Title

Natural history and galsulfase treatment in mucopolysaccharidosis VI (MPS VI, Maroteaux–Lamy syndrome)—10-year follow-up of patients who previously participated in an MPS VI survey study

Journal

American Journal of Medical Genetics Part A, 164(8)

ISSN

1552-4825

Authors

Giugliani, Roberto
Lampe, Christina
Guffon, Nathalie
et al.

Publication Date

2014-08-01

DOI

10.1002/ajmg.a.36584

Peer reviewed

Published in final edited form as:
Am J Med Genet A. 2014 August ; 164(8): 1953–1964. doi:10.1002/ajmg.a.36584.

Natural History and Galsulfase Treatment in Mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy Syndrome) — 10 Year Follow-up of Patients Who Previously Participated in an MPS VI Survey Study

Roberto Giugliani[1,*], **Christina Lampe**[2], **Nathalie Guffon**[3], **David Ketteridge**[4], **Elisa Leão Teles**[5], **James E. Wraith**[6], **Simon A Jones**[6], **Cheri Piscia-Nichols**[7], **Ping Lin**[7], **Adrian Quartel**[7], and **Paul Harmatz**[8]

[1]Medical Genetics Service, HCPA, Department of Genetics, UFRGS, and INAGEMP, Porto Alegre, Brazil

[2]Department of Pediatric and Adolescent Medicine, Villa Metabolica, University Medical Center of the University of Mainz, Germany

[3]Hôpital Femme Mère Enfant, Bron, France

[4]Women's and Children's Hospital, North Adelaide, Australia

[5]Hospital Pediátrico Integrado, Centro Hospitalar de S. João, Porto, Portugal

[6]Manchester Children's Hospital, Centre for Genomic Medicine, St Mary's Hospital, CMFT, University of Manchester, Manchester, UK

[7]BioMarin Pharmaceutical Inc., Novato, CA, USA

[8]Children's Hospital & Research Center Oakland, Oakland, CA, USA

Abstract

Mucopolysaccharidosis VI (MPS VI) is a clinically heterogeneous and progressive disorder with multiorgan manifestations caused by deficient N-acetylgalactosamine-4-sulfatase activity. A cross-sectional Survey Study in individuals (n=121) affected with MPS VI was conducted between 2001–2002 to establish demographics, urinary glycosaminoglycan (GAG) levels, and clinical progression of disease. We conducted a Resurvey Study (ClinicalTrials.gov: NCT01387854) to obtain 10-year follow-up data, including medical histories and clinical assessments (n=59), and survival status over 12-years (n=117). Patients received a mean (SD) of 6.8 (2.2) years of galsulfase ERT between baseline (Survey Study) and follow-up. ERT patients increased in height by 20.4 cm in the 4–7 year-old baseline age group and by 16.8 cm in the 8–12 year-old baseline age group. ERT patients <13 years old demonstrated improvement in forced vital capacity (FVC) by 68% and forced expiratory volume in 1 second (FEV1) by 55%, and those ≥13 years old increased FVC by 12.8% and maintained FEV1. Patients with >200 μg/mg baseline uGAG levels increased FVC by 48% in the <13 year-old and by 15% in the ≥13 year-old baseline

[*]**CORRESPONDING AUTHOR: Roberto Giugliani, MD**, Medical Genetics Service, Hospital de Clinicas de Porto Alegre, Rua Ramiro Barcelos 2350, 90035-903 Porto Alegre, RS, Brazil, rgiugliani@hcpa.ufrgs.br, Phone: 55-51-3359-6341, Fax: 55-51-3359-8010.

age group. ERT patients who completed the 6-minute walk test demonstrated a mean (SD) increase of 65.7 (100.6) m. Cardiac outcomes did not significantly improve or worsen. Observed mortality rate among naïve patients was 50% (7/14) and 16.5% (17/103) in the ERT group (unadjusted hazard ratio, 0.24; 95% CI, 0.10 to 0.59). Long-term galsulfase ERT was associated with improvements in pulmonary functions and endurance, stabilized cardiac function and increased survival.

Keywords

(MeSH); Mucopolysaccharidosis VI; Maroteaux-Lamy syndrome; N-Acetylgalactosamine-4-Sulfatase; Enzyme Replacement Therapy; Follow-Up Studies; Multicenter Study [Publication Type]; Survival Rate; Exercise Tolerance; Respiratory Function Tests

INTRODUCTION

Mucopolysaccharidosis VI (MPS VI, OMIM #253200), also known as Maroteaux-Lamy syndrome, is a clinically progressive disorder with a spectrum of mild to severe phenotypes. MPS VI is caused by deficient activity of the lysosomal enzyme N-acetyl-galactosamine-4-sulfatase (also known as arylsulfatase B, ASB; EC 3.1.6.12) which hydrolyzes the sulfate moiety of the glycosaminoglycan (GAG) dermatan sulfate [Neufeld and Muenzer, 2001]. Patients with rapidly progressing disease often have short stature with coarse facial features, joint and skeletal abnormalities, spinal cord compression, compromised cardiovascular and pulmonary function, corneal clouding, recurrent respiratory and ear infections, and early mortality in the late teens to early twenties, often from cardiopulmonary failure. MPS VI patients present with classical symptoms by 6 to 24 months of age. [Neufeld and Muenzer, 2001; Valayannopoulos et al., 2010]. Although symptoms may appear later in life in those with slowly progressing disease, these patients nonetheless demonstrate severe morbidity and early mortality by the third to fifth decade of life [Thümler et al., 2012]. The patients often require clinical intervention related to one or more organ dysfunction such as corneal transplants, cardiac valve replacement, hip replacement or spinal cord decompression surgery by their late teen to adult years (reviewed in [Giugliani et al., 2007; Valayannopoulos et al., 2010]). Although MPS VI patients do not typically exhibit neurocognitive deficits, physical limitations particularly with decreased sight and hearing can affect learning and development.

A cross-sectional Survey Study of 121 MPS VI patients was conducted in 2001–2002 to establish demographics, urinary GAG levels and clinical progression of MPS VI [Swiedler et al., 2005]. There was heterogeneity in the clinical presentation of MPS VI patients in this large survey representing an estimated 10% of the world-wide MPS VI patient population. The accelerated clinical course, presenting with short stature, lower body weights, reduced pulmonary function, impaired endurance and reduced joint range of motion was associated with elevated urinary GAG levels (>200 μg/mg creatinine). Further studies have shown that certain genetic alterations in the ASB gene correlate with high uGAG levels predicting rapidly progressing clinical outcomes [Karageorgos et al., 2007].

Currently galsulfase (recombinant human ASB; rhASB; Naglazyme®) enzyme replacement therapy (ERT) is the only approved therapy for MPS VI. Galsulfase is approved by the regulatory agencies in the United States, European Union, Brazil, Australia and several other countries. International management guidelines for MPS VI recommend galsulfase ERT as the first-line therapy for treating MPS VI patients [Giugliani et al., 2007]. Three clinical trials, including a randomized double-blind placebo-controlled Phase 3 trial, showed improved endurance based on increased 12-minute walk test (12MWT) and 3-minute stair-climb (3MSC) measurements, and decreased urinary GAGs, demonstrating efficacy of galsulfase in the MPS VI patients [Harmatz et al., 2006; Harmatz et al., 2005a; Harmatz et al., 2005b; Harmatz et al., 2004]. An analysis of pooled data from the clinical trial program showed improvement in pulmonary function tests and growth velocity in patients (n=56, mean age approximately 12 years, range 5 to 29 years) who received ERT for up to 240 weeks [Decker et al., 2010; Harmatz et al., 2010]. Similarly, long-term ERT of up to 96 weeks reduced intraventricular septal hypertrophy and prevented progression of cardiac valve abnormalities in patients <12 years of age [Braunlin et al., 2012]. While the clinical trials and extension studies suggest significant clinical benefit of galsulfase treatment in MPS VI, the Resurvey Study provides information on the long-term effects of galsulfase treatment (ie, up to mean 6.8 years) on the natural progression of MPS VI.

METHODS

Study Design

The Resurvey Study (ASB-00-03; ClinicalTrials.gov number: NCT01387854) was a multicenter, multinational study to obtain repeat 10-year cross-sectional data on patients who took part in the Survey Study (ASB-00-02) in 2001–2002 [Swiedler et al., 2005]. Only patients who previously participated in the Survey Study ASB-00-02 and had met the criteria of a MPS VI diagnosis were eligible. Of the 121 patients who participated in the Survey Study, 59 patients from 1 site in the USA, four sites in Europe, one site in Australia and one site in Brazil enrolled in the Resurvey Study. Survival status was available for 117 of 121 Survey Study participants as of October 24, 2013, for a total survival follow-up of up to 12 years. The remaining four patients were considered lost to follow-up, since no information was available after three attempts to reach them via study sites.

The study protocol was approved by local institutional review boards (IRB) or ethics committees (EC), and the study was conducted in accordance with good clinical practice guidelines (ICH E6) and the ethical principles established by the Declaration of Helsinki. All patients provided a written, signed informed consent or, in the case of patients <18 years of age, their legally authorized representative provided a written consent. All patients underwent clinical and laboratory assessments as indicated.

