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Long-term Efficacy and Safety of Laronidase in the Treatment of Mucopolysaccharidosis I

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What's Known on This Subject

MPS I is a life-threatening lysosomal storage disease caused by deficiency of α -L-iduronidase. A 52-week phase 1/2 trial (10 patients) and a 26-week phase 3 randomized, placebo-controlled trial (45 patients) of enzyme-replacement therapy with laronidase demonstrated safety and clinical benefit.

What This Study Adds

This 4-year phase 3 extension trial of laronidase is the first trial evaluating long-term safety and efficacy of enzyme replacement for MPS I. The data provided will help guide patient and physician expectations regarding the magnitude and chronology of treatment effects.

ABSTRACT

OBJECTIVE. Our goal was to evaluate the long-term safety and efficacy of recombinant human α -L-iduronidase (laronidase) in patients with mucopolysaccharidosis I.

PATIENTS AND METHODS. All 45 patients who completed a 26-week, double-blind, placebo-controlled trial of laronidase were enrolled in a 3.5-year open-label extension study. Mean patient age at baseline was 16 (range: 6–43) years. All patients had attenuated disease (84% Hurler-Scheie, 16% Scheie phenotypes). Clinical, biochemical, and health outcomes measures were evaluated through the extension phase. Changes are presented as the mean $\pm$ SEM.

RESULTS. All 40 patients (89%) who completed the trial received at least 80% of scheduled infusions. As shown in earlier trials, urinary glycosaminoglycan levels decreased within the first 12 weeks and liver volume decreased within the first year. Percent predicted forced vital capacity remained stable, with a linear slope of -0.78 percentage points per year. The 6-minute walk distance increased 31.7 ± 10.2 m in the first 2 years, with a final gain of 17.1 ± 16.8 m. Improvements in the apnea/hypopnea index (decrease of 7.6 ± 4.5 events per hour among the patients with significant baseline sleep apnea) and shoulder flexion (increase of $17.4^\circ \pm 3.6^\circ$) were most rapid during the first 2 years. Improvements in the Child Health Assessment Questionnaire/Health Assessment Questionnaire disability index (decrease of 0.31 ± 0.11 , signifying a clinically meaningful improvement in activities of daily living) were gradual and sustained over the treatment period. Laronidase infusions were generally well tolerated except in 1 patient who experienced an anaphylactic reaction. Infusion-associated reactions, which occurred in 53% of the patients, were mostly mild, easily managed, and decreased markedly after 6 months. One patient died as a result of an upper respiratory infection unrelated to treatment. Antibodies to laronidase developed in 93% of the patients; 29% of the patients were seronegative at their last assessment.

CONCLUSIONS. This trial demonstrates the long-term clinical benefit and safety of laronidase in attenuated patients with mucopolysaccharidosis I and highlights the magnitude and chronology of treatment effects. Prompt diagnosis and early treatment will maximize treatment outcomes. *Pediatrics* 2009;123:229–240

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00146770).

Key Words

clinical trial, enzyme replacement therapy, mucopolysaccharidosis I, laronidase

Abbreviations

MPS I—mucopolysaccharidosis I
FVC—forced vital capacity
6MWT—6-minute walk test
IAR—infusion-associated reaction
Ig—immunoglobulin
ELISA—enzyme-linked immunosorbent assay
AHI—apnea/hypopnea index
CHAQ/HAQ—Child Health Assessment Questionnaire/Health Assessment Questionnaire
LVH—left ventricular hypertrophy

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MUCOPOLYSACCHARIDOSIS TYPE I (MPS I) (Hurler, Online Mendelian Inheritance in Man [OMIM] 607014; Hurler-Scheie, OMIM 607015; Scheie, OMIM 607016) is a lysosomal storage disorder caused by deficiency of the enzyme α -L-iduronidase. Deficiency of this enzyme impairs the ability of cells to degrade the glycosaminoglycans heparan and dermatan sulfate and leads to a chronic and progressive multisystem disease. Inheritance is autosomal recessive, with a disease incidence of ~1 in 100 000 newborns.^{1,2}

The clinical features and course of MPS I are highly variable and consist of progressive multisystem involvement affecting respiratory, cardiac, skeletal, ophthalmologic, and in some cases central nervous system function. Disease heterogeneity is thought to be related primarily to the large number of different mutations in the *IDUA* gene encoding α -L-iduronidase.³ Historically, patients have been categorized into 3 phenotypes with no objective means of delineation: Hurler (early onset, rapidly progressive, neurodegenerative), Scheie (later onset, less rapid progression, no neurodegeneration), and Hurler-Scheie (onset and progression between Hurler and Scheie extremes, with mild or absent central nervous system involvement).⁴ More recently, the terms “severe MPS I” and “attenuated MPS I” are being used to denote Hurler patients and the combined group of Hurler-Scheie and Scheie patients, respectively.

Several clinical trials have demonstrated that enzyme replacement therapy with laronidase (human recombinant α -L-iduronidase, Aldurazyme [Biomarin Pharmaceutical, Inc, Novato, CA, and Genzyme Corp, Cambridge, MA]) is safe and effective in patients with MPS I across a wide range of ages (young children to adults) and disease severity (severe and attenuated).^{5–8} In particular, a double-blind, randomized, international, placebo-controlled phase 3 trial demonstrated that compared with placebo, 6 months of treatment with laronidase decreased glycosaminoglycan storage and led to clinically meaningful improvements in pulmonary function (percent predicted forced vital capacity [FVC]) and exercise capacity (6-minute walk test [6MWT]). In addition, laronidase improved sleep apnea and shoulder flexion in patients with severe symptoms.⁸ In this phase 3 extension trial (ClinicalTrials.gov identifier: NCT00146770), we provide additional data on the magnitude and chronology of clinical response to laronidase over 4 years of treatment.

