. Huang, F.J. Tsai, Y.T. Chen, W.L. Hwu, Pompe disease in infants: improving the prognosis by newborn screening and early treatment, Pediatrics 124 (2009) e1116–e1125.

[7] Y.H. Chien, N.C. Lee, C.A. Chen, F.J. Tsai, W.H. Tsai, J.Y. Shieh, H.J. Huang, W.C. Hsu, T.H. Tsai, W.L. Hwu, Long-term prognosis of patients with infantile-onset Pompe disease diagnosed by newborn screening and treated since birth, J. Pediatr. 166 (2015) 985–991 (e981-982).

[8] S.S. Peng, W.L. Hwu, N.C. Lee, F.J. Tsai, W.H. Tsai, Y.H. Chien, Slow, progressive myopathy in neonatally treated patients with infantile-onset Pompe disease: a muscle magnetic resonance imaging study, Orphanet J. Rare Dis. 11 (2016) 63.

[9] J.F. Caruso, J.F. Signorile, A.C. Perry, B. Leblanc, R. Williams, M. Clark, M.M. Bamman, The effects of albuterol and isokinetic exercise on the quadriceps muscle group, Med. Sci. Sports Exerc. 27 (1995) 1471–1476.

[10] J.T. Kissel, M.P. McDermott, J.R. Mendell, W.M. King, S. Pandya, R.C. Griggs, R. Tawil, F.-D. Group, Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumeral dystrophy, Neurology 57 (2001) 1434–1440.

[11] D.D. Koeberl, S. Li, J. Dai, B.L. Thurberg, D. Bali, P.S. Kishnani, Beta2 agonists enhance the efficacy of simultaneous enzyme replacement therapy in murine Pompe disease, Mol. Genet. Metab. 105 (2012) 221–227.

[12] S.O. Han, R. Pope, S. Li, P.S. Kishnani, R. Steet, D.D. Koeberl, A beta-blocker, propranolol, decreases the efficacy from enzyme replacement therapy in Pompe disease, Mol. Genet. Metab. 117 (2016) 11–119.

[13] D.D. Koeberl, S. Austin, L.E. Case, E.C. Smith, A.F. Buckley, S.P. Young, D. Bali, P.S. Kishnani, Adjunctive albuterol enhances the response to enzyme replacement therapy in late-onset Pompe disease, FASEB J. 28 (2014) 2171–2176.

[14] Y.H. Chien, N.C. Lee, P.H. Huang, W.T. Lee, B.L. Thurberg, W.L. Hwu, Early pathologic changes and responses to treatment in patients with later-onset Pompe disease, Pediatr. Neurol. 46 (2012) 168–171.

[15] Y.H. Chien, N.C. Lee, Y.J. Tsai, B.L. Thurberg, F.J. Tsai, W.L. Hwu, Prominent vacuolation of the eyelid levator muscle in an early-treated child with infantile-onset Pompe disease, Muscle Nerve 50 (2014) 301–302.

[16] Y.H. Chien, N.C. Lee, S.F. Peng, W.L. Hwu, Brain development in infantile-onset Pompe disease treated by enzyme replacement therapy, Pediatr. Res. 60 (2006) 349–352.

[17] Y.T. Zeng, W.L. Hwu, P.C. Torng, N.C. Lee, J.Y. Shieh, L. Lu, Y.H. Chien, Longitudinal follow-up to evaluate speech disorders in early-treated patients with infantile-onset Pompe disease, Eur. J. Paediatr. Neurol. (2016), http://dx.doi.org/10.1016/j.ejpn.2016.12.004.

[18] P.K. Huang, C.C. Wang, S.N. Chiu, E.T. Wu, Y.H. Chien, W.L. Hwu, J.K. Wang, M.H. Wu, Torsade de pointes ventricular tachycardia during elective intubation in a patient with Pompe disease, Paediatr. Anaesth. 18 (2008) 346–348.

[19] L. Martineau, M.A. Horan, N.J. Rothwell, R.A. Little, Salbutamol, a beta 2-adrenoceptor agonist, increases skeletal muscle strength in young men, Clin. Sci. 83 (1992) 615–621.

[20] A. Kalsen, M. Hostrup, J. Bangsbo, V. Backer, Combined inhalation of beta2-agonists improves swim ergometer sprint performance but not high-intensity swim performance, Scand. J. Med. Sci. Sports 24 (2014) 814–822.

[21] R. Jockers, S. Angers, A. Da Silva, P. Benaroch, A.D. Strosberg, M. Bouvier, S. Marullo, Beta(2)-adrenergic receptor down-regulation. Evidence for a pathway that does not require endocytosis, J. Biol. Chem. 274 (1999) 28900–28908.

[22] L.E. Case, C. Bjartmar, C. Morgan, R. Casey, J. Charrow, J.P. Clancy, M. Dasouki, S. DeArmey, K. Nedd, M. Nevins, H. Peters, D. Phillips, Z. Spigelman, C. Tifft, P.S. Kishnani, Safety and efficacy of alternative alglucosidase alfa regimens in Pompe disease, Neuromuscul. Disord. 25 (2015) 321–332.

[23] C.M. van Gelder, E. Poelman, I. Plug, M. Hoogeveen-Westerveld, N.A. van der Beek, A.J. Reuser, A.T. van der Ploeg, 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. 39 (2016) 383–390.