



# Outcomes of Long-Term Treatment with Laronidase in Patients with Mucopolysaccharidosis Type I

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**Objective** To evaluate long-term outcomes of laronidase enzyme replacement therapy in patients with attenuated mucopolysaccharidosis type I.

**Study design** Retrospective analyses of case notes, laboratory results, and data from clinical trials were used to evaluate urinary glycosaminoglycans, forced vital capacity (FVC), 6-minute walk test (6MWT), height-for-age Z score, cardiac valve function, corneal clouding, and visual acuity in 35 patients with attenuated mucopolysaccharidosis type I (Hurler-Scheie and Scheie syndromes) for up to 10 years following the initiation of laronidase therapy.

**Results** Statistically significant ( $P < .001$ ) reductions in mean urinary glycosaminoglycan levels relative to baseline were observed 6 months after treatment initiation and were sustained throughout follow-up. Disease remained stable after treatment initiation with no statistically significant changes in mean FVC, 6MWT, or height-for-age Z score. At last assessments, mitral and aortic valve function remained stable in 65% (22/34) of patients; corneal clouding remained stable in 78% (18/23); visual acuity remained stable in 33% (8/24) and improved in 42% (10/24) of patients. Younger patients (<10 years at treatment initiation) maintained disease measures closer to norms for age for FVC, 6MWT, and height and showed fewer deteriorations in mitral and aortic valve disease and corneal clouding compared with patients aged  $\geq 10$  years at treatment initiation.

**Conclusion** Laronidase treatment resulted in disease stabilization in the majority of patients with a mean follow-up of 6.1 years. Data suggest that early treatment may result in better outcomes. (*J Pediatr* 2016;178:219-26).

**M**ucopolysaccharidosis type I (MPS I) is an autosomal recessive lysosomal storage disorder affecting approximately 1:100 000 live births.<sup>1</sup> MPS I is characterized by deficiency of the lysosomal enzyme alpha-L-iduronidase. This deficiency causes accumulation of the glycosaminoglycans (GAGs) dermatan and heparan sulfate in cells throughout the body, resulting in the characteristic, multisystem phenotype typified by short stature, abnormal facies, hepatomegaly, cognitive impairment, joint contractures, skeletal abnormalities, cardiac disease, respiratory disorders, corneal clouding, visual impairment, and cervical myelopathy.<sup>2</sup> Disease severity and rate of progression are variable. At its most severe, MPS I (Hurler syndrome) presents in infancy with death within 10 years as a result of cardiorespiratory failure and neurologic disease.<sup>1,2</sup> Patients with attenuated MPS I (Hurler-Scheie and Scheie syndromes) may survive into adulthood, generally without cognitive impairment but with significant morbidity.<sup>3</sup>

Treatment options for MPS I include enzyme replacement therapy (ERT) with laronidase (Aldurazyme; Sanofi Genzyme, Boston, Massachusetts, and BioMarin Pharmaceutical, Novato, California), hematopoietic stem cell transplantation (considered most beneficial for patients with Hurler syndrome younger than 2 years of age with developmental quotients of  $>70$ ), and symptom-based and palliative care.<sup>2</sup>

Interpretation of outcome reports for laronidase is complicated by disease rarity, clinical heterogeneity, and a paucity of long-term outcome studies. We add to the collective experience of laronidase treatment in MPS I by reporting clinical outcomes across several disease manifestations for 35 patients with attenuated MPS I (Hurler-Scheie and Scheie syndromes) treated for up to 10 years.

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6MWT	6-minute walk test
ERT	Enzyme replacement therapy
FVC	Forced vital capacity
GAG	Glycosaminoglycan
MPS I	Mucopolysaccharidosis type I
uGAG	Urinary glycosaminoglycan

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(<http://www.nationalarchives.gov.uk/doc/open-government-licence/version/3/>), <http://dx.doi.org/10.1016/j.jpeds.2016.08.033>

## Methods

Clinical data were reviewed retrospectively for living and deceased patients with a diagnosis of MPS I classified clinically (Table I; available at [www.jpeds.com](http://www.jpeds.com)) and/or by molecular analysis as having attenuated disease, who started laronidase treatment between 2000 and 2009 at the Department of Genetic Medicine, St Mary's Hospital, Manchester, UK, and who did not undergo hematopoietic stem cell transplantation. One patient was excluded because clinical notes were not available for review.

The study involved anonymous data collected from case notes; ethics committee approval was not required. Good Clinical Practice standards were adhered to throughout.

For each patient, the last data collected before ERT initiation were used as the baseline for clinical outcomes measured. ERT was initiated within 6 months of baseline measurement of clinical measures in 89% of cases. In the majority of these, the ERT was started within 1 month of baseline measurement. Patients were prescribed weekly infusions of laronidase at the approved dose (100 U/kg). Follow-up included data collected within 6 months of baseline and annual clinical outcome measures.