Clinical Assessments

The list of assessments performed was the same as that completed in the Survey Study and all patients were evaluated at a single time point [Swiedler et al., 2005]. The list of assessments described in this report includes galsulfase treatment history; standing height and weight; endurance, pulmonary and cardiac function tests; and health assessment

questionnaires. The participating sites were also asked to provide a summary of patients known to have died since the Survey Study.

Endurance was assessed by the 6-minute walk test (6MWT) [Guyatt et al., 1989; Nixon et al., 1996]. The 12-lead electrocardiograms (ECGs) were done at all sites and standard 2-dimensional Doppler echocardiograms (ECHOs) were done at a subset of sites in Survey and Resurvey studies. The number and percentage of patients with stenosis or regurgitation (valve problem status) were determined by valve type. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) were performed in accordance to the American Thoracic Society (ATS) standards [1995] and each site's Respiratory Department policy and procedure for spirometry. The highest of the three values for FVC and FEV1 was reported.

All patients were asked to complete health assessment questionnaires. Patients who were ≤18 years at Resurvey completed the Childhood Health Assessment Questionnaire (CHAQ) [Singh et al., 1994], and those >18 years at Resurvey completed the Health Assessment Questionnaire (HAQ) [Fries 1991; Ramey et al., 1992].

Since no treatment was given as part of this clinical protocol, ERT or infusion-related adverse events were not collected.

Laboratory Assessments

Urinary GAG (uGAG) levels were determined by spectrophotometric detection of metachromatic change in the 1,9-dimethyl-methylene blue (DMMB) dye upon GAG binding [Whitley et al., 1989] during the Survey Study (performed at BioMarin Pharmaceutical Inc. Labs) or by measuring the change in absorbance at 656_{nm} of the DMMB dye upon GAG binding during the Resurvey Study (performed at Cambridge Biomedical, Inc., Boston, www.cambridgebiomedical.com). Urinary GAG levels were measured on the first morning voided samples and normalized to urine creatinine levels.

Statistical Methods

Paired t-tests were performed to compare patient's paired data (Resurvey vs Survey study) for clinical and laboratory assessments, and were two-sided at the 0.05 level (unless indicated otherwise). Version 9.3 (or higher) of SAS® statistical software package or Microsoft Excel program were used to generate all summaries, listings, graphs, and statistical analyses. First or last treatment dates for ERT were missing for four patients who had the year but not the month in the database which were imputed according to standard statistical methods. All results are presented as mean ± SD (range) unless otherwise indicated.

Kaplan-Meier survival analyses were performed to compare the overall survival for ERT-treated vs ERT-naïve patients, and the difference in overall survival was compared using the Logrank and Wilcoxan tests. The missing dates of death (for three naïve patients with only year of death known and for four naive patients known to have died within a certain range of time) were imputed using the most conservative method wherein the latest day/month/year was set as the death date for naïve deceased patients. The hazard ratio estimated by using

Cox proportional hazards model (both for univariable as well as multivariable analyses) are presented as hazard ratio (HR) with 95% confidence intervals (CIs).

RESULTS

Demographics

Of the 59 patients enrolled in the Resurvey Study, 55 received galsulfase ERT. The mean duration of ERT for the 52 patients with known ERT start dates was 6.8 ± 2.2 years (Table I and Supplementary eTable I in supporting information online). The ERT group had similar numbers of male (n=29) and female (n=26) patients. There were four patients in the naïve group, three males and one female (Table I). The results in this report are stratified according to the baseline age groups and not their ages at Resurvey. Similarly, stratifications based on uGAGs are per baseline uGAG levels (ie, uGAG levels at the Survey Study and are pre-ERT). In this report, patients with baseline uGAG levels > 200 μg/mg creatinine pre-ERT are referred to as the high uGAG group with more rapidly progressive disease.

Urinary GAGs

Urinary GAG levels at follow-up were <100 μg/mg creatinine in all patients (n=55) who were exposed to galsulfase ERT, including 33 of 55 (60%) patients whose uGAG levels were >200 μg/mg creatinine at baseline 10 years ago (Fig 1 and Supplementary eTable I in supporting information online). The mean uGAG level at baseline was 321.34 ± 199.86 μg/mg creatinine for all participants (n=118) [Swiedler et al., 2005]. Urinary GAG levels decreased by 87.9% in the ERT patients (n=55) vs 49.8% in the naïve patients (n=3) at follow-up compared to baseline (Supplementary eTable I in supporting information online). Different methods were used to measure uGAG levels for the Survey (baseline) and Resurvey (follow-up) studies limiting the conclusions that can be drawn when directly comparing these values.

Anthropometrics

The mean height of the ERT group (n=51) was 117.2 ± 25.1 cm at baseline and 129.9 ±21.4 cm at follow-up (Table II). All age groups <18 years baseline age increased in height during the study period (Table II and Supplementary eTable I in supporting information online). The mean height of patients increased by 20.4 ± 12.4 cm in the 4–7 year-old baseline age group (n=19) and by 16.8 ± 6.3 cm in the 8–12 year-old baseline age group (n=13) (TABLE II). The baseline Z-scores, as determined by the CDC growth curve measurements (ref: [Grummer-Strawn et al., 2010; Kuczmarski et al., 2002]) were below −2 SD except for the youngest patients in the 4–7 year-old age group (Table II).

The baseline uGAG levels correlated inversely with the age-adjusted short stature in the MPS VI population [Swiedler et al., 2005]. Similarly, baseline uGAG levels correlated inversely with the final heights in the Resurvey study (Table II). The final heights in all baseline age groups ranged from 142 to 158 cm in those with low baseline uGAG levels (≤ 200 μg/mg creatinine) as compared to 113 to 119 cm in the high baseline uGAG subgroups. The majority of patients <13 year-old baseline age (n=27) had high uGAG levels, but still exhibited increased heights from 16 to 18 cm.

All age groups demonstrated increases in mean body mass index (BMI) compared to baseline though the follow-up BMI remained within the normal range (18.5, 25.0 kg/m^2) (ref: [Casey et al., 1992; Centers for Disease Control and Prevention 2011]. The mean BMI based on standing height in the ERT group (n=51) increased from 19.9 ± 3.8 kg/m^2 (range, 14.7, 29.9) at baseline to 24.1 ± 4.7 kg/m^2 (range, 16.2, 36.6) at follow-up. The naïve group (n=3) posted a mean BMI increase from 24.2 ± 0.8 kg/m^2 (range 23.3, 24.8) to 27.6 ± 2.3 kg/m^2 (range 25.2, 29.8) during the same period.

Six-minute walk test

The mean six-minute walk text (6MWT) distance for the ERT group (n=54) changed from 304.0 ± 108.4 m at baseline to 320.4 ± 195.7 m at follow-up, an increase of 16.4 ± 155.9 m (Table III). When excluding the eight patients who could not attempt the 6MWT at follow-up (as a walk distance value of 0.0 m was entered for these subjects), seven of whom were wheelchair bound, there was an increase of 65.7 ± 100.6 m from a baseline of 310.4 ± 111.8 m (Table III). Of those who completed the walk test (n=46), all age subgroups showed improvement in the mean distance walked over the study period (Table III). The mean increase in the distance walked at follow-up by the baseline age 4–12 year-old group was 71.0 ± 108.5 m and was 57.4 ± 89.2 m by the baseline age ≥13 year-old group.

ERT patients with high baseline uGAGs showed lower or no improvement in endurance as compared to those with uGAG levels <200 μg/mg creatinine at baseline (Table III). The increase in the distance walked by the patients with baseline uGAG levels of <100 μg/mg creatinine (n=14) was 74.0 ± 77.2 m while the increase in mean walk distance in the high baseline uGAG group (n=32) was minimal at −14.8 ± 179.0 m.

Pulmonary function tests

FVC and FEV1 increased by 29% and 18% over baseline at 10-year follow-up (Fig 2 and Supplementary eTable II in supporting information online). The mean change in FVC from baseline was 0.37 L (*P*<.0001) in the ERT group (n=48) and −0.70 L in the naïve group (n=3). The mean change in FEV1 was 0.21 L (*P*=.001) in the ERT group (n=47) and −0.60 L in the naive group (n=3) (Supplementary eTable II in supporting information online).

FVC improvements were observed across all baseline age groups, with the greatest increase seen in the <13 y old baseline age group (Fig 2, Supplementary eTable II). This increase of 68% (FVC) and 55% (FEV1) over baseline is in part due to growth. [Decker et al., 2010; Harmatz et al., 2010]. The older patients (≥13 year-old baseline age) also showed an increase of 12.8% in FVC compared to baseline, with minimal increase in FEV1.

In patients with high baseline uGAG levels, FVC improvements were seen in both younger (<13 year-old baseline age) and older (≥13 year-old baseline age) patient subgroups (Supplementary eTable II in supporting information online): FVC improved by 48% in the younger patient subgroup and by 15% in the older patient subgroup.