METHODS

Trial Design

This 3.5-year extension trial (May 2001–March 2005) was open to patients who successfully completed the 26-week randomized, placebo-controlled trial of laronidase for MPS I. Inclusion criteria for the randomized, controlled trial are detailed in Wraith et al⁸ and included age ≥ 5 years, leukocyte α -L-iduronidase activity $\leq 10\%$ of normal, FVC $\leq 80\%$ of normal, and ability to walk at least 5 m in 6 minutes. All patients provided written informed consent. Eligible patients rolled over from the placebo-controlled trial without interruption of infu-

TABLE 1 Schedule of Assessments From Entry to Week 182 of the Extension Trial

Evaluation	Baseline	Trial Week Assessment Intervals	Week 182
Urinary glycosaminoglycan	✓	Every 12 wk until week 168	✓
Liver volume	✓	Weeks 24, 72, 120	✓
6MWT	✓	Every 12 wk until week 120, week 144	✓
FVC	✓	Every 12 wk until week 120, week 144	✓
Knee and shoulder range of motion ^a	✓	Every 12 wk until week 120, week 144	✓
CHAQ/HAQ	✓	Every 12 wk until week 72, week 120, week 144	✓
Visual acuity	✓	Weeks 24, 72, 120	✓
Sleep study	✓	Weeks 24, 72, 120	✓
IgG	✓	Every 4 wks until week 24, then every 12 wk until week 168	✓
Physical exam	✓	Week 4, 12, then every 12 wk until week 120, then week 144	✓
Standard laboratory safety evaluations	✓	Week 4, 12, then every 12 wk until week 120, then week 144	✓

^a Includes flexion and extension.

sions. Where appropriate, patients were transitioned from the initial study center to local study sites to receive weekly infusions. All patients returned to their primary study center for scheduled assessments.

Laronidase Treatment

Patients received weekly infusions of laronidase at a dose of 100 U/kg body weight (0.58 mg/kg) diluted in 100 to 250 mL of normal saline containing 0.1% human serum albumin over 4 hours. For the last 2.5 years of the extension study, 19 European patients received laronidase without human serum albumin in accordance with the European product label. All patients were pretreated orally with an antipyretic and an antihistamine 1 hour before each infusion.

Assessments

All assessments were performed as previously described⁷ at baseline of the double-blind trial, entry to the extension trial, and at varying intervals until the final visit at week 182 of the extension trial (Table 1).

Safety assessments included adverse event reporting, physical examinations, vital signs, electrocardiograms, echocardiograms, clinical laboratory evaluations, and immunologic assessments. An infusion-associated reaction (IAR) was defined as any laronidase-related adverse event occurring on the day of infusion. Immunoglobulin G (IgG) levels to laronidase were measured by using a modified enzyme-linked immunosorbent assay (ELISA)⁵ and confirmed by radioimmunoprecipitation. The presence of anti-laronidase IgE was detected by radioimmunoprecipitation, and complement activation and serum tryptase were assessed by standard techniques.

Analyses

For all analyses, baseline refers to the value obtained just before the first infusion with laronidase. For the patients who received laronidase in both trials, baseline was the start of the placebo-controlled trial; for the patients who received placebo in the double-blind trial and then crossed over to laronidase in the extension trial, baseline was the start of the extension trial. Only observed data were summarized; efficacy data were not carried forward for missed assessments.

All statistical analyses were performed by using SAS 8.0 software (SAS Institute, Inc, Cary, NC), and the results are presented as the mean $\pm$ SE of the SEM unless otherwise specified. The absolute changes in percent predicted FVC and the 6MWT were estimated by using linear mixed modeling techniques.^{9,10} Percent predicted FVC was used for this analysis to account for age-related changes in lung function and growth. Correlations were evaluated by using Pearson's correlation coefficient, and statistical significance was defined as $P < .05$.

For longitudinal analyses of efficacy, time points were matched up by treatment baseline. The time between assessments varied depending on whether patients began laronidase treatment at the beginning of the placebo-controlled trial or at the beginning of the extension study. Time points therefore represent the average time on treatment among all patients; however, most averaged values were no more than 12 weeks apart. The mean response for all patients was determined at each time point up to 3.5 or 4 years of treatment, depending on the patient's randomization in the placebo-controlled trial. For the longitudinal analyses involving mixed linear modeling, follow-up time points were estimated only up to 3.5 years of treatment, because this was the longest period of time the full cohort was on treatment. Mean changes in clinical and laboratory parameters were calculated from baseline to the final week 182 assessment for all patients who completed the trial (after 3.5 years of treatment for the placebo-laronidase patients and 4 years of treatment for the laronidase-laronidase patients).

Age-related normal values for urinary glycosaminoglycan excretion and liver volume are from Kakkis et al.⁵ Liver volume was expressed as a percent of body weight (cc/g) to account for increases related to growth. For the 6MWT, an abnormal baseline value was defined as <310 m (lower limit of normal for adult women, whose stature would more closely reflect the reduced stature of most patients with MPS I).¹¹ For the apnea/hypopnea index (AHI; number of episodes of apnea or hypopnea per hour), all values >60 were censored at 60 because of the inability to calculate AHI accurately above this value. Significant sleep apnea at baseline was defined as an AHI of ≥ 10 events per hour in patients <15 years of age and ≥ 15 events per hour in patients ≥ 15 years of age. For shoulder range of motion, a baseline value of $<180^\circ$ was considered abnormal.¹² For the Child Health Assessment Questionnaire/Health Assessment Questionnaire (CHAQ/HAQ) disability index, a value >0 was considered abnormal. For visual acuity, the left and right eye corrected

TABLE 2 Baseline Characteristics of Patients

Baseline Characteristic	N = 45
Male/female ratio	22:23
Age distribution at baseline, n (%)	
≤ 12 y	22 (49)
13 to ≤ 18 y	11 (24)
19 to ≤ 65 y	12 (27)
Baseline age, mean $\pm$ SD (range), y	15.7 $\pm$ 8.03 (6.3–43.3)
Height, mean $\pm$ SD (range), cm	136.3 $\pm$ 14.1 (97.2–163.8)
Weight, mean $\pm$ SD (range), kg	39.1 $\pm$ 13.7 (17.8–81.2)
Classification, n (%)	
Hurler-Scheie ^a	38 (84)
Scheie	7 (16)
Years since symptom onset, mean $\pm$ SD (range)	13.0 $\pm$ 8.0 (3.6–39.7)
Years since diagnosis, mean $\pm$ SD (range)	9.3 $\pm$ 6.3 (0.2–24.1)

^a Including 1 patient initially classified as Hurler and reclassified as Hurler-Scheie by the investigator on the basis of age and clinical characteristics.

results were log-transformed (base 10), averaged, and the average was transformed back to original units. If the corrected results were missing at baseline or at the final assessment, the uncorrected results (for both time points) were used for analysis. A baseline value worse than 20/20 was considered abnormal.

At the final study assessment, the proportion of patients whose clinical status improved, remained stable, or declined over the course of the 3.5 to 4 years on treatment was determined by using the following thresholds: percent predicted FVC, $\geq 15\%$ relative change¹³; 6MWT, ≥ 54 m¹⁴; shoulder flexion, $\geq 20^\circ$; AHI, ≥ 10 events per hour for baseline values ≤ 40 and $\geq 25\%$ change for baseline values >40 ; visual acuity, ≥ 2 -line change^{15,16}; and CHAQ/HAQ disability index, ≥ 0.24 .¹⁷

The percentage of patients experiencing IARs and the percentage of infusions associated with at least 1 IAR were summarized in sequential 3-month time intervals from baseline.