Outcome measures included urinary glycosaminoglycan (uGAG) excretion, 6-minute walk test (6MWT), forced vital capacity (FVC), height-for-age Z score, cardiac status (measured by left ventricular function and aortic and mitral valve function), corneal clouding, and visual acuity. Duration of follow-up varied for each outcome. Not all patients provided data at every assessment because of a lack of cooperation, learning difficulties, or inability to complete some outcome measures adequately (such as 6MWT, FVC in young children).

uGAGs were measured as described previously<sup>4</sup> and reported as mean percentages of baseline values. Respiratory function was measured by spirometry and reported as FVC in liters as a percentage of the predicted volume for height. The 6MWT was conducted by physiotherapists as described previously<sup>4</sup> and reported as meters walked in 6 minutes. Patients' height-for-age Z scores via the use of World Health Organization standards<sup>4</sup> were recorded up to the age of 21 years (for older patients, the sex-specific reference for 19 years of age was used).

Cardiac status was assessed with echocardiography and included mitral and aortic valve function (regurgitation or stenosis) recorded subjectively as none/mild/moderate/severe according to the cardiologist's report; valve thickening alone was not recorded.

Corneal clouding was recorded subjectively as none/mild/moderate/severe by the treating physician or ophthalmologist. Visual acuity was documented and converted to a measure of vision loss according to the *The International Classification of Diseases, Ninth Revision* codes (best corrected if available; best uncorrected if no corrected measurement was available). For aortic valve, mitral valve, corneal clouding, and visual acuity, changes in categories (normal, mild, or moderate involvement) were noted at follow-up time points relative to baseline.

Antibody levels to laronidase were measured in all patients by Sanofi Genzyme as described previously,<sup>4</sup> either as part of the laronidase phase 3 clinical trial, or as standard pharmacovigilance analysis. In 1 patient with high antibody titers (patient #17, see the section "Additional Investigations"), inhibition of cellular uptake of enzyme was tested at St Mary's hospital via methods described by Saif et al.<sup>5</sup>

## Statistical Analyses

For uGAG, height-for-age Z scores, % predicated FVC, and 6MWT endpoints, a repeated measures mixed model was applied. The covariates included age group (3 categories:  $\leq 4$ , 5-9, and  $\geq 10$  years at treatment initiation), sex, ethnicity, duration on therapy, and a duration on therapy  $\times$  age group interaction effect, with a patient-level random slope and intercept effect. Baseline value also was included as a covariate for the height-for-age Z scores, % predicted FVC, and 6MWT endpoints. Linear slope estimates from mixed models are from baseline through patients' follow-up. The repeated measures mixed model analysis was based on observed data; missing data were not imputed. Figure 1 presents the mean values by age group for each year on ERT ( $\pm$ SE) via the use of observed cases. Outcomes were considered statistically significant if the *P* value was  $\leq .05$ . Aortic valve, mitral valve, corneal clouding, and visual acuity shift analyses for age categories present the patient's change in score from baseline using last observation carried forward methodology (using the last postbaseline value). For each endpoint, the shift analysis classifies a patient's last postbaseline value as having worsened relative to baseline (deteriorated), remained the same as baseline (stable), or improved relative to baseline (improved). These results are presented overall and stratified by baseline age.