Cardiovascular parameters

Of the 55 patients in the study, evaluable ECHOs were available for 33 patients at follow-up, of which 31 had evaluable baseline ECHOs. Paired analyses for the various ECHO parameters were performed on patients with evaluable ECHOs at both baseline and follow-up. Overall, there was neither significant improvement nor worsening of the cardiac valve outcomes (Table IV). There was no significant change in left ventricular dimension at end diastole or systole (LVED or LVES, respectively), left ventricular shortening fraction (LVSF), left ventricular septal (LVSW) or posterior wall thickness (LVPW) from baseline to follow-up (Supplementary eTable III in supporting information online).

The 12-lead ECG results did not indicate major conduction abnormalities at baseline or follow-up (Supplementary eTable III in supporting online). The PR, QRS, QT and QTc intervals were within normal reference ranges as described in the literature [Mason et al., 2007]. However, sinus tachycardia was recorded in 11 (20.0%) patients during follow-up vs 7 (12.7%) at baseline, and left and right axis deviations were noted in 11 (20.0%) patients at follow-up vs 1 (1.8%) patient at baseline, though this was an isolated finding in these patients.

Quality of life assessments

There was no change in the disability, or pain and arthritis scores between the 2 timepoints (Supplementary eTable IV in supporting information online). Patients ≤18 years old reported moderate disability scores and those >18 years old scored as mild at baseline and follow-up. Similarly, mean pain and arthritis scores were in the mild category for ≤18 year-olds as well as >18 year-old patients at both timepoints.

Survival

Survival data were available for 117 of the 121 patients enrolled in the Survey Study, of which 103 patients received galsulfase ERT and 14 were ERT naive (Table V). Of the 117 patients, 24 died since the Survey Study; mortality rate was 16.5% in the ERT group (died=17/103) vs 50% in the naïve group (died=7/14) (Table V). The Kaplan-Meier analysis indicated that patients treated with ERT had significant survival benefit over naïve patients The Kaplan-Meier curve for the treated patients in Figure 3A showed a statistically significant separation (Logrank P=.0006, Wilcoxon P=.0002) from the Kaplan-Meier curve for the naïve patients. Cox proportional hazard regression model was used to determine the association of ERT with long-term survival of MPS VI patients. ERT was shown to be positively associated with survival (unadjusted HR, 0.24; 95% CI, 0.10 to 0.59). After adjustment for baseline age and baseline uGAG groups, the adjusted HR for ERT was 0.11 (95% CI, 0.04 to 0.29).

Although there was a significant age difference at the time of enrollment in the Survey Study between the naïve and treatment groups (mean age 19.8 vs 13.7 years; Table V), this did not appear to impact the mortality rate. The mean age at enrollment in the Survey Study for the deceased naïve and deceased treatment patients was 14.4 and 15.4 years, respectively. Moreover, the mean age at the time of death was 19.2 and 22.9 years in the naïve and treated groups, respectively (Table V).

The Kaplan-Meier survival analysis of age and uGAG subgroups in the ERT treated patients suggest that those with low baseline uGAG ≤200 μg/mg creatinine have a better survival probability than those with high baseline uGAG levels (Fig 3B and Table V). The survival probability of <13 year-old baseline age patients with baseline uGAG levels ≤200 μg/mg creatinine was higher than those with high baseline uGAGs. The survival probability of the ≥13 year-old patients with high baseline uGAG levels was lower compared to all other ERT subgroups (Fig 3B).

DISCUSSION

There are few large studies outside the randomized clinical trials (RCTs) that define the natural history of MPS VI on a population-wide basis including those on long-term galsulfase treatment to determine impact on the clinical disease course [Brands et al., 2013b; Hendriksz et al., 2013; Swiedler et al., 2005]. One of the largest population-wide studies reported to date on MPS VI was a cross-sectional Survey Study of 121 patients conducted 10 years ago [Swiedler et al., 2005]. In this cross-sectional Survey Study, it was concluded that the pre-ERT uGAG levels predict clinical morbidity. Patients with high baseline uGAG levels (>200 μg/mg creatinine) had an accelerated clinical course of disease with poor endurance (impaired 6MWT), reduced pulmonary function, reduced joint range of motion, and short stature. Cardiac abnormalities including stenosis and/or regurgitation in one or more cardiac valves were present in nearly all of the patients (96%). Most patients who were over 20 years of age had uGAG levels <100 μg/mg creatinine (all except one patient whose uGAG level was 152 μg/mg creatinine). This observation suggested a correlation between a low baseline uGAG level and longer survival or slower progression of disease. Since the time of the Survey Study, galsulfase ERT has become available and considered standard of care [Giugliani et al., 2007]; thus allowing the ability to assess whether long-term exposure to galsulfase ERT can alter the course of MPS VI clinical natural history.

The observations from the 10-year follow-up described in this report are the longest longitudinal data assessments in any MPS VI study to date. The majority of the patients in the study were young (60% were 4–12 year-olds and 18% were 13–18 year-olds) at baseline and these patients continued to increase in height over this time period. Growth rates at any specific age in the 4–7 year-old and the 8–12 year-old baseline age groups were impossible to calculate given that there were only two widely separated data timepoints in this report.

Improved endurance was seen in all ERT patient subgroups (by baseline age) that completed the walk test. There was an increase in pulmonary function with significant increases in the FVC and FEV1 in the ERT patients. This increase in pulmonary function may be due in part to growth in the younger patients and as an effect of ERT. Cardiac function had stabilized except for a small increase in the number of patients with aortic regurgitation. In patients with rapidly progressive disease, both endurance and pulmonary functions were stabilized in the ERT group. Thus, the progression of symptoms attributed to the MPS VI disease has stabilized or improved in the ERT-treated patients, the majority of whom had rapidly progressive disease.

Endurance testing in MPS VI patients as measured by the 6MWT provides an indication of cardiopulmonary health, endurance, mobility and extent of morbidity [Morales-Blanhir et al., 2011]. In the Resurvey Study, the patients who completed the 6MWT walked a mean of 65.7 m ($P<.0001$) more at follow-up. This gain was consistent with that posted for the patients receiving ERT in the Phase 3 randomized clinical trial (53 m at week 24, $P=.007$) and in the final analysis of the open-extension part of the Phase 3 trial (80 m at week 96, $P<.001$); both values were from the 6-minute timepoint assessment of the 12MWT [Harmatz et al., 2006; Harmatz et al., 2008]. Further, among Resurvey Study patients who completed the walk test, all baseline age groups made similar gains in the distance walked.

The mean increases in pulmonary function measures (FVC and FEV1) in the 4–12 year-old age group in the Resurvey Study were statistically significant and similar to improvements in pulmonary function seen after up to 240 weeks of ERT in the galsulfase clinical trial extension program [Harmatz et al., 2010]. The improvement in pulmonary function observed after long-term galsulfase treatment may be related to an increase in skeletal growth (height). In addition to growth, other studies have suggested direct effect of ERT on lung function [Harmatz et al., 2010]. A 96-week follow-up of older patients (≥12 year-old baseline age group) participating in galsulfase clinical trials and extension program found a 22.6% increase in FVC, which was attributed to direct effects of ERT on lung function [Harmatz et al., 2010]. In the Resurvey Study, the FVC increased by 12.8% over baseline in the older patients (≥13 year-old baseline age group) indicating sustained and long-term improvement in pulmonary function in ERT treated patients. This increase is considered clinically significant as pulmonary function generally declines with age in all individuals, including in those with MPS disorders [Lin et al., 2013].

Cardiac involvement particularly mitral and aortic valve thickening resulting in stenosis/regurgitation, and intraseptal or ventricular hypertrophy are commonly seen in MPS VI and other MPS diseases where dermatan sulfate accumulation is the primary storage defect [Azevedo et al., 2004; Brands et al., 2013c; Braunlin et al., 2012; Dangel 1998; Fesslová et al., 2009; Golda et al., 2012; Swiedler et al., 2005]. Mitral and aortic valve abnormalities are typical cardiac manifestations in MPS VI; however, pulmonary and tricuspid valves are less commonly involved (reviewed in[Golda et al., 2012]). The Survey Study found that of the 68 patients with ECHO data, nearly all (96%) had evidence of stenosis and/or regurgitation. [Swiedler et al., 2005]. Although the cardiac valve pathology was not graded in the Resurvey study, we did not notice any significant improvement or worsening of the cardiac valve outcomes based on the number of patients with or without valve abnormalities, though aortic regurgitation rate was somewhat increased (25/31 at follow-up vs 16/31 at baseline). Further, the follow-up of ERT patients at Resurvey found no change in LVSF, LVED, LVES, LVSF, LVSW or LVPW findings when compared to baseline suggesting no change in ventricular dimensions, mass or function. Results of a long term observational study led to the conclusion that ERT neither resolves nor prevents cardiac valve problems [Hendriksz et al., 2013], consistent with the findings in this study. Thus, the progressive valve pathology is difficult to reverse by ERT, although the disease progression is slowed or stabilized.