RESULTS

Patients

All 45 patients who participated in the 26-week, placebo-controlled trial entered this open-label extension trial; 22 patients had initially received laronidase and 23 had initially received placebo. Tables 2 and 3 show the baseline characteristics of the trial population. Based on age and clinical condition, all patients were considered to have attenuated MPS I (either Hurler-Scheie or Scheie phenotype). Eighty-two percent of patients were Caucasian, and 71% of patients were 18 years of age or younger. On average, patients had experienced symptoms for over a decade and had considerable disease burden.

Forty (89%) of the 45 subjects completed the trial. All patients who completed the trial received at least 80% of their scheduled infusions. Two patients withdrew voluntarily: 1 after 17 infusions because of needle phobia, and 1 after 134 infusions because of scheduling difficulties during the school year. One patient withdrew after

TABLE 3 Changes in Clinical Domains from Baseline to Final Assessment

Clinical Domain	Baseline ^a		Final (After 3.5 or 4 y of Treatment) ^a				
	Proportion of Patients With Abnormal Value, % (n)	Mean Value $\pm$ SD	Mean Value $\pm$ SD (n)	Mean Change $\pm$ SEM (n)	Responses to Treatment in Individuals		
Substrate storage							
Urinary glycosaminoglycan, μ g/mg creatinine ^b	100 (45)	220.9 $\pm$ 90.3	54.3 $\pm$ 31.1 (39)	72% $\pm$ 3% Improvement (39)	•100% of patients improved •15% attained normal values •72% were within twice the upper limit of normal		
Liver volume, cc/g	68 (44)	3.54 $\pm$ 1.02	2.04 $\pm$ 0.36 (38)	38% $\pm$ 2% Improvement (38)	•95% had normal values •92% of patients with abnormal values attained normal values •No patient's value increased		
					Improved, % ^c	Stable, % ^c	Declined, % ^c
Clinical end points ^a							
Percent predicted normal FVC	100 (45)	49.9 $\pm$ 13.9	48.3 $\pm$ 13.7 (40)	0.78 $\pm$ 0.32 Percentage point decline per year (45) ^d	18	55	28
Distance walked in the 6MWT, m	33 (45)	334.0 $\pm$ 129.5	373.3 $\pm$ 133.0 (40)	17.1 $\pm$ 16.8 Improvement (45) ^d	50	28	23
AHI, events per h	51 (39)	17.5 $\pm$ 15.5	12.1 $\pm$ 16.6 (34)	4.4 $\pm$ 2.3 Improvement (32)	31	63	6
Shoulder range of motion, °	100 (42)	90.1 $\pm$ 31.7	108.1 $\pm$ 20.8 (40)	17.4 $\pm$ 3.6 Improvement (37)	46	49	5
Corrected visual acuity ^e	93 (43)	1.66 $\pm$ 0.34	1.60 $\pm$ 0.34 (39)	0.03 $\pm$ 0.03 Improvement (39)	24	66	10
CHAQ/HAQ disability index	100 (44)	1.91 $\pm$ 0.61	1.53 $\pm$ 0.77 (35)	0.31 $\pm$ 0.11 Improvement (35)	57	20	23

n, indicates the total number of patients with available data.

^a Baseline and/or final assessment values were not available for all patients in all clinical domains.

^b Normal range in μ g/mg creatinine: 24.6 to 71.0 for patients aged 5 to 12 years, 7.0 to 38.5 for patients aged 13 to 18 years, and 4.2 to 16.9 for adults.

^c Clinically meaningful change as defined in Methods; note that percentages may not add up to 100 due to rounding.

^d Forty-five patients contribute data to the regression model that estimates this result.

^e Snellen visual acuity values were log-transformed; 1.66 corresponds to 20/46; 1.60 corresponds to 20/40.

80 infusions because of pregnancy; this patient subsequently delivered a healthy child and resumed treatment with commercially available drug after a 2-year hiatus.¹⁸ One patient with upper airway obstructive disease died as a result of causes unrelated to treatment (upper respiratory infection) after 16 infusions, and 1 patient who received 44 infusions withdrew after experiencing an anaphylactic reaction (see "Safety").

Measures of Clinical Efficacy (Table 3)

Urinary Glycosaminoglycan Excretion

All patients had elevated urinary glycosaminoglycan levels at baseline; values ranged between 2- and 16-fold higher than the upper limit of normal for the appropriate age range. Levels declined rapidly (60%–70% reduction in most patients) during the first 12 weeks of treatment and then plateaued or continued to decline more slowly (Fig 1, A). At the final assessment, 15% (6 of 39) of patients had attained normal values for age, and 72% (28 of 39) had values that were within twice the upper limit of normal (Table 3).

Hepatomegaly

During the first year of treatment, liver volume decreased from a mean of 3.54% of body weight to 2.32% of body weight and then slowly thereafter (Fig 1B). Liver volume normalized in 92% of patients (24 of 26) who

had hepatomegaly at baseline and available data from the final assessment.

Respiratory Function

Baseline spirometry revealed severe reduction in vital capacity without evidence of obstruction, consistent with severe restrictive lung disease (Table 3).¹³ Fig 2A shows the distribution of percent predicted FVC by patient age at baseline. There was a downward trend with age for patients <25 years old (mostly Hurler-Scheie patients) ($r = -0.41$, $P = .008$), corresponding to more advanced disease progression. The 4 patients who were >25 years of age had somewhat higher values, and all were classified with Scheie syndrome, reflecting less disease burden. When expressed as an absolute change in the percentage predicted FVC from baseline, pulmonary function seemed to be stable over the course of treatment with a slight decline of 0.78 ± 0.32 percentage points per year (Fig 2B). The absolute value of FVC increased steadily (Fig 2C), with a mean increase of 0.09 ± 0.02 L after 1 year of treatment and 0.25 ± 0.05 L at the final assessment. In 73% (29 of 40) of patients, FVC improved or remained stable over the course of the trial (Table 3).