## Results

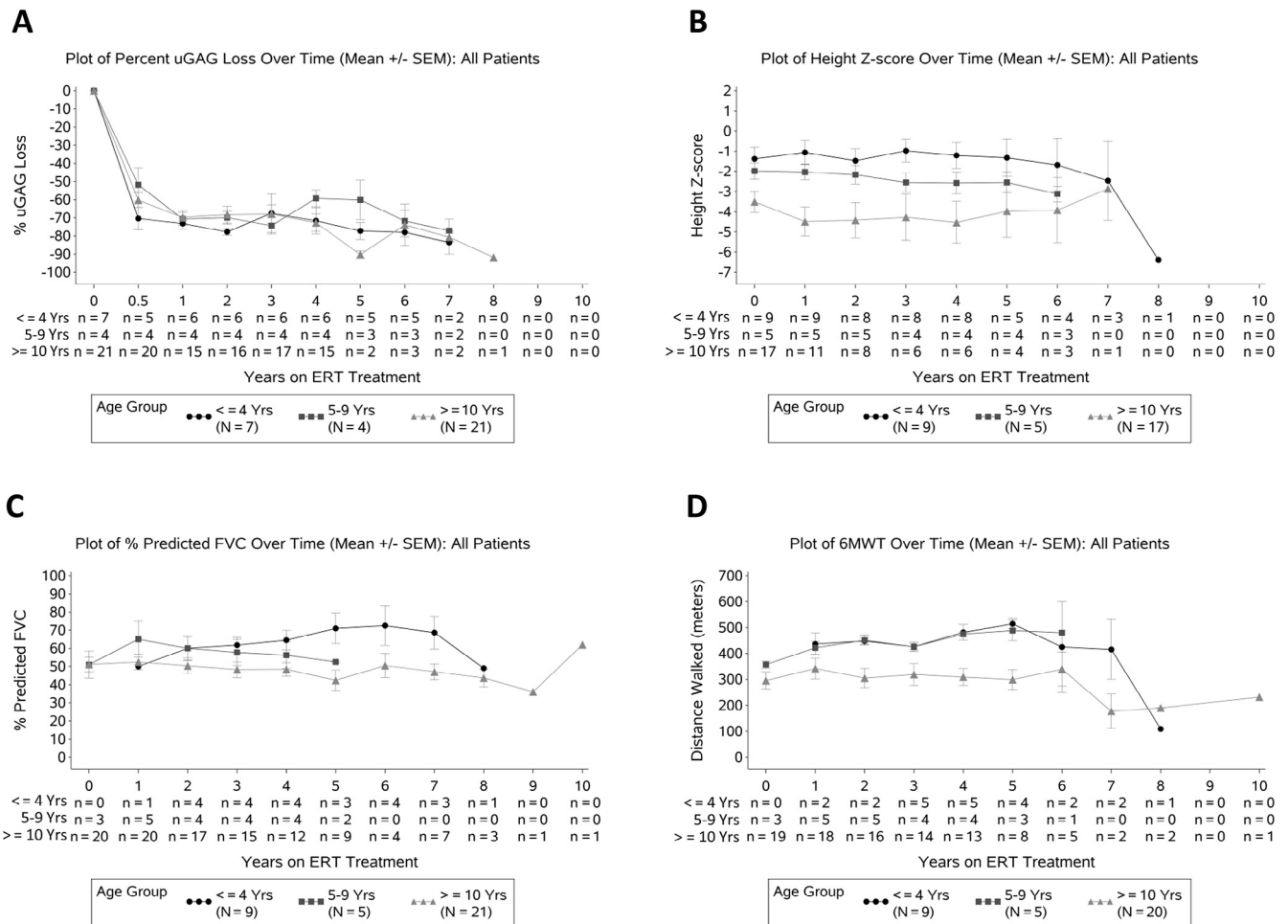
Thirty-five patients with attenuated MPS I were prescribed laronidase throughout the study. One discontinued ERT after 1 year because the patient declined weekly intravenous infusions and clinic attendance. Three patients died during follow-up. Patient characteristics are shown in Table I.

### Urinary GAGs

Baseline uGAG data were available for 91% (32/35) of patients. Mean uGAG levels decreased by more than 50% from baseline within 6 months of laronidase therapy regardless of age at initiation. Reductions remained between 50% and 90% of baseline values throughout follow-up (Figure 1, A). Percentage reduction from baseline was statistically significant ( $P < .001$ ) at all time points (6-months to 7 years). On the basis of the repeated measures mixed model analysis, female patients had, on average, 9.2% less reduction in uGAG levels over time than male patients ( $P = .01$ ).

### Height-for-Age Z Score

Baseline height-for-age Z scores were available for 89% (31/35) of patients. At baseline, the mean height-for-age Z score



**Figure 1.** Mean values by age group for each year on ERT. **A**, Percentage change in uGAGs (mean  $\pm$  SEM). Data represent mean percent change in uGAG compared with baseline uGAG. **B**, Height-for-age Z score (mean  $\pm$  SEM). For patients up to 21 years of age, height-for-age Z scores are reported via World Health Organization standards; for older patients, the sex-specific reference for 19 years of age was used. **C**, Percent predicted FVC (mean  $\pm$  SEM). Data represent FVC in liters as a percentage of the predicted volume for height. **D**, 6MWT (mean  $\pm$  SEM). Data shown are meters walked in 6 minutes.

of children <10 years of age was closer to the expected norm than for patients aged  $\geq 10$  years at the start of ERT (mean of  $-1.60$  and  $-3.50$ , respectively;  $P \leq .05$ ). Patients  $\leq 4$  years of age at baseline had height-for-age Z scores closer to the normal range throughout follow-up ( $P < .001$ ) than patients  $\geq 10$  years of age at baseline (Figure 1, B); however, within an age cohort, the changes in height-for-age Z score up to 7 years follow-up were not statistically significant (slope for patients  $\geq 10$  years at baseline:  $-0.13$  [SEM 0.36]; 5-9 years:  $-0.05$  [SEM 0.56];  $\leq 4$  years:  $-0.02$  [SEM 0.42]). Height-for-age Z score deteriorated after 7 years of therapy in one patient (see the section “Additional Investigations”). Patients of Asian descent (all Pakistani) had lower height-for-age Z scores over time compared with patients of European origin ( $P < .001$ ).

### Respiratory Function

Baseline spirometry data, available for 66% (23/35) of patients, showed a mean of 51% of predicted FVC for height

(Figure 1, C). Nine of 12 missing patients at baseline were  $< 5$  years of age; spirometry tests were not performed for these patients. No statistically significant difference in change in % predicted FVC was found compared with baseline for any of the 3 age groups. Outcomes indicated largely stable disease with a change in % predicted FVC for children  $\leq 4$  years:  $+4.83$  (SEM: 3.4); children 5-9 years:  $+4.44$  (SEM 4.4); patients  $\geq 10$  years:  $+0.23$  (SEM 2.06). On the basis of the repeated measures mixed model analysis, female patients had, on average, % predicted FVC scores 8.8 points greater over time compared with male patients ( $P = .03$ ). Patients of Asian origin had lower % predicted FVC compared with patients of European origin ( $P < .001$ ).