The patients treated with ERT had a survival advantage over the untreated patients, as demonstrated by reduced overall mortality rates among the ERT patients vs the naïve group

(16.5% vs 50.0%). There was an observed difference in survival between those patients with high pre-ERT uGAG levels, with 12/67 (17.9%) deaths in the ERT group and 6/7 (85.7%) in the naïve group suggesting that patients with rapidly progressive disease may also benefit by ERT treatment. The unadjusted hazard ratio of 0.242 indicates that ERT patients have a 75.8% reduction in the chance of death than those not on ERT. After adjusting for covariates (baseline age and baseline uGAG groups), there remained a very strong benefit of ERT treatment. The adjusted hazard ratio of 0.107 indicates an 89.3% reduction in the chance of death among patients who were ERT treated compared with patients who were not on ERT. Because most patients in this study did not receive ERT until their teen years, it is hypothesized that early initiation of ERT in life may further improve long-term survival.

Although adverse events (AEs) related to galsulfase-treatment, or seroconversion status of galsulfase-treated patients were not collected as part of the Resurvey Study, several other long-term studies confirm that galsulfase is safe and tolerable; and infusion-associated reactions (IARs) are manageable [Brands et al., 2013b; Harmatz et al., 2008; Hendriksz et al., 2013; Lin et al., 2010]. Galsulfase treatment-related serious AEs are rare: only 31 events were reported for 11 patients in a 5-year follow-up of patients in the CSP (n=123) [Hendriksz et al., 2013].

Other studies, including a Dutch 5-year follow-up study (n=12) and a 2-year Taiwanese follow-up study (n=9) also did not report any major safety concerns [Brands et al., 2013b; Lin et al., 2010]. In the galsulfase clinical trials where safety data were collected up to a 5 year period, 14% of the AEs were galsulfase treatment-related, of which only 2% were described as severe [Harmatz et al., 2008]. The most common severe AEs included chest pain, dyspnea, laryngeal edema, and conjunctivitis [BioMarin 2013]. In contrast, most IARs, which occurred in >50% of patients in the clinical studies, were mild-to-moderate, and were easily managed by altering the infusion rate, interrupting infusion and/or premedications with antihistamines, anti-inflammatory and/or antipyretics. Fewer IARs were reported in the CSP, possibly due to underreporting of the AE due to voluntary participation [Hendriksz et al., 2013], IARs are common occurrence in other studies. For instance, the Taiwanese study reported IARs in three of nine patients at some point during treatment, all of which were manageable with premedications [Lin et al., 2010].

There was a high rate of compliance during the clinical trials and their extension program with 53 of 56 enrollees (94.6%) completing the study; the three withdrawals were unrelated to the galsulfase treatment. Of the 59 patients in the open-label clinical trial phase, none discontinued galsulfase treatment due to adverse events [BioMarin 2013]. Seroconversion occurs by 6–7 months in almost all patients after galsulfase ERT initiation [Brands et al., 2013a; Hendriksz et al., 2013]. Antibody titers are heterogeneous ranging from modest to high [Brands et al., 2013a; Harmatz et al., 2006; Hendriksz et al., 2013], and may remain stable over several years [Brands et al., 2013a]. Although an in vitro study suggested that high antibody titers may potentially interfere with galsulfase protein uptake by cells [Brands et al., 2013a], a regression analysis of data from CSP showed no correlation of anti-galsulfase antibody titers with uGAG levels (determined at the time of antibody analysis after ERT initiation) (r=−0.067; P=.32), and similarly individual increases in titers did not correlate with a decrease in efficacy as determined by endurance measures or an increase in

AEs [Hendriksz et al., 2013]. One patient in the Dutch study, with an ASB gene mutation resulting in a complete absence of the ASB protein, had high baseline uGAG levels. This patient developed high and sustained anti-ASB antibody titers after galsulfase ERT, but showed reduction of uGAGs from >1000 μg/mg creatinine to 115 μg/mg [Brands et al., 2013a]. Thus, current evidence suggests that the antibody response against galsulfase does not affect uGAG reduction or galsulfase clinical efficacy [Brands et al., 2013a].

The progressive nature of the disease in the absence of ERT suggests an adverse impact on the activities of daily life, quality of life and survival [Neufeld and Muenzer 2001; Swiedler et al., 2005]. In the Resurvey Study, there was no change in the quality of life measures (CHAQ/HAQ scores) from baseline in spite of the fact that most of these participants had rapidly-progressing phenotypes (Fig 1 and Swiedler et al., [2005]). The effect of galsulfase ERT on multiorgan physiology along with better standard of care may have contributed to arresting a decline in the quality of life in these patients. Similar trends in the quality of life measures were also reported for MPS VI and other lysosomal storage disorders for which ERTs are now available [Brands et al., 2013a; Clarke et al., 2009; Freedman et al., 2013].

The disease progression in MPS VI patients with severe or rapidly progressive disease (ie, based on high baseline uGAG levels) appears to have been stabilized by ERT. While the greatest improvements in height and endurance were seen primarily in patients with lower baseline uGAG levels ≤200 μg/mg creatinine, clinical parameters (such as walk distance in 6MWT and pulmonary function) in the high baseline uGAG group remained stable in the ERT group. However, additional or newer approaches may be required to increase the clinical benefit of galsulfase ERT in patients with rapidly progressive disease, such as different dosing schedules [Cotugno et al., 2010]) and/or substrate reduction therapy, both of which have not yet been tested in clinical studies [Schuchman et al., 2013; Simonaro et al., 2010; van Gelder et al., 2012]. Neonatal screening leading to early diagnosis and prompt ERT initiation may be key to improve the management and outcomes of patients with rapidly progressive disease [Furujo et al., 2011; Giugliani 2012; Horovitz et al., 2013; McGill et al., 2010].

In conclusion, long-term galsulfase ERT results in improved survival, continued growth, improvement in endurance and pulmonary function, and stabilization of cardiac and quality of life measures in the MPS VI patients. Even in patients with more severe disease, galsulfase ERT results in stabilization of endurance and pulmonary function as well as improved survival. Clinical benefits of galsulfase ERT are likely to be enhanced by early initiation of the therapy in MPS VI patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by BioMarin Pharmaceutical Inc. and, in part, with funds provided by the National Institutes of Health/National Center for Research Resources (NIH/NCRR) CTSA grant UL1RR024131 (Dr. Harmatz). The authors thank Ajay K. Malik (BioMarin) for medical writing support and Robert Matousek (BioMarin) for statistical analysis.

Authors Quartel and Lin are employees and stockholders of BioMarin; Piscia-Nichols is a former employee of BioMarin. All other investigators provided consulting services, received research grants, and participated in advisory board meetings and received speaker honoraria and travel support from BioMarin Pharmaceutical Inc.

REFERENCES

Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995; 152(3):1107–1136. [no authors]. [PubMed: 7663792]

Azevedo AC, Schwartz IV, Kalakun L, Brustolin S, Burin MG, Beheregaray AP, Leistner S, Giugliani C, Rosa M, Barrios P, Marinho D, Esteves P, Valadares E, Boy R, Horovitz D, Mabe P, da Silva LC, de Souza IC, Ribeiro M, Martins AM, Palhares D, Kim CA, Giugliani R. Clinical and biochemical study of 28 patients with mucopolysaccharidosis type VI. Clin Genet. 2004; 66(3):208–213. [PubMed: 15324318]

BioMarin. Naglazyme (galsulfase) Prescribing Information. 2013

Brands M, Hoogeveen-Westerveld M, Kroos M, Nobel W, Ruijter GJ, Ozkan L, Plug I, Grinberg D, Vilageliu L, Halley D, Ploeg A, Reuser A. Mucopolysaccharidosis type VI phenotypes-genotypes and antibody response to galsulfase. Orphanet J Rare Dis. 2013a; 8(1):51. [PubMed: 23557332]

Brands M, Oussoren E, Ruijter G, Vollebregt A, van den Hout H, Joosten K, Hop W, Plug I, van der Ploeg A. Up to five years experience with 11 mucopolysaccharidosis type VI patients. Mol Genet Metab. 2013b; 109(1):70–76. [PubMed: 23523338]

Brands MM, Frohn-Mulder IM, Hagemans ML, Hop WC, Oussoren E, Helbing WA, van der Ploeg AT. Mucopolysaccharidosis: cardiologic features and effects of enzyme-replacement therapy in 24 children with MPS I, II and VI. J Inherit Metab Dis. 2013c; 36(2):227–234. [PubMed: 22278137]

Braunlin E, Rosenfeld H, Kampmann C, Johnson J, Beck M, Giugliani R, Guffon N, Ketteridge D, Sá Miranda CM, Scarpa M, Schwartz IV, Leão Teles E, Wraith JE, Barrios P, Dias da Silva E, Kurio G, Richardson M, Gildengorin G, Hopwood JJ, Imperiale M, Schatz A, Decker C, Harmatz P. Enzyme replacement therapy for mucopolysaccharidosis VI: long-term cardiac effects of galsulfase (Naglazyme(®)) therapy. J Inherit Metab Dis. 2012; 36(2):385–394. [PubMed: 22669363]

Casey VA, Dwyer JT, Coleman KA, Valadian I. Body mass index from childhood to middle age: a 50-y follow-up. Am J Clin Nutr. 1992; 56(1):14–18. [PubMed: 1609751]

Centers for Disease Control and Prevention. Body Mass Index. 2011. http://wwwcdcgov/healthyweight/assessing/bmi/indexhtml.