With regard to AHI, 94% (30 of 32) of patients with complete data showed improvement or remained stable. In the 20 patients with significant sleep apnea at base-

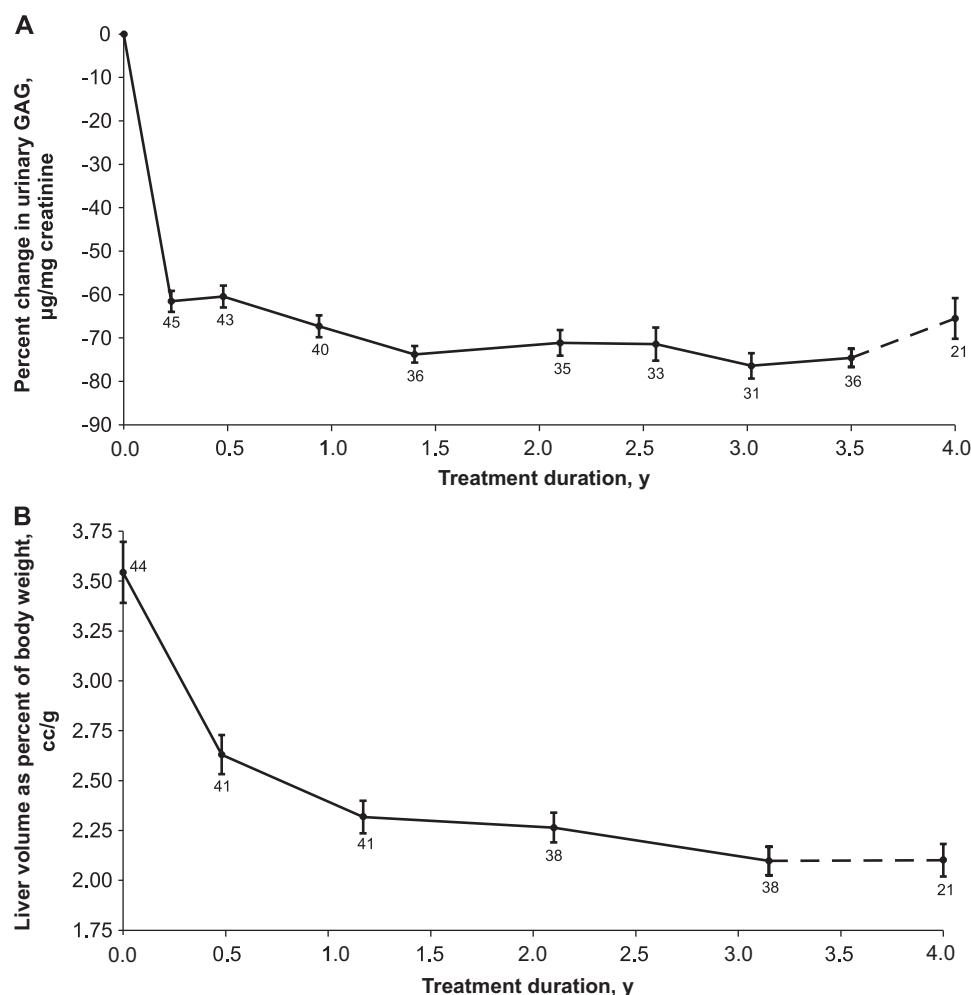


FIGURE 1

Urinary glycosaminoglycan levels and liver volume versus laronidase treatment duration. Solid line, all patients; dotted line, patients from the laronidase arm of the placebo-controlled trial, who received an additional 6 months of treatment. Bars represent $\pm$ SEM, and numbers denote the number of patients at each assessment interval. A, Mean percent change in urinary glycosaminoglycan levels ($\mu\text{g}/\text{mg}$ creatinine). B, Mean liver volume (cc/g) as a percentage of body weight.

line, the most improvement was noted during the first 6 months of laronidase treatment (mean decrease of 7.1 ± 1.7 events per hour; $n = 19$), with a final mean decrease of 7.6 ± 4.5 events per hour at the final assessment ($n = 16$). Final assessment data were available in 16 of the 20 patients with abnormal baseline AHI; of these, 10 improved, 2 declined, and 4 remained stable.

Mobility

Baseline 6MWT distance approximated the lower limit of normal for adult women (310 m), reflecting underlying disease and short stature (Tables 2 and 3).¹¹ Linear mixed modeling of patient data estimated an increase of 23.1 ± 5.7 m after 1 year of treatment and 31.7 ± 10.2 m after 2 years of treatment (Fig 3A). After 3.5 years of treatment, the change in distance walked from baseline decreased and became more variable for an estimated increase of 17.1 ± 16.8 m. Among patients whose walk distance declined during the study, several had health complications that would be expected to affect performance such as neurosurgery for Chiari mal-

formation, surgery for heel cord lengthening, degenerative hip disease, and a 33-kg weight increase. Overall, 78% (31 of 40) of patients showed either improvement or stabilization in the 6MWT at the final assessment (Fig 3B).

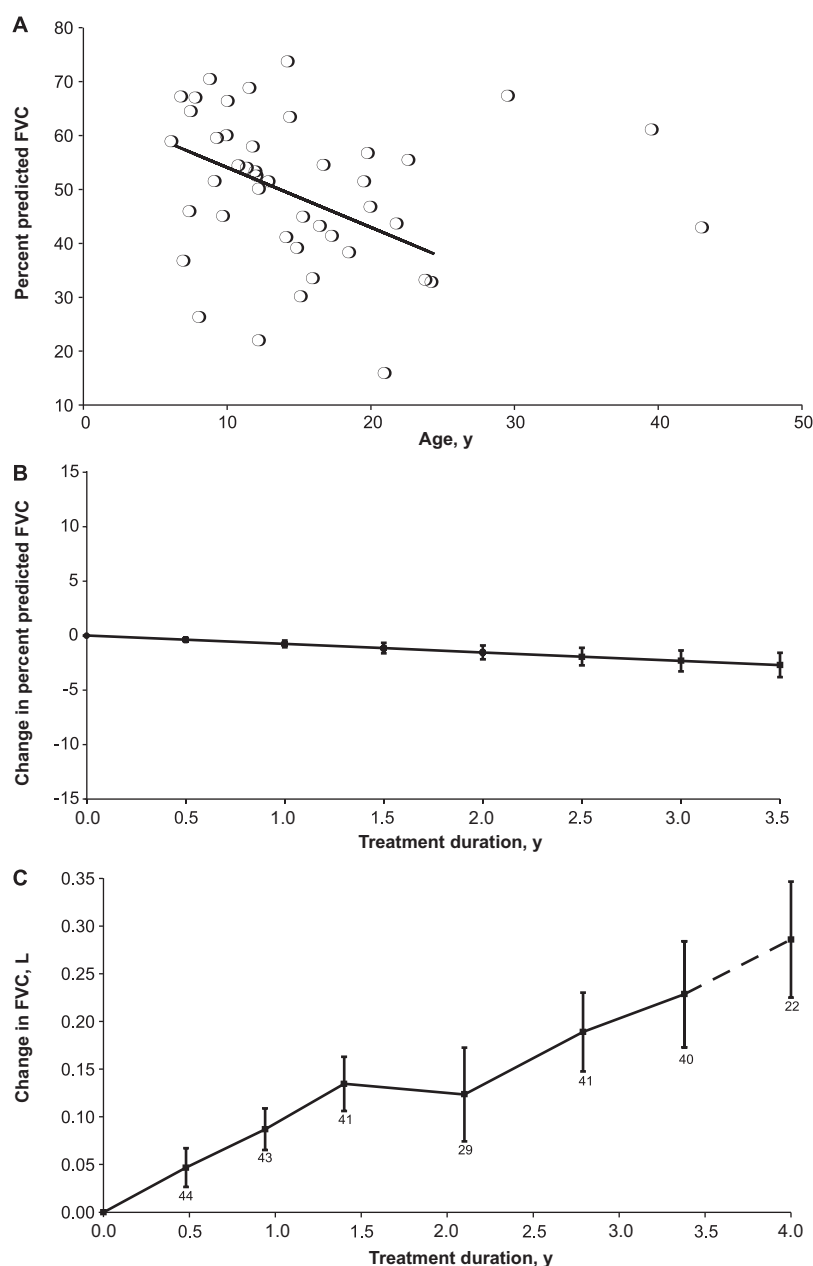
All measures of joint range of motion (shoulder and knee flexion and extension) showed gradual improvement with treatment. The most important functional measure (shoulder flexion) improved significantly in most patients (Table 3; Fig 4). Patients who had the most severe baseline impairment had the most pronounced increases in shoulder flexion (Fig 4C; $r = -0.77$; $P < .001$). At the end of the trial, 17 patients had an increase of $\geq 20^\circ$, 18 remained stable ($<20^\circ$ change), and 2 patients had a decrease of $\leq 20^\circ$. Thus, overall, shoulder flexion improved or remained stable in 95% (35 of 37) of patients (Fig 4B).