### Six-Minute Walk Test (6MWT)

Baseline data were available for 63% (22/35) of patients. There was no statistically significant change in the 6MWT from baseline (change in 6MWT slope for children  $\leq 4$  years:  $+31.48$  [SEM: 29.9]; 5-9 years:  $+26.47$  [SEM: 34.3]; and patients  $\geq 10$

**Table II.** Shift data for mitral and aortic valves, corneal clouding, and visual acuity at patients' last assessments (1-10 years) overall, and according to patient age at treatment initiation

Clinical measures	Baseline age, y (n)	At last follow-up (1-10 y)		
		Deteriorated	Stable	Improved
Mitral valve	Overall	11/34 (32%)	22/34 (65%)	1/34 (3%)
	≤4 (9)	2/9 (22%)	7/9 (78%)	0
	5-9 (5)	0	5/5 (100%)	0
	Total <10 (14)	2/14 (14%)	12/14 (86%)	0
Aortic valve	Overall	10/34 (29%)	22/34 (65%)	2/34 (6%)
	≤4 (9)	2/9 (22%)	7/9 (78%)	0
	5-9 (5)	0	4/5 (80%)	1/5 (20%)
	Total <10 (14)	2/14 (14%)	11/14 (79%)	1/14 (7%)
Corneal clouding	Overall	4/23 (17%)	18/23 (78%)	1/23 (4%)
	≤4 (8)	1/8 (13%)	6/8 (75%)	1/8 (13%)
	5-9 (3)	0	3/3 (100%)	0
	Total <10 (11)	1/11 (9%)	9/11 (82%)	1/11 (9%)
Visual acuity	Overall	3/12 (25%)	9/12 (75%)	0
	≤4 (7)	4/7 (57%)	0	3/7 (43%)
	5-9 (3)	0	2/3 (67%)	1/3 (33%)
	Total <10 (10)	4/10 (40%)	2/10 (20%)	4/10 (40%)
	Overall	6/24 (25%)	8/24 (33%)	10/24 (42%)
	≤4 (7)	4/7 (57%)	0	3/7 (43%)
	5-9 (3)	0	2/3 (67%)	1/3 (33%)
	Total <10 (10)	4/10 (40%)	6/14 (43%)	6/14 (43%)

patients with follow-up data (to 10 years), 65% (22/34) remained stable with respect to baseline at their last assessment, 32% (11/34) deteriorated, and 3% (1/34) improved (Table II and Figure 2, A). Seventy-two percent (8/11) of deteriorations occurred in patients with mild valve involvement at baseline (5 developed moderate and 3 developed severely impaired function); 18% (2/11) occurred in patients with moderate involvement at baseline (1 developed severe disease and 1 required surgery), and 1 patient with normal function at baseline developed mild mitral valve stenosis/regurgitation. Fewer children aged <10 years experienced deterioration compared with patients aged ≥10 years at treatment initiation (14% vs 45% at last assessment; Table II).

At baseline, 66% (23/35) of patients had normal aortic valve function; 26% (9/35) had mild and 9% (3/35) had moderate stenosis/regurgitation. Of the 34 patients for whom follow-up data (to 10 years) were available, 65% (22/34) remained stable with respect to baseline at their last assessment, 29% deteriorated (10/34), and 6% (2/34) improved (Table II and Figure 2, B). Ninety percent (9/10) of deteriorations occurred in patients with normal valve function at baseline (6 developed mild and 3 developed moderate stenosis/regurgitation); 1 patient with mild aortic valve involvement at baseline developed severe stenosis/regurgitation. Fewer children aged <10 years at treatment initiation deteriorated compared with patients aged ≥10 years (14% vs 40%; Table II).