Clarke LA, Wraith JE, Beck M, Kolodny EH, Pastores GM, Muenzer J, Rapoport DM, Berger KI, Sidman M, Kakkis ED, Cox GF. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics. 2009; 123(1):229–240. [PubMed: 19117887]

Cotugno G, Tessitore A, Capalbo A, Annunziata P, Strisciuglio C, Faella A, Aurilio M, Di Tommaso M, Russo F, Mancini A, De Leonibus E, Aloj L, Auricchio A. Different serum enzyme levels are required to rescue the various systemic features of the mucopolysaccharidoses. Hum Gene Ther. 2010; 21(5):555–569. [PubMed: 20021231]

Dangel JH. Cardiovascular changes in children with mucopolysaccharide storage diseases and related disorders--clinical and echocardiographic findings in 64 patients. Eur J Pediatr. 1998; 157(7):534–538. [PubMed: 9686810]

Decker C, Yu Z-F, Giugliani R, Schwartz IV, Guffon N, Teles EL, Miranda CS, Wraith E, Beck M, Arash L, Scarpa M, Ketteridge D, Hopwood J, Plecko B, Steiner R, Whitley C, Kaplan P, Swiedler S, Conrad S, Harmatz P. Enzyme replacement therapy for mucopolysaccharidosis VI: Growth and pubertal development in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. J Pediatr Rehabil Med. 2010; 3(2):89–100. [PubMed: 20634905]

Fesslová V, Corti P, Sersale G, Rovelli A, Russo P, Mannarino S, Butera G, Parini R. The natural course and the impact of therapies of cardiac involvement in the mucopolysaccharidoses. Cardiol Young. 2009; 19(2):170–178. [PubMed: 19195419]

Freedman R, Sahhar M, Curnow L, Lee J, Peters H. Receiving Enzyme Replacement Therapy for a Lysosomal Storage Disorder: A Preliminary Exploration of the Experiences of Young Patients and Their Families. J Genet Couns. 2013; 22(4):517–532. [PubMed: 23536258]

Fries JF. The hierarchy of quality-of-life assessment, the Health Assessment Questionnaire (HAQ), and issues mandating development of a toxicity index. Control Clin Trials. 1991; 12(4 Suppl): 106S–117S. [PubMed: 1663848]

Furujo M, Kubo T, Kosuga M, Okuyama T. Enzyme replacement therapy attenuates disease progression in two Japanese siblings with mucopolysaccharidosis type VI. Mol Genet Metab. 2011; 104(4):597–602. [PubMed: 21930407]

Giugliani R. Newborn screening for lysosomal diseases: current status and potential interface with population medical genetics in Latin America. J Inherit Metab Dis. 2012; 35(5):871–877. [PubMed: 22231381]

Giugliani R, Harmatz P, Wraith J. Management guidelines for mucopolysaccharidosis VI. Pediatrics. 2007; 120(2):405–418. [PubMed: 17671068]

Golda A, Jurecka A, Tylki-Szymanska A. Cardiovascular manifestations of mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome). Int J Cardiol. 2012; 158(1):6–11. [PubMed: 21737154]

Grummer-Strawn LM, Reinold C, Krebs NF, Centers for Disease C. Prevention. Use of World Health Organization and CDC growth charts for children aged 0–59 months in the United States. MMWR Recomm Rep. 2010; 59(RR-9):1–15. [PubMed: 20829749]

Guyatt GH, Veldhuyzen Van Zanten SJ, Feeny DH, Patrick DL. Measuring quality of life in clinical trials: a taxonomy and review. CMAJ. 1989; 140(12):1441–1448. [PubMed: 2655856]

Harmatz P, Giugliani R, Schwartz I, Guffon N, Teles EL, Miranda CS, Wraith E, Beck M, Arash L, Scarpa M, Yu Z-F, Wittes J, Berger K, Newman M, Lowe A, Kakkis E, Swiedler S. Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. J Pediatr. 2006; 148(4):533–539. [PubMed: 16647419]

Harmatz P, Giugliani R, Schwartz IV, Guffon N, Teles EL, Miranda CS, Wraith E, Beck M, Arash L, Scarpa M, Ketteridge D, Hopwood J, Plecko B, Steiner R, Whitley C, Kaplan P, Yu Z-F, Swiedler S, Decker C. Long-term follow-up of endurance and safety outcomes during enzyme replacement therapy for mucopolysaccharidosis VI: Final results of three clinical studies of recombinant human N-acetylgalactosamine 4-sulfatase. Mol Genet Metab. 2008; 94(4):469–475. [PubMed: 18502162]

Harmatz P, Ketteridge D, Giugliani R, Guffon N, Teles EL, Miranda CS, Yu Z-F, Swiedler S, Hopwood J. Direct comparison of measures of endurance, mobility, and joint function during enzyme-replacement therapy of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): results after 48 weeks in a phase 2 open-label clinical study of recombinant human N-acetylgalactosamine 4-sulfatase. Pediatrics. 2005a; 115(6)

Harmatz P, Kramer WG, Hopwood JJ, Simon J, Butensky E, Swiedler SJ. Pharmacokinetic profile of recombinant human N-acetylgalactosamine 4-sulphatase enzyme replacement therapy in patients with mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): a phase I/II study. Acta Paediatr Suppl. 2005b; 94(447):61–68. discussion 57. [PubMed: 15895715]

Harmatz P, Whitley C, Waber L, Pais R, Steiner R, Plecko B, Kaplan P, Simon J, Butensky E, Hopwood J. Enzyme replacement therapy in mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). J Pediatr. 2004; 144(5):574–580. [PubMed: 15126989]

Harmatz P, Yu Z-F, Giugliani R, Schwartz IV, Guffon N, Teles EL, Miranda CS, Wraith E, Beck M, Arash L, Scarpa M, Ketteridge D, Hopwood J, Plecko B, Steiner R, Whitley C, Kaplan P, Swiedler S, Hardy K, Berger K, Decker C. Enzyme replacement therapy for mucopolysaccharidosis VI: evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. J Inherit Metab Dis. 2010; 33(1):51–60. [PubMed: 20140523]

Hendriksz C, Giugliani R, Harmatz P, Lampe C, Martins AM, Pastores G, Steiner R, Leão Teles E, Valayannopoulos V. Design, baseline characteristics, and early findings of the MPS VI (mucopolysaccharidosis VI) Clinical Surveillance Program (CSP). J Inherit Metab Dis. 2013; 36(2):373–384. [PubMed: 22127392]

Horovitz D, Magalhães T, Acosta A, Ribeiro E, Giuliani L, Palhares D, Kim C, de Paula AC, Kerstenestzy M, Pianovski M, Costa MI, Santos F, Martins AM, Aranda C, Neto JC, Holanda GBM, Cardoso L, da Silva C, Bonatti R, Ribeiro B, Rodrigues MdC, Llerena J. Enzyme replacement therapy with galsulfase in 34 children younger than five years of age with MPS VI. Mol Genet Metab. 2013; 109(1):62–69. [PubMed: 23535281]

Karageorgos L, Brooks DA, Pollard A, Melville EL, Hein LK, Clements PR, Ketteridge D, Swiedler SJ, Beck M, Giugliani R, Harmatz P, Wraith JE, Guffon N, Leao Teles E, Sa Miranda MC, Hopwood JJ. Mutational analysis of 105 mucopolysaccharidosis type VI patients. Hum Mutat. 2007; 28(9):897–903. [PubMed: 17458871]

Kuczmarski R, Ogden C, Guo S, Grummer-Strawn L, Mei Z, Wei R, Curtin L, Roche A, Johnson C. 2000 CDC growth charts for the United States: Methods and development. Vital Health Stat. 2002; 11(246):1–190.