Activities of Daily Living

Patients had moderate to severe physical disability and limitations in activities of daily living, as reflected by the mean baseline CHAQ/HAQ disability index score of 1.91

FIGURE 2

FVC. A, Percent predicted FVC versus patient age at baseline. Regression line was fit to data from patients <25 years old ($r = -0.41$; $P = .008$). B, Absolute change in percent predicted FVC versus laronidase treatment duration. Regression line was estimated by using linear mixed modeling techniques^{9,10} (see "Methods"). C, Mean absolute change in FVC. Solid line, all patients; dotted line, patients from the laronidase arm of the placebo-controlled trial, who received an additional 6 months of treatment. Bars represent $\pm$ SEM, and numbers denote the number at each assessment interval.



(Table 3; 0 indicates no disability; 3 maximum disability). The disability index decreased gradually by a mean of 0.31, reflecting a clinically meaningful improvement (Fig 5). By trial end, the disability index remained stable or improved in 77% (27 of 35) of the patients with final assessment data. Improvement in pain, as reflected by a mean decrease of 0.34 ± 0.14 in the Pain Index (baseline mean value: 0.93 ± 0.84 ; final mean value: 0.56 ± 0.52), was seen among the 30 patients with available data.

Additional Assessments

At baseline, corrected visual acuity was worse than 20/20 for the majority of patients (Table 3), and 26% (11 of 43) had visual acuity worse than 20/60. With treatment, 24% (9 of 37) patients with final assessment data

experienced a clinically significant improvement in visual acuity (Table 3); this included 4 of the 11 patients whose corrected visual acuity was worse than 20/60 at baseline. Corneal clouding did not change appreciably over the course of the trial.

At baseline, nearly all patients had normal cardiac function. Echocardiography revealed valvular heart disease in most patients consisting of thickened aortic valves and/or myxomatous mitral valves, often with stenosis and regurgitation, and mild left ventricular hypertrophy (LVH) in 10 patients. Electrocardiography revealed normal sinus rhythm in nearly all patients. Over the course of the trial, the incidence of aortic stenosis remained unchanged, whereas the incidence of mitral valve stenosis decreased. Valvular regurgitation progressed slightly. At the final as-

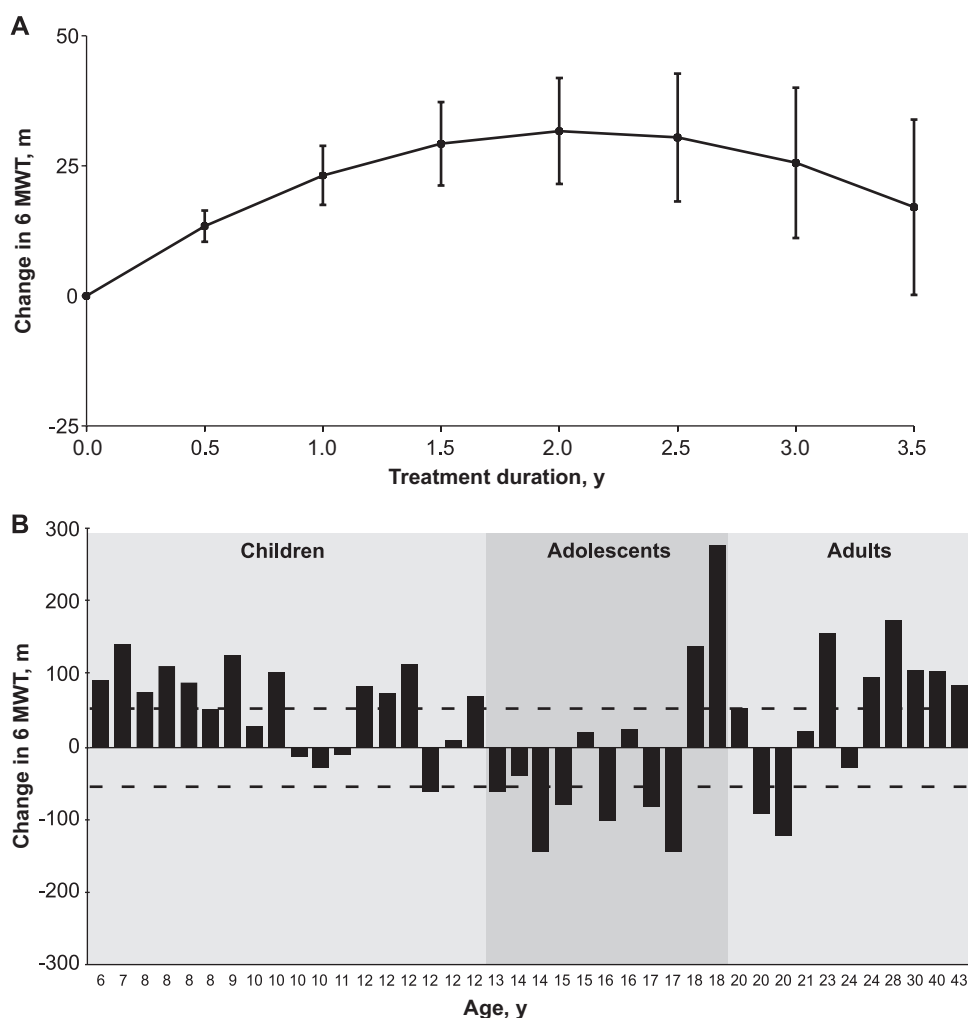


FIGURE 3

6MWT. A, Mean absolute change in 6MWT distance versus laronidase treatment duration. Curved regression line was estimated by using linear mixed modeling techniques^{9,10} (see "Methods"). Bars represent $\pm$ SEM. B, Individual changes from baseline to final assessment. Horizontal dotted lines denote upper and lower limit of clinically significant change (see "Methods").

assessment, LVH had resolved in 4 patients (40%), and 1 patient had developed new mild LVH. There were no clinically significant changes on electrocardiogram.