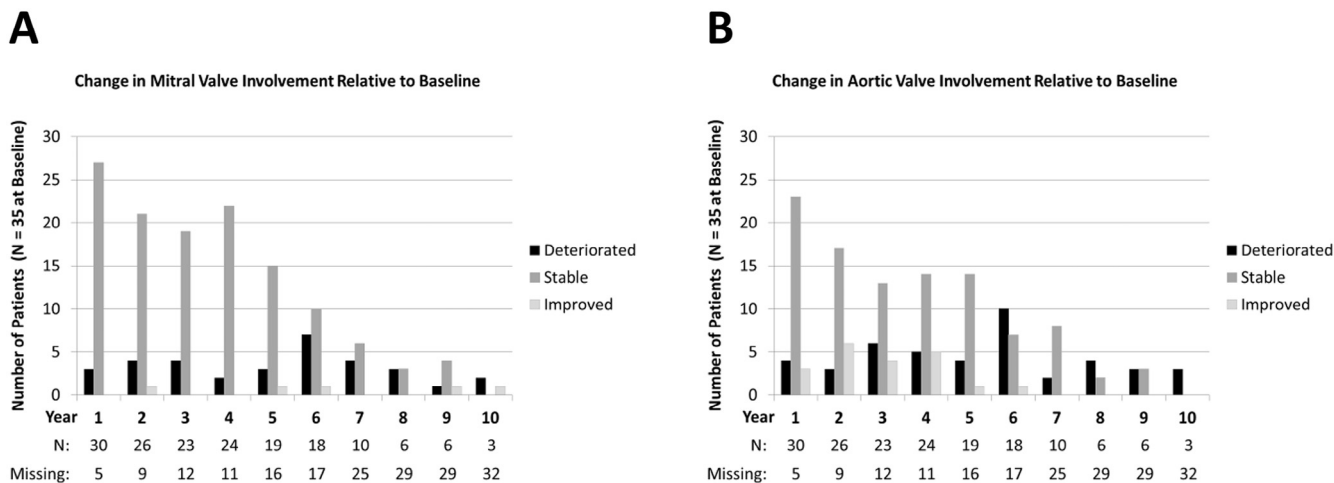
years: +15.45 [SEM: 17.84]; Figure 1, D). After 6 years, mean values deteriorated because of a decline in 1 patient (see the section "Additional Investigations").

**Cardiac Assessments**

At baseline, 14% (5/35) of patients had normal mitral valve function; 77% (27/35) had mild stenosis/regurgitation, and 9% (3/35) had moderate stenosis/regurgitation. Of the 34

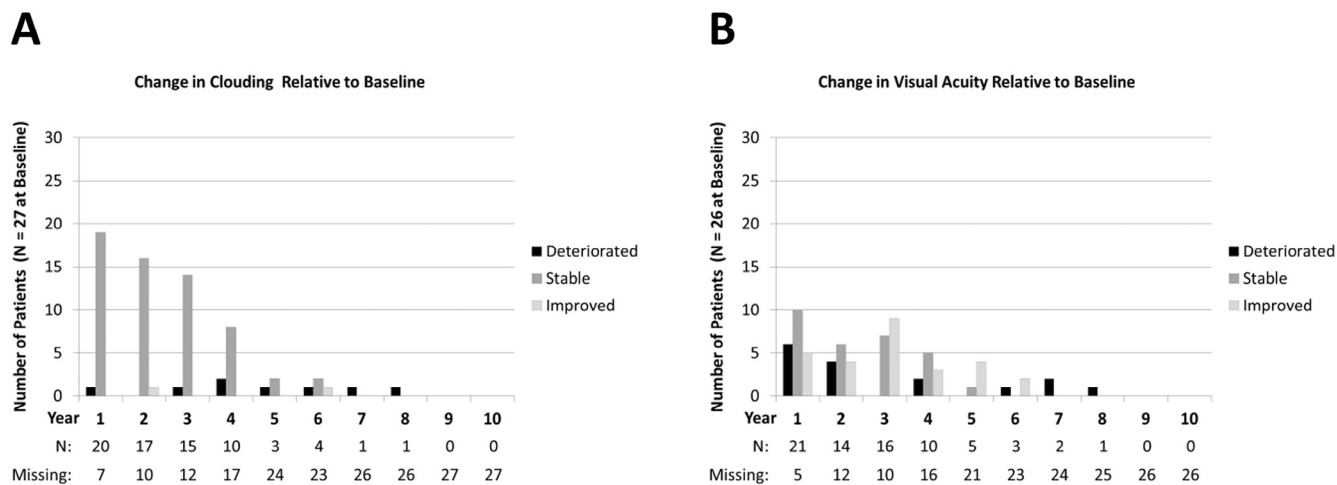
**Corneal Clouding**

Baseline assessment of corneal clouding was available for 77% of patients (27/35); all had evidence of corneal clouding—67% (18/27) with mild and 15% (4/27) with moderate clouding; 11% of patients (3/27) had severe clouding, 2 of whom underwent penetrating keratoplasty during the study. The grafts were clear at last review. Two patients had grafts at



**Figure 2.** Change in A, mitral valve and B, aortic valve involvement over time in patients treated with laronidase. The data show the number of patients who deteriorated, remained stable, or improved at their last assessment compared with baseline in terms of mitral or aortic valve stenosis and regurgitation.





**Figure 3.** Change in **A**, corneal clouding and **B**, visual acuity over time in patients treated with laronidase. The data show the number of patients who deteriorated, remained stable, or improved at their last assessment compared with baseline.

baseline; 1 had severe, persistent graft clouding and the other had a clear graft which remained clear during 4 years of follow-up. Twenty-three of 34 patients had follow-up data up to 8 years (Table II and Figure 3, A); 78% (18/23) remained stable, 17% (4/23) deteriorated (2 patients progressed from moderate to severe visual loss, and 2 from severe to profound), and 4% (1/23) had improved from baseline to last assessment. Of children aged <10 years at treatment initiation, 9% deteriorated compared with 25% of patients aged  $\geq 10$  years (Table II).