Lin HY, Chen MR, Chuang CK, Chen CP, Lin DS, Chien YH, Ke YY, Tsai FJ, Pan HP, Lin SJ, Hwu WL, Niu DM, Lee NC, Lin SP. Enzyme replacement therapy for mucopolysaccharidosis VI--experience in Taiwan. J Inherit Metab Dis. 2010; 33(Suppl 3):S421–S427. [PubMed: 20924685]

Lin S-P, Shih S-C, Chuang C-K, Lee K-S, Chen M-R, Niu D-M, Chiu PC, Lin SJ, Lin H-Y. Characterization of pulmonary function impairments in patients with mucopolysaccharidoses-changes with age and treatment. Pediatr Pulmonol. 2013

Mason J, Ramseth D, Chanter D, Moon T, Goodman D, Mendzelevski B. Electrocardiographic reference ranges derived from 79,743 ambulatory subjects. J Electrocardiol. 2007; 40(3):228–234. [PubMed: 17276451]

McGill JJ, Inwood AC, Coman DJ, Lipke ML, de Lore D, Swiedler SJ, Hopwood JJ. Enzyme replacement therapy for mucopolysaccharidosis VI from 8 weeks of age--a sibling control study. Clin Genet. 2010; 77(5):492–498. [PubMed: 19968667]

Morales-Blanhir JE, Palafox Vidal CD, Rosas Romero Mde J, Garcia Castro MM, Londono Villegas A, Zamboni M. Six-minute walk test: a valuable tool for assessing pulmonary impairment. J Bras Pneumol. 2011; 37(1):110–117. [PubMed: 21390439]

Neufeld, E.; Muenzer, J. The mucopolysaccharidoses. In: Valle, D.; Beaudet, A.; Vogelstein, B.; Kinzler, K.; Antonarakis, S.; Ballabio, A., editors. Scriver's Online Metabolic and Molecular Bases of Inherited Disease: McGraw-Hill Global Education Holdings. LLC; 2001. p. 2465-2494. [Accessed. 14 May, 2013]

Nixon PA, Joswiak ML, Fricker FJ. A six-minute walk test for assessing exercise tolerance in severely ill children. J Pediatr. 1996; 129(3):362–366. [PubMed: 8804324]

Ramey DR, Raynauld JP, Fries JF. The health assessment questionnaire 1992: status and review. Arthritis Care Res. 1992; 5(3):119–129. [PubMed: 1457486]

Schuchman EH, Ge Y, Lai A, Borisov Y, Faillace M, Eliyahu E, He X, Iatridis J, Vlassara H, Striker G, Simonaro CM. Pentosan polysulfate: a novel therapy for the mucopolysaccharidoses. PloS one. 2013; 8(1):e54459. [PubMed: 23365668]

Simonaro C, Ge Y, Eliyahu E, He X, Jepsen K, Schuchman E. Involvement of the Toll-like receptor 4 pathway and use of TNF-alpha antagonists for treatment of the mucopolysaccharidoses. Proc Natl Acad Sci U S A. 2010; 107(1):222–227. [PubMed: 20018674]

Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum. 1994; 37(12):1761–1769. [PubMed: 7986222]

Swiedler S, Beck M, Bajbouj M, Giugliani R, Schwartz I, Harmatz P, Wraith J, Roberts J, Ketteridge D, Hopwood J, Guffon N, Sá Miranda C, Teles EL, Berger K, Piscia-Nichols C. Threshold effect of urinary glycosaminoglycans and the walk test as indicators of disease progression in a survey of subjects with Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). Am J Med Genet A. 2005; 134A(2):144–150. [PubMed: 15690405]

Thümler A, Miebach E, Lampe C, Pitz S, Kamin W, Kampmann C, Link B, Mengel E. Clinical characteristics of adults with slowly progressing mucopolysaccharidosis VI: a case series. J Inherit Metab Dis. 2012; 35(6):1071–1079. [PubMed: 22441840]

Valayannopoulos V, Nicely H, Harmatz P, Turbeville S. Mucopolysaccharidosis VI. Orphanet J Rare Dis. 2010; 5:5. [PubMed: 20385007]

van Gelder CM, Vollebregt AA, Plug I, van der Ploeg AT, Reuser AJ. Treatment options for lysosomal storage disorders: developing insights. Expert Opin Pharmacother. 2012; 13(16):2281–2299. [PubMed: 23009070]

Whitley CB, Ridnour MD, Draper KA, Dutton CM, Neglia JP. Diagnostic test for mucopolysaccharidosis. I. Direct method for quantifying excessive urinary glycosaminoglycan excretion. Clin Chem. 1989; 35(3):374–379. [PubMed: 2493341]

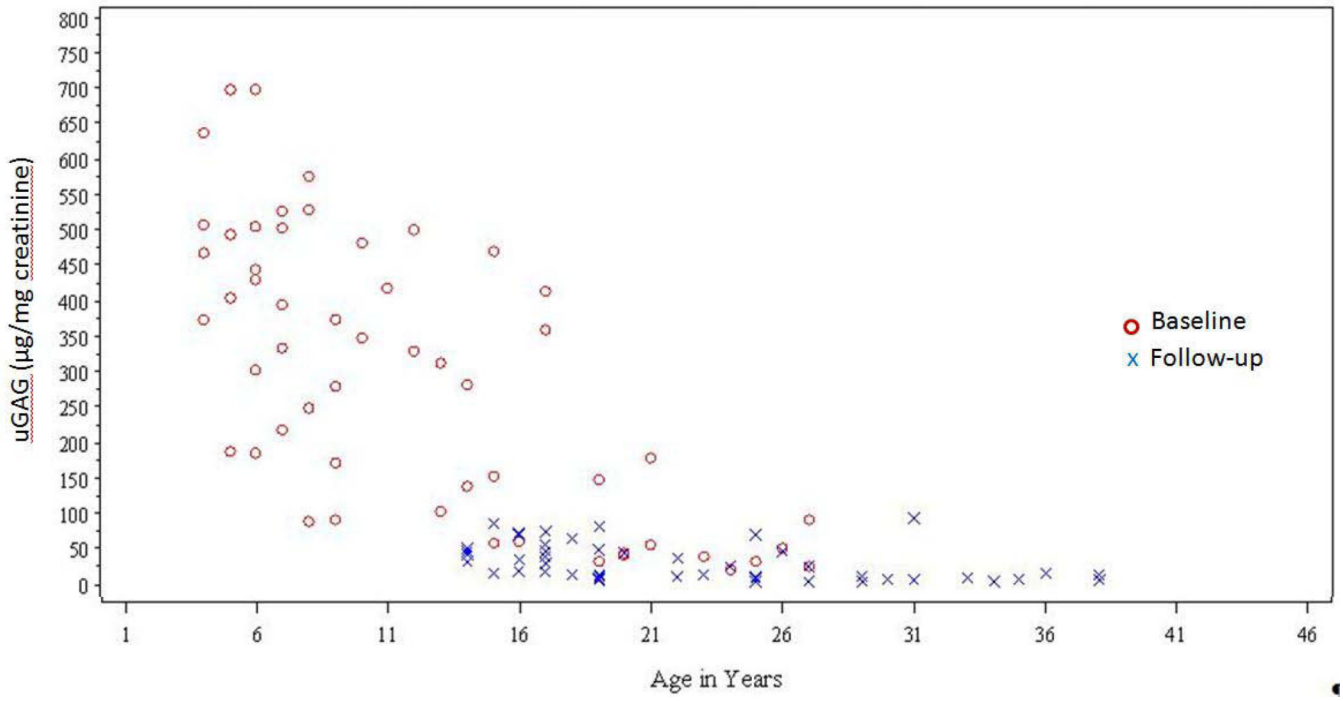


FIGURE 1.

Urinary GAG levels of patients at baseline and follow-up. Each red circle represents an individual patient at baseline and blue crosses indicate patients at resurvey. The X-axis represents the age at baseline and at resurvey.