Approximately two thirds of patients had short stature at baseline (>2 SDs below normal for age and gender). After treatment, the median height velocity normalized in pediatric patients. Patients with the most severe short stature (>3 SDs below normal for age and gender) showed the greatest catch-up growth.

Distribution of Treatment Effects

Improvements in the main measures of clinical efficacy (percent predicted FVC, 6MWT, AHL, shoulder range of motion, and corrected visual acuity) occurred in variable combinations throughout the patient population. Overall, 87.5% of patients (35 of 40) showed improvement in at least 1 domain, and 55% (22 of 40) showed improvement in 2 or 3 domains. Conversely, 48% of patients (19 of 40) declined in at least 1 domain, and 18% (7 of 40) declined in 2 or 3 domains. No patient declined in >3 domains.

Safety

Laronidase was found to be well tolerated and safe in most patients with an adverse event profile that was similar to that of the 26-week placebo-controlled trial.⁸ All patients experienced at least 1 adverse event; however, most adverse events were mild and were attributed to underlying disease rather than treatment. Adverse events related to treatment were reported in 30 patients (67%). Of 682 total related adverse events, 414 (61%) were IARs experienced by a single patient (see below).

Related adverse events that occurred in at least 10% of patients were as follows: rash (22%), arthralgia (20%), headache (18%), flushing (16%), injection site reaction (13%), arthropathy (11%), abdominal pain (11%), back pain (11%), fever (13%), skeletal pain (11%), and nausea (11%). Serious adverse events related to treatment (9 total) were reported in 3 patients (7%); 7 of these were also characterized as IARS (see below); the remaining 2 were back pain (1 patient) and vein disorder (1 patient).