### Visual Acuity

Data were available for 74% (26/35) of patients at baseline; 35% (9/26) had normal vision, 42% (11/26) had mildly impaired vision, 4% (1/26) had moderate vision loss, 15% (4/26) had severe vision loss, and 4% (1/26) had profound vision loss. Twenty-four patients had follow-up data up to 8 years: 33% (8/24) remained stable; 25% (6/24) deteriorated with respect to baseline (5 patients developed mild vision loss and one patient's visual acuity deteriorated from severe to profound); and 42% (10/24) of patients improved (Table II and Figure 3, B). A greater percentage of children aged <10 years at baseline deteriorated compared with patients aged  $\geq 10$  years at baseline (40% versus 14%; Table II).

### Additional Investigations

During follow-up, 74% (25/34 of patients tested) were found to have antibodies to laronidase. Of the 25 patients with antibodies, titers decreased with time in 44% (11/25) with 16% (4/25) testing negative for antilaronidase antibodies at their last assessment. Titers increased in 8% (2/25) of patients. In 1 patient aged  $\leq 4$  years at baseline (#17), antibodies to laronidase inhibited cellular uptake of enzyme (by more than 80%), which may explain this patient's apparent reduced responsiveness to ERT (Figure 4; available at [www.jpeds.com](http://www.jpeds.com)).

## Discussion

Laronidase is a disease-modifying treatment for patients with attenuated MPS I. Long-term outcome studies published to date include only 8 patients followed for 6 years or more.<sup>6-8</sup> With two-thirds of patients in this study receiving treatment for 6-10 years, we provide further insights into long-term outcome, which may help guide patients' and physicians' expectations. Because this was a retrospective study, complete patient data were not available at all time points. The amount of missing data varied depending on the endpoint and patient, with the cardiac status endpoints missing the least amount (18% on average) and visual acuity assessments missing the most (51% on average).

This study demonstrated a biochemical reduction and subsequent stabilization, but not normalization, of mean uGAGs. Clinically, there was significant stabilization of mean values for FVC, 6MWT, and height-for-age Z score. Cardiac valve status and corneal clouding stabilized in the majority of patients up to 10 years' follow-up. Disease stabilization without major deterioration over a number of years can be considered a clinically important treatment outcome, given the progressive nature of this disease, which ultimately leads to significant morbidity, disability, and premature death in patients with Hurler-Scheie phenotypes and morbidity in patients with Scheie phenotypes.<sup>1,2,9</sup> In the absence of treatment, data from the phase 3 clinical trial of laronidase have shown that patients with MPS I experience a decline in pulmonary function and 6MWT scores, as well as an increase in their GAG values.<sup>4</sup>

Results of this study suggest better outcomes for height, % predicted FVC, and 6MWT in patients who started treatment at earlier ages. Children <10 years of age at baseline maintained measures closer to age-related norms compared with patients  $\geq 10$  years at baseline. Without treatment, deterioration would be expected on the basis of differences in baseline values

for children,  $\leq 4$  years, 5-9 years, and  $\geq 10$  years (Figure 1, B-D). Disease stabilization in children  $<10$  years of age at baseline is particularly salient because children diagnosed at an early age are likely to have earlier onset, more severe, and more rapidly progressive disease.<sup>10</sup> In our cohort, all 21 patients in the  $\geq 10$  age group at baseline had presenting symptoms prior to age 10 (average 3.9 years, range prenatal-9 years).

As mentioned previously, the baseline data for this patient group show a greater disease burden in the absence of treatment compared with the younger age groups. Although disease is stabilized in most patients, those diagnosed at a young age who did not initiate treatment until much later maintain greater disease burden throughout. Maintaining clinical status closer to age-expected norms may have profound implications for psychosocial development<sup>11</sup> and for reducing the limitations that MPS I may incur on daily life.<sup>12</sup> Three of the 35 patients in the study died during the review period; 2 of cardiac complications (1 following surgery for mitral valve replacement) and 1 of sudden death (which may also be related to cardiac involvement). All 3 were older than 10 years of age at the start of ERT, had well-established disease at the time of ERT, and received treatment for 3-6 years. These outcomes may support early initiation of treatment.

Better outcomes in children treated before 10 years of age were also suggested by shift analyses for mitral valve, aortic valve, and corneal clouding (Table II). For visual acuity, more deteriorations were observed in children  $<10$  years compared with children  $>10$  years at treatment initiation, although improvements occurred at similar rates for both age groups. Loss of visual acuity in MPS I is thought to be related to dermatan sulfate deposition in the cornea<sup>13</sup>; however, vision also may be affected by other ocular manifestations of MPS I, such as swelling of the optic nerve, optic atrophy, glaucoma, and retinal pigment epithelium degeneration,<sup>14</sup> for which the effects of ERT may differ and are not well understood. Improvement in visual acuity without improvement in corneal clouding has been reported previously.<sup>15</sup> Vision loss is a significant complication of MPS I, which may negatively impact independent living and quality of life. Although outcomes of this study are encouraging, difficulties in measurement (small patient numbers, the subjective nature of corneal clouding assessment, test-to-test variability, difficulties of assessing young children, and determining whether changes are within the normal or mild loss of vision range) make results difficult to interpret.