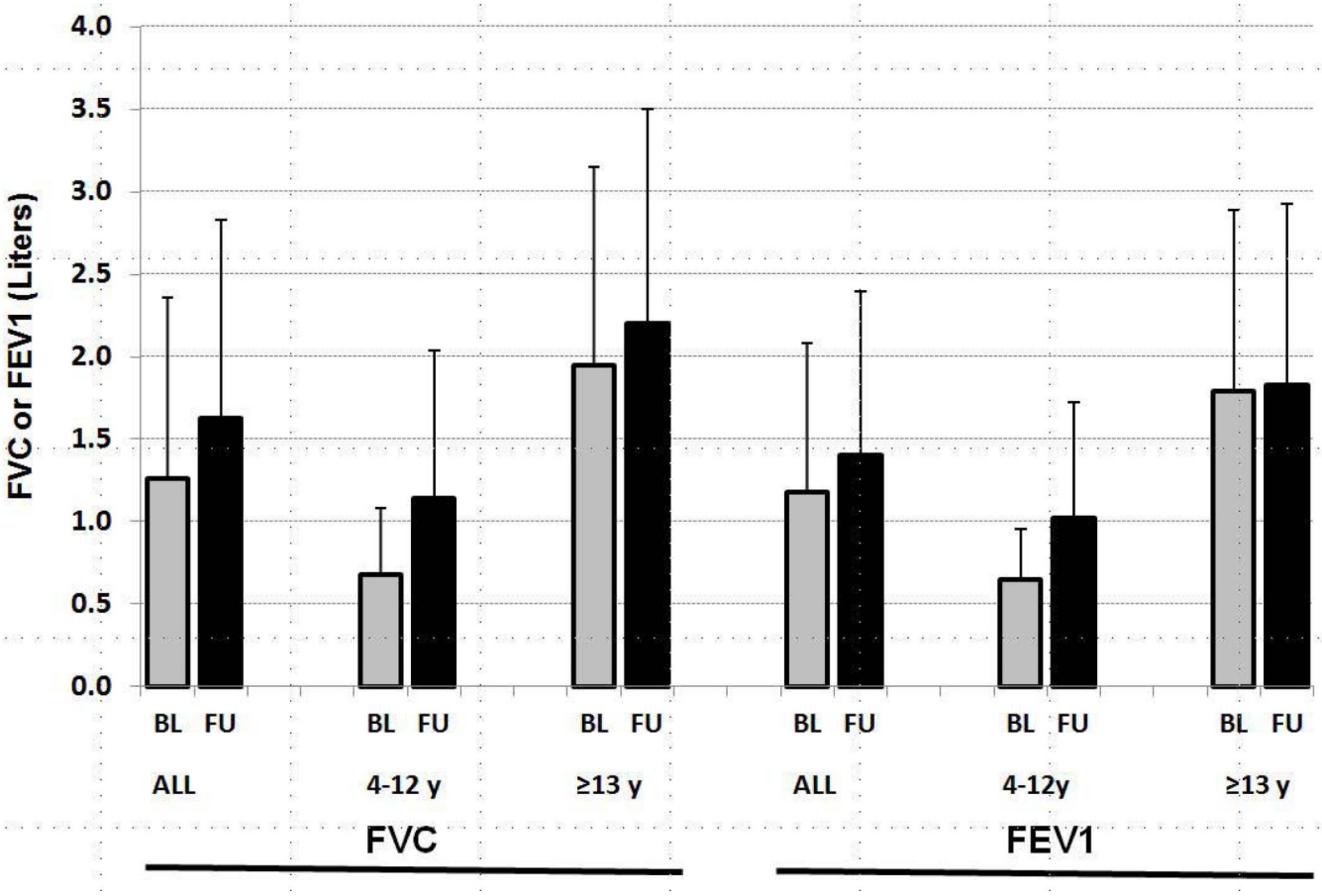
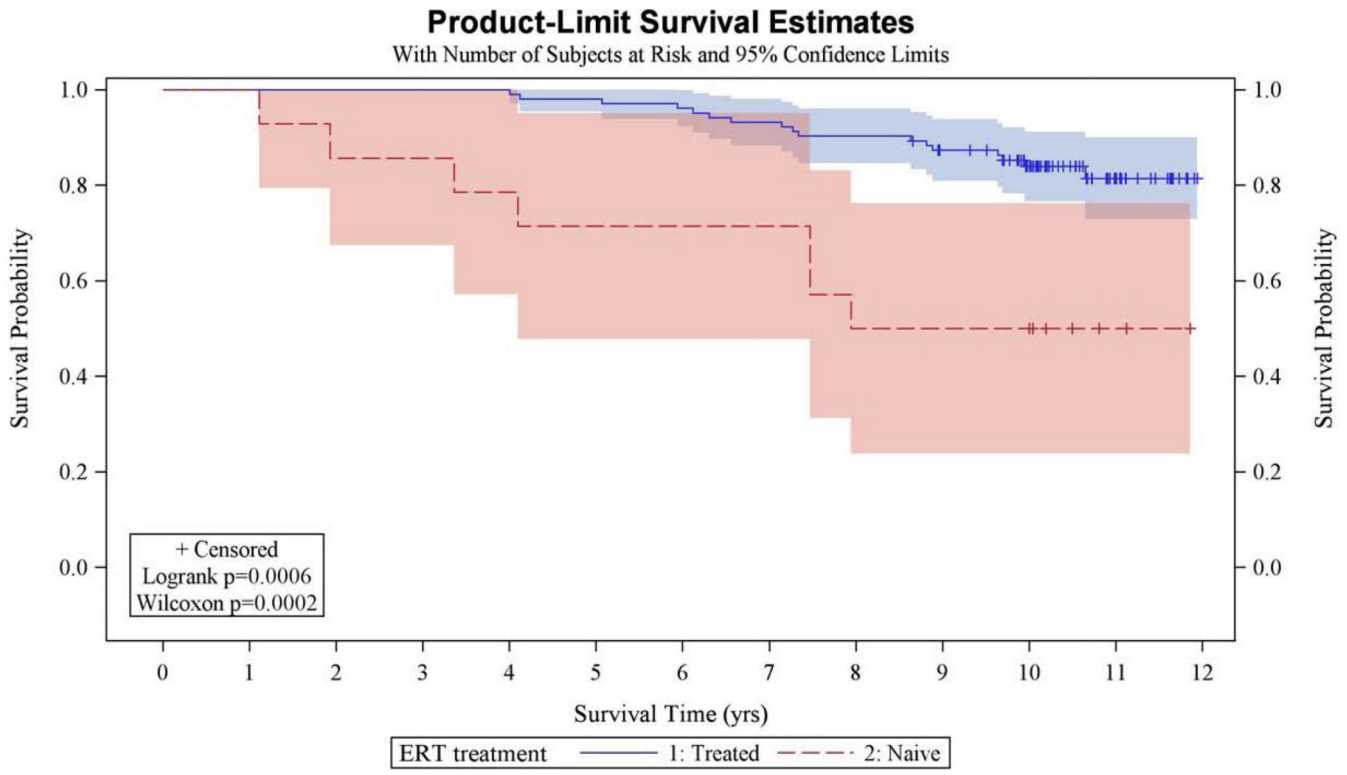


FIGURE 2.

FVC and FEV1 at baseline and follow-up. The error bars are SD. The number of patients in each group, absolute values and ranges are shown in Supplementary eTable II (in supporting information online).



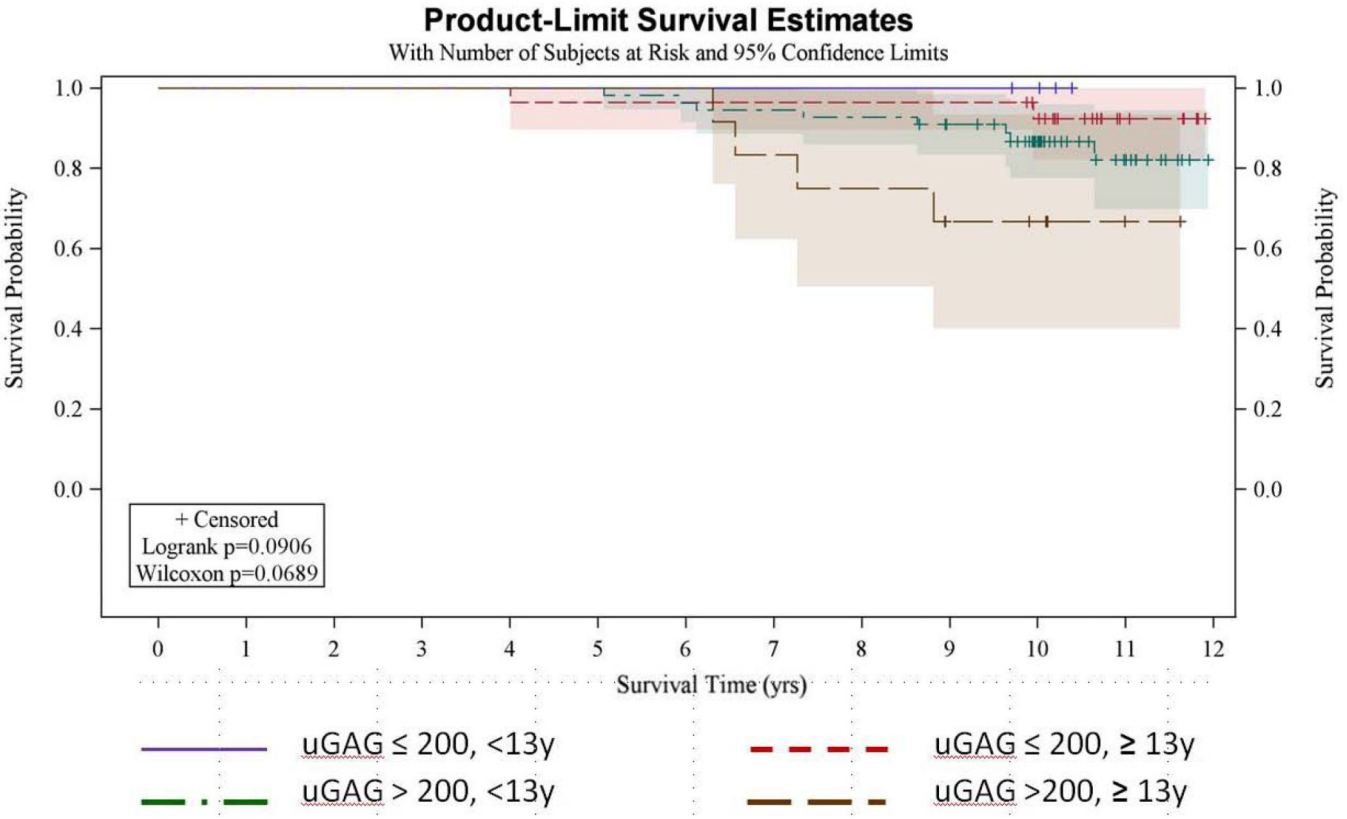


FIGURE 3.