Most adverse events related to treatment were IARs,

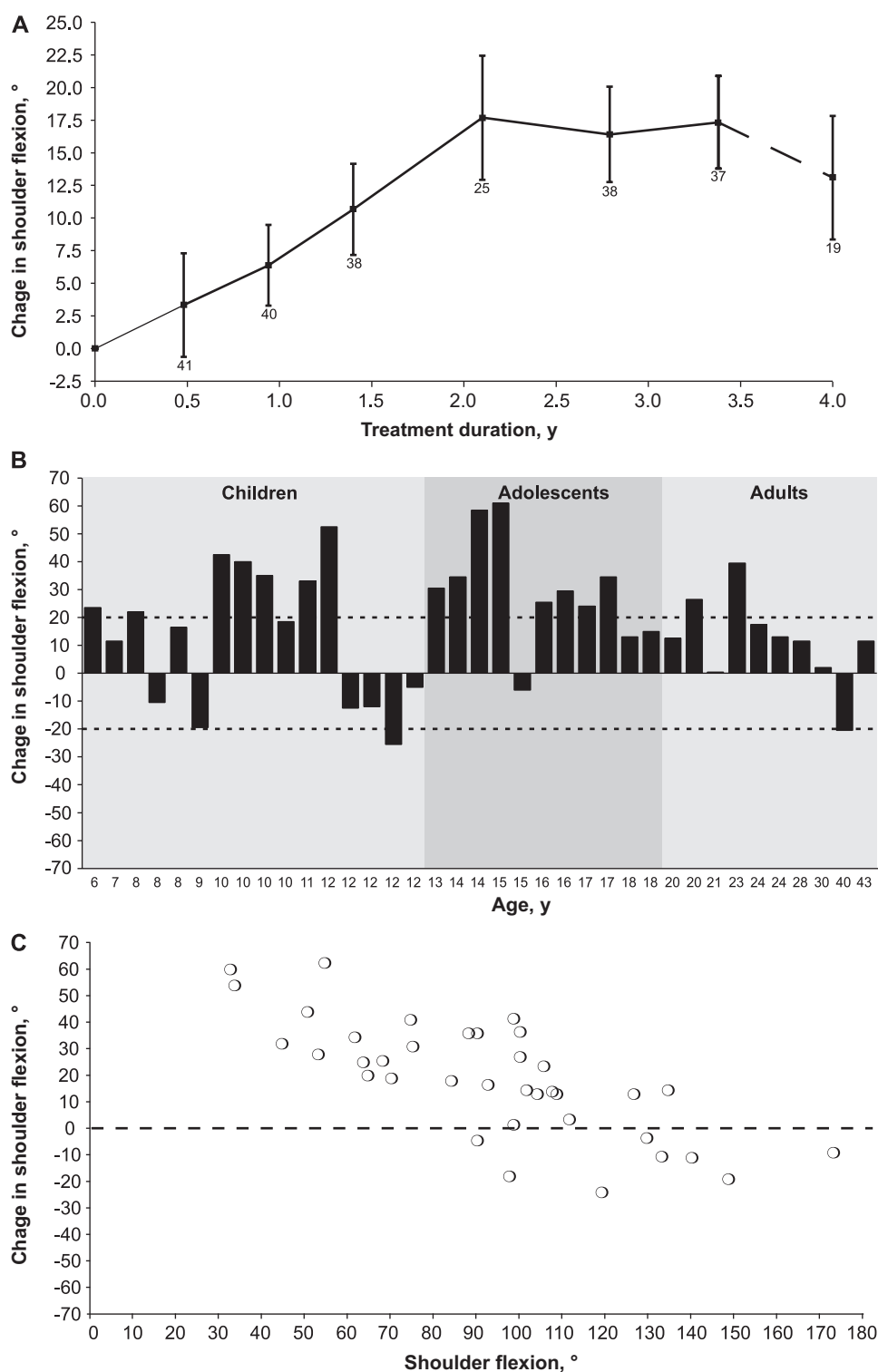


FIGURE 4

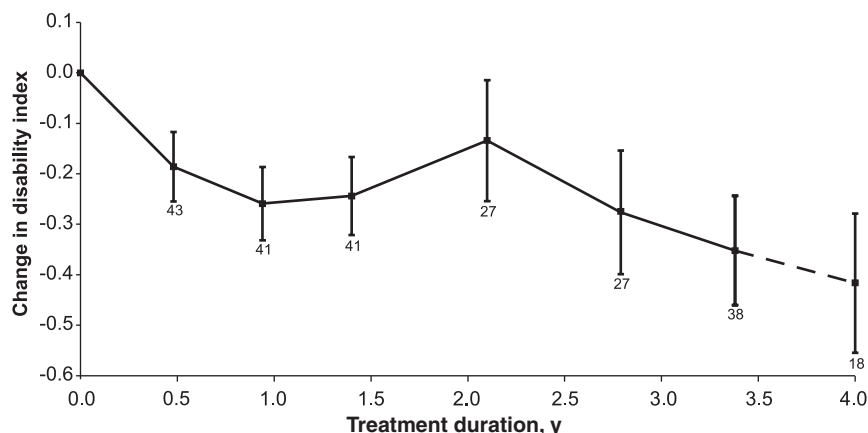
Shoulder flexion. A, Mean absolute change in shoulder flexion versus laronidase treatment duration. Solid line, all patients; dotted line, patients from the laronidase arm of the placebo-controlled trial, who received an additional 6 months of treatment. Bars represent $\pm$ SEM, and numbers denote the number at each assessment interval. B, Individual changes from baseline to final assessment. Horizontal dotted lines denote upper and lower limit of clinically significant change (see "Methods"). C, Absolute change in shoulder flexion from baseline to final assessment versus baseline shoulder flexion. Patients with the least range of motion at baseline showed the most improvement with treatment ($r = -0.77$; $P < .001$; $n = 37$).

which were reported in 53% (24 of 45) of patients and were associated with 3.6% (271 of 7593) of infusions. Most IARs were mild and consisted of fever, mild flush-

ing, and/or rash and did not require intervention or alteration of the infusion protocol. Most IARs occurred within the first 6 months of infusions and decreased in

FIGURE 5

Mean absolute change in CHAQ/HAQ disability index versus laronidase treatment duration. Solid line, all patients; dotted line, patients from the laronidase arm of the placebo-controlled trial, who received an additional 6 months of treatment. Bars represent $\pm$ SEM, and numbers denote the number at each assessment interval. The disability index ranges from 0 to 3 (no disability to severe disability), and a decrease of ≥ 0.24 represents a clinically significant improvement.¹⁷



frequency over time (Fig 6). One patient experienced 71% of all IARs, none of which were classified as serious. These reactions consisted of repeated episodes of fever and localized rash at the venipuncture site that began at infusion 39 and occurred during most of this patient's subsequent infusions. The patient remained IgE-negative, complement activation-negative, and had serum tryptase results within the normal reference range. Pretreatment with steroid did not seem to prevent IARs, and the patient continued to receive infusions.

Seven serious IARs occurred in 2 patients, 1 of whom experienced mild to moderate abdominal pain, fever, hypotension, and vomiting (all on the same day) after infusion 121, leading to hospitalization. All events resolved within 2 days of onset.

The second patient experienced an anaphylactic reaction during infusion number 44. This 16-year-old boy had severe upper airway disease with swallowing difficulty and respiratory compromise, a baseline percent predicted FVC of 29%, and an AHI of 53 events per hour. He had no IARs during his first 30 infusions, but during infusion 31, he experienced severe respiratory distress. A complement activation assay was positive. Treatment was suspended for 13 weeks during which significant upper airway and pulmonary disease were confirmed, and he was diagnosed with generalized anxiety and depressive disorder. Anti-laronidase IgE and serum tryptase were positive, but laronidase skin testing

was negative. Several mild IARs occurred after treatment was resumed, including mild maculopapular rash, flushing, and periorbital swelling, but no serious IARs occurred until infusion number 44 (62 weeks after beginning treatment), when 3 hours into the infusion the patient developed hypoxia, generalized rash with urticaria, and respiratory arrest consistent with an anaphylactic reaction. Tracheotomy was required with subsequent recovery, and the patient was withdrawn from the trial.

One patient died during the trial of causes unrelated to laronidase treatment. This 7-year-old boy had moderately severe respiratory and somatic disease and died 6 days after his sixteenth infusion. Autopsy revealed evidence of viral pneumonia, and the physician involved in the care of the patient deemed the death to be most likely because of complications of underlying disease and upper respiratory tract infection.

IgG antibodies to laronidase developed in 93% of patients (42 of 45), with 29% of patients (13 of 45) seronegative at their last assessment. Three of these tolerant patients (1 of whom withdrew from the trial after 16 infusions) remained seronegative at all assessments. Although the level of IgG antibodies did not seem to correlate with the incidence of IARs, most IARs occurred just after seroconversion (data not shown). As discussed earlier, the single patient who had an anaphylactic reaction was found to be IgE-positive. As shown in Fig 7,

FIGURE 6

IARs versus laronidase treatment duration. Percentage of patients with at least 1 IAR during each 3-month interval beginning at the time indicated (solid circles; up to $n = 45$) and percentage of infusions with IARs during each 3-month interval (open circles). Solid line, all patients matched for treatment duration; dotted line, patients from the laronidase arm of the placebo-controlled trial, who received an additional 6 months of treatment.

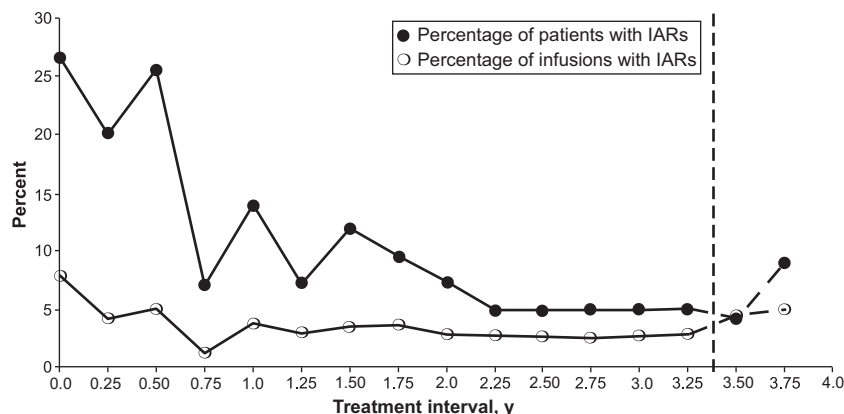
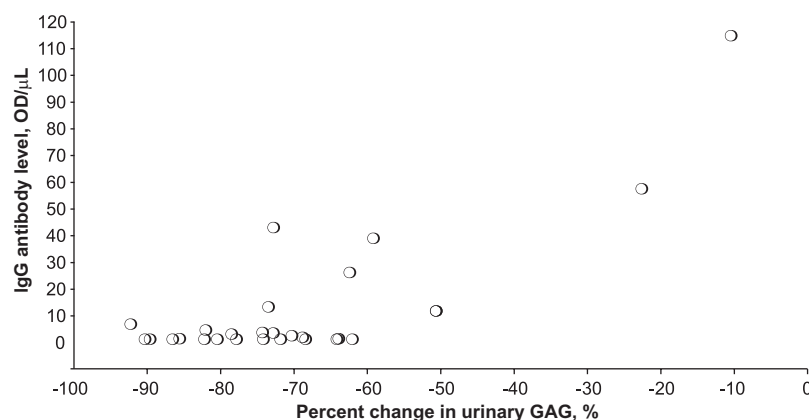