It is notable that aortic and mitral valve stenosis/regurgitation remained stable in the majority of patients. Cardiac involvement is a frequent finding in patients with attenuated MPS I<sup>3,16</sup> and a major cause of morbidity and mortality.<sup>17</sup> Given that follow-up was prolonged, impaired function may have been expected to occur more widely. In patients with cardiac valve involvement at baseline (88% or 30/34 for mitral and 35% or 12/34 for aortic valve involvement), stability was seen in the majority of patients (67% or 20/30 and 8/12 for both mitral and aortic valve involvement). Deterioration was seen more commonly in patients who were older at the time of treatment initiation. Importantly, the vast majority of patients younger than 10 years of age at start of ERT had only mild

cardiac disease at baseline. We do note that the clinical course of cardiac disease was highly variable, with no clear reason for why some patients progress and others stabilize. Although age and the extent of involvement at start of ERT may be influencing factors, as discussed previously, there are likely other complex individual factors at play. Moreover, cardiac assessment as recorded for the purposes of this study has limitations including difficulties in accurately assessing function via echocardiography (especially in patients whose cooperation may be limited), and only subjective and nonstandardized assessment of stenosis/regurgitation was reported. As such, the grading system used here may make interpretation of small changes in disease severity difficult to interpret.

Further limitations in interpretation of results include the heterogeneity of the patient population, which may have influenced mean outcomes. Patients of Asian origin in this cohort, for example, were affected more severely in terms of height and pulmonary function compared with patients of European origin, a factor that may relate to differing genetic profiles (all patients of Asian origin were Pakistani and homozygous for the L490P mutation; there were no patients of European origin who were homozygous for this mutation).<sup>3</sup> Other outcome measures also may be affected by patient demographics. GAG excretion is known to be affected by age<sup>18</sup> and in this study was shown to be affected by sex. FVC may be influenced by age, sex (as shown in this study), as well as ethnicity.<sup>19</sup> Age also may be a factor in the 6MWT, because performance may depend on attention span and the ability to comply with instructions. The 6MWT also may be affected by cardiorespiratory function, joint pain, flexibility, and stature, all of which may be variably affected by ERT. Mean outcomes for 6MWT, height-for-age Z score, FVC, and GAGs were also negatively influenced by outcomes in 1 patient in this study, who developed antibody-induced cellular uptake inhibition of enzyme. Many patients, especially those with low endogenous enzyme levels, develop antibodies to laronidase but total antibody titers are not predictive of compromised treatment and, often, patients do not suffer clinical effects.<sup>4</sup> Inhibition of catalytic activity by itself may not be functionally significant but inhibition of cellular uptake may compromise treatment response.<sup>5,20</sup> Immune system responses to exogenous enzyme should, therefore, be assessed and taken into consideration when evaluating treatment outcomes. We do appreciate that long-term outcomes with treatment would be best addressed in a well-controlled prospective study; however, such studies are difficult to perform in the rare disease space, and it may be that even longer-term results over a number of centers are required to achieve a significant conclusion.

Results of this study are similar to previously reported short-term outcomes and demonstrate that laronidase reduces GAG storage<sup>4,6,8,12,15,21-26</sup> and may stabilize or improve respiratory function,<sup>4,6,12,15,24,26</sup> growth,<sup>6,15,21,24</sup> mobility,<sup>4,12,15,22,24</sup> some cardiac manifestations,<sup>6,12,15,24,25</sup> corneal clouding,<sup>6,12</sup> and visual acuity.<sup>6,12,14,15</sup> This study suggests that treatment effectiveness persisted for up to 10 years; however, as shown in previous studies, treatment may not prevent deterioration in all patients.<sup>6,7,12,27</sup> Although GAG clearance may be a biomarker

of treatment response, irreversible damage secondary to GAG-induced inflammatory responses may occur. Early treatment, before irreversible change takes place, is likely the most important factor in influencing outcomes,<sup>24,25,28,29</sup> although this view is not supported universally.<sup>27</sup> Other factors may include differences in disease severity and progression and affected systems, immune responses (discussed previously), and tissue-specific factors that affect response, including biodistribution of protein, burden of storage, residual enzyme activity, and irreversibility of disease due to downstream cascades. Delays in diagnosis continue despite treatment availability<sup>10</sup> and highlight the need for greater awareness among pediatricians of common MPS I presenting symptoms, which can be nonspecific for attenuated disease (Table 1).<sup>9</sup> Previous studies have shown that the optimal time for initiation of therapy is before the onset of symptoms,<sup>24,25,30</sup> although unless diagnosed due to a family history (26% of patients in this study presented because of family history), very few children initiate ERT this early. Newborn screening may provide a means of ensuring that children with MPS I are treated early enough to prevent disease manifestations.<sup>25</sup> ■

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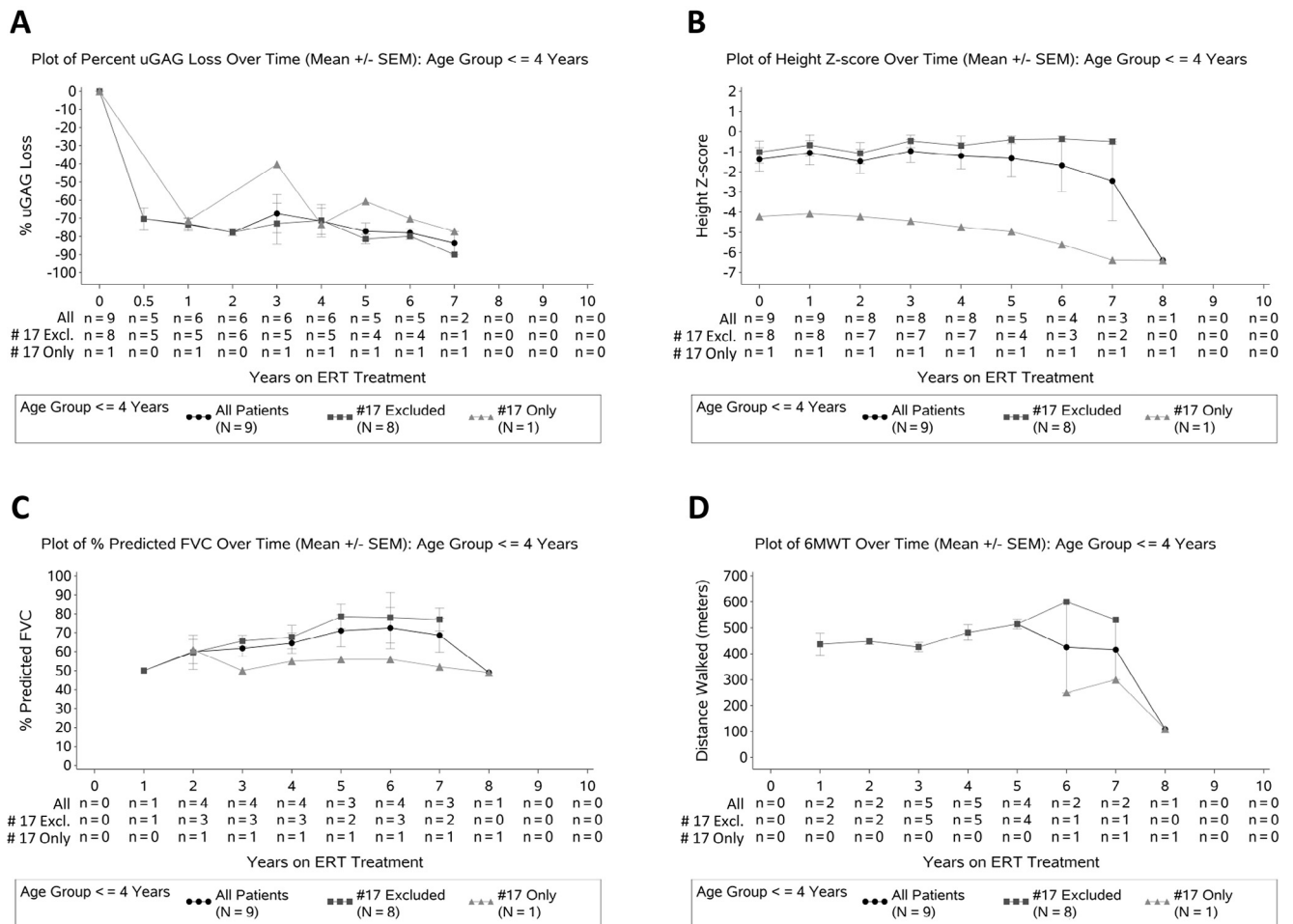
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**Figure 4.** Impact of outcomes in patient #17 (who exhibited antibody-induced cellular uptake inhibition of enzyme) on mean treatment outcomes for **A**, uGAG loss (mean  $\pm$  SEM); **B**, height-for-age Z score (mean  $\pm$  SEM); **C**, FVC ratio (mean  $\pm$  SEM); and **D**, 6MWT (mean  $\pm$  SEM).

**Table I.** Patient characteristics

Ethnicity	European origin: 22 Asian origin 12: (all Pakistani) Uncertain: 1
Sex	13 male; 22 female
Age at presentation	26% (9/35 patients) presented because of family history (affected siblings/family members). Of the remaining 26 patients, the mean age of presentation was 3.85 years; median 4 y; range 0.25-9 y
Symptoms at presentation (some patients had multiple reasons/symptoms)	Hepatosplenomegaly (n = 8); umbilical hernia (n = 5); joint stiffness (n = 7); ENT and/or respiratory problems (n = 6); dysmorphism including short stature, skeletal dysplasia, "trigger" fingers, scoliosis, enlarged head (n = 15); developmental delay (n = 3); abnormal gait (n = 1); corneal clouding (n = 2); poor