Product-limit survival estimates of Resurvey Study patients. (A) Kaplan-Meier survival curves of ERT (n=103) (blue dashed line) and naïve (n=14) (red solid line) patient groups. The 95% confidence limits are indicated by blue (ERT) or red (naïve) shaded boxes. The calculated *P* values were: Logrank *P*=.0006, Wilcoxan *P*=.0002. (B) Kaplan-Meier survival curves of patients analyzed by baseline age and baseline uGAG levels. Survival probability curves are as follows: low baseline uGAG and <13 year-old age (blue solid line), low baseline uGAGs and ≥13 year-old (red dashed line), high baseline uGAG and <13 year-old age (green dashed line), and high baseline uGAGs and ≥13 year-old (brown dashed line). Three ERT patients with missing baseline uGAG values were excluded in this analysis. The calculated *P* values (Logrank *P*=.0906, Wilcoxan *P*=.0689) for the differences in survival were not statistically significant (at *P*=.05), as 95% CI bands were generally overlapping. These results do not indicate statistically significant differences among the four ERT subgroups.

TABLE I

Demographics and ERT Exposure

		ERT Group		Naïve Group	
		Baseline	**Follow-up**	**Baseline**	**Follow-up**
AGE					
All patients	n	55	55	4	4
	mean (SD)	12.0 (6.8)	22.0 (6.9)	30.5 (8.1)	40.5 (8.8)
	range	4.0, 27.0	14.0, 38.0	19.0, 37.0	28.0, 48.0
PATIENTS BY AGE GROUP					
4–12 y group	n	33	0	0	0
13–18 y group	n	10	22	0	0
19–24 y group	n	8	14	1	0
≥25 y group	n	4	19	3	4
SEX					
Male	n	29	29	3	3
Female	n	26	26	1	1
ERT DURATION (y)[1,2]					
all patients (n=52)	mean (SD)		6.8 (2.2)		
	range		0.5, 10.4		

[1] Excludes 2 patients with unknown ERT duration and 1 patient with an entry of 14.1 y in eCRF.

[2] ERT exposure by baseline age groups is shown in Supplement TABLE I.

TABLE II

Height by baseline age and baseline uGAG variables in the ERT group

Patient groups	n	Z-score[1]	Height (cm)		
		Baseline	Baseline	Follow-up	Change
		Mean (SD)	Mean (SD)	Mean (SD)	
ALL	51	—4.0 (2.4)	117.2 (25.1)	129.9 (21.4)	12.7 (11.8)
PATIENTS BY BASELINE AGE					
4–7 y	19	—3.9 (2.5)	97.1 (8.2)	117.5 (17.9)	20.4 (12.4)
8–12 y	13	—4.9 (2.3)	107.4 (11.7)	124.2 (16.4)	16.8 (6.3)
13–18 y	7	—4.4 (3.0)	134.4 (21.3)	139.1 (21.4)	4.6 (4.9)
19–24 y	8	—3.0 (1.8)	148.4 (16.0)	149.2 (15.8)	0.8 (1.2)
≥25 y	4	—2.5 (1.4)	152.4 (9.9)	153.1 (10.2)	0.7 (0.6)
PATIENTS BY BASELINE uGAGs[2]					
<100	14	—2.2 (1.0)	149.5 (13.2)	153.7 (9.0)	4.2 (8.2)
100–200	8	—3.0 (2.5)	127.7 (16.1)	143.0 (16.7)	15.3 (18.3)
>200	29	—5.1 (2.2)	98.8 (8.4)	114.8 (11.9)	16.0 (9.1)
PATIENTS BY BASELINE AGE (AND WITH BASELINE uGAGs ≤200 ug/mg creatinine)					
4–7 y	2	—0.1 (0.4)	114.6 (4.2)	157.6 (11.5)	43.1 (7.3)
8–12 y	3	—2.0 (1.5)	121.2 (8.6)	142.4 (10.8)	21.2 (4.1)
13–18 y	5	—2.9 (1.8)	145.0 (13.0)	149.5 (14.5)	4.5 (4.2)
19–24 y	8	—3.0 (1.8)	148.4 (16.0)	149.2 (15.8)	0.8 (1.2)
≥25 y	4	—2.5 (1.4)	152.4 (9.9)	153.1 (10.2)	0.7 (0.6)
PATIENTS BY BASELINE AGE (AND WITH BASELINE uGAGs >200 ug/mg creatinine)					
4–7 y	17	—4.3 (2.2)	95.0 (5.60	112.7 (11.2)	17.7 (9.9)
8–12 y	10	—5.7(1.8)	103.3 (9.2)	118.7 (13.7)	15.5 (6.3)
13–18 y	2	—8.2 (1.1)	108.0 (9.9)	113.0 (1.4)	5.0 (8.5)

[1] Z-scores are based on CDC curves for normal population.

[2] uGAGs expressed as µg/mg creatinine.

TABLE III

Change in Distance Walked (meters) from Baseline in 6MWT

Patient groups	n	Baseline		Change from baseline	
		Mean (SD)	Range	Mean (SD)	Range
CHANGE IN WALK DISTANCE BY BASELINE AGE IN ERT PATIENTS					
6MWT — all patients' results					
All	54	304.0 (108.4)	41.0 to 502.6	16.4 (155.9)	—374.8 to 362.0
4–12 y	33	278.9 (102.0)	41.0 to 483.4	21.2 (162.3)	—374.8 to 362.0
≥13 y	21	343.4 (108.7)	112.0 to 502.6	8.9 (147.9)	—341.5 to 189.0
≥18 y	12	363.2 (90.4)	231.2 to 502.6	50.8 (126.1)	—271.8 to 189.0
Patients who completed 6MWT at follow-up[a]					
All	46	310.4 (111.8)	71.5, 502.6	65.7 (100.6)[b]	—125.0, 362.0
4–12 y	28	282.6 (103.7)	71.5, 483.4	71.0 (108.5)	—125.0, 362.0
≥13 y	18	353.7 (113.0)	112.0, 502.6	57.4 (89.2)	—109.8, 189.0
≥18 y	11	371.5 (89.9)	231.2, 502.6	80.2 (78.4)	—48.1, 189.0
CHANGE IN WALK DISTANCE BY BASELINE uGAG LEVELS IN ERT PATIENTS					
<100 μg/mg	14	390.7 (70.6)	231.2, 502.6	74.0 (77.2)[C]	—48.1, 189.0
100–200 μg/mg	8	378.2 (95.2)	233.0, 483.4	40.3 (139.0)	—271.8, 164.0
>200 μg/mg	32	247.5 (88.6)	41.0, 420.0	—14.8 (179.0)	—374.8, 362.0
CHANGE IN WALK DISTANCE BY BASELINE uGAG LEVELS IN NAIVE PATIENTS					
<100 μg/mg	3	365.8 (187.2)	154.2, 510.0	11.2 (155.0)	—154.2, 153.0

[a] Excludes 8 patients who did not attempt the 6MWT. Of these, 7 were confirmed wheelchair-bound and 1 patient had an entry "the patient cannot walk" in the eCRF.

[b] $P<.0001$

[c] $P=.0033$

TABLE IV

Echocardiograms of ERT Patients

ECHO Findings	Number of patients[1]	
	Baseline	Follow-up
Stenosis or regurgitation	29/31	31/33
Stenosis and regurgitation	10/31	9/33
Regurgitation		
Aortic	16/31	25/31
Mitral	20/31	22/31
Pulmonary	5/31	2/31
Stenosis		
Mitral valve	9/31	12/31
Aortic value	5/31	4/31
Pulmonary value	0/31	0/31
Tricuspid valve	0/31	0/31

[1] ECHO data was available for 31 patients at baseline and 33 patients at Resurvey. All valve comparisons were performed pairwise (n=31)

TABLE V

Survival of ERT and Naïve Patients

Parameters[1]		Treatment Groups	
		ERT	Naïve
ALL patients with survival data			
	n	103	14
	Baseline age (y)	13.7 (9.8)	19.8 (12.8)
Deceased patients[2]			
	Mortality[3]	17/103 (16.5%)	7/14 (50%)
	Baseline age (y)	15.4 (12.4)	14.4 (13.5)
	Age at death (y)	22.9 (11.4)	19.2 (15.0)
Patients by baseline uGAG levels			
≤200 μg/mg	n	33	7
	Baseline age (y)	21.2 (11.4)	30.4 (9.3)
	Mortality	2/33 (6.1%)	1/7 (14.3%)
>200 μg/mg	n	67	7
	Baseline age (y)	9.4 (4.2) y	9.3 (3.4) y
	Mortality	12/67 (17.9%)	6/7 (85.7%)
missing uGAG value	n	3	
	Baseline age (y)	26.7 (19.5) y	
	Mortality	3/3 (100%)	

[1] Baseline age or age at death are indicated as mean (SD) in years. Mortality is shown as n of total (%).

[2] Baseline age or age at death of deceased patients refer to 17 ERT and 7 naïve deceased patients.

[3] Logrank P=.0006