FIGURE 7

IgG antibody level to laronidase versus percent change in urinary glycosaminoglycan level at final assessment. Patients with positive IgG antibody status by ELISA and negative by radioimmunoprecipitation were assigned an antibody level of 0. Patients with negative IgG antibody status by ELISA and positive by radioimmunoprecipitation were excluded, because radioimmunoprecipitation results are not quantitative. There was an inverse correlation between IgG antibody level and percent reduction in urinary glycosaminoglycan level ($r = 0.81$; $P < .001$; $n = 27$). Baseline urinary glycosaminoglycan levels were elevated in all patients. Analyses at earlier time points showed the same trend.



antibody levels inversely correlated with the degree of urinary glycosaminoglycan reduction ($r = 0.81$; $P < .001$; $n = 27$). However, no correlations were observed between antibody levels and changes in FVC and 6MWT (data not shown).

Analysis of safety, immunogenicity, and efficacy data found that there was no significant change to the safety profile of laronidase when it was administered without human serum albumin in the 19 European patients.

DISCUSSION

This trial of 45 patients represents the largest single cohort of patients with MPS I treated with enzyme replacement therapy and highlights the long-term safety and efficacy of laronidase among children and adults with attenuated MPS I disease and a wide range of long-standing clinical manifestations. One of the key clinical observations in this trial is that various aspects of MPS I respond differentially to enzyme replacement therapy and have different time courses of response. These differences presumably reflect the complex underlying pathophysiology of MPS I, as well as the variable biodistribution of enzyme in tissues. The chronology of responses (months for urinary glycosaminoglycan, liver volume, and sleep apnea; years for endurance, mobility, and activities of daily living) is important for guiding treatment expectations. Similarly, it is important to be aware that the most common drug-related adverse events, IARs, are generally mild and decline after the first few months of treatment. However, severe IARs, including anaphylactic reactions, may occur and consideration must be given to the level of care at the infusion facility. This trial shows for the first time that long-term use of enzyme replacement in MPS I leads to measurable improvements in activities of daily living and pain as revealed by decreases in the CHAQ/HAQ disability index and pain score. Although quality of life benefits have been reported anecdotally and in case studies and case series,^{6,7,19,20} earlier and shorter clinical trials have not captured this benefit quantitatively.

The results of this trial also demonstrate the limitations of assessing the mean change in single efficacy end points in a heterogeneous, progressive, multisystem organ disease such as MPS I. Not only were patients at

different stages of their disease, but disease burden in different organs varied widely both within and between patients. For any single end point, patients at each extreme of severity are likely to be more limited in their capacity to show change, which serves to reduce the mean group response. A composite end point approach, in which change is assessed over several end points within the same patient, may be the most sensitive and accurate measure of the treatment response. Composite end points and disease severity scores have been used to gauge change in other complex diseases such as Gaucher disease,^{21,22} multiple sclerosis,²³ and rheumatoid arthritis.²⁴

In a progressive, life-threatening disease, treatment success can be measured not only as direct clinical improvements, but also as stabilization of disease or a decreased rate of progression. Because of the rarity of the disorder, there are few data on the natural history of MPS I; however, given the impaired clinical status of the patient cohort at baseline (Tables 2 and 3), disease progression would have been expected over a 3.5- to 4-year period. Instead, stabilization or improvements were noted in most patients, both collectively and individually, across multiple end points (Table 3). The near normal rate of lung volume growth, as reflected by stabilization of percent predicted FVC, is notable, given that the cross-sectional baseline data showed a downward trend in percent predicted FVC with advancing age for the patients <25 years old (Fig 2A). This suggests that early treatment would help to stabilize pulmonary function at a higher level and thereby potentially diminish respiratory complications that are a major source of morbidity and mortality in MPS I.

CONCLUSIONS

Long-term treatment with laronidase effectively treats many of the important aspects of MPS I, including respiratory dysfunction, poor endurance, restricted mobility, hepatomegaly, and decreased quality of life. Prompt disease recognition and early and sustained treatment with laronidase will maximize these important benefits of treatment.

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DOCTORS WHO SAY THEY'RE SORRY

"The willingness of doctors at several major medical centers to apologize to patients for harmful errors is a promising step toward improving the quality of a medical system that kills tens of thousands of patients a year inadvertently. For years, experts have lamented that medical malpractice litigation is an inefficient way to deter lethal or damaging medical errors. Most victims of malpractice never sue, and there is some evidence that many patients who do sue were not harmed by a physician's error but instead suffered an adverse medical outcome that could not have been prevented. The details of what went wrong are often kept secret as part of a settlement agreement. What is needed, many specialists agree, is a system that quickly brings an error to light so that further errors can be headed off and that compensates victims promptly and fairly. Many doctors, unfortunately, have been afraid that admitting and describing their errors would only invite a costly lawsuit. Now, as described by Kevin Sack in *The Times*, a handful of prominent academic medical centers have adopted a new policy of promptly disclosing errors, offering honest apologies and providing fair compensation. It appears to satisfy many patients, reduce legal costs and the litigation burden and, in some instances, helps reduce malpractice premiums. At the University of Illinois, for example, of 37 cases where the hospital acknowledged a preventable error and apologized, only one patient filed suit. At the University of Michigan Health System, existing claims and lawsuits dropped from 262 in August 2001 to 83 in August 2007, and legal costs fell by two-thirds. To encourage greater candor, more than 30 states have enacted laws making apologies for medical errors inadmissible in court. That sounds like a sensible step that should be adopted by other states or become federal law."

New York Times. May 22, 2008

Noted by JFL, MD

Long-term Efficacy and Safety of Laronidase in the Treatment of Mucopolysaccharidosis I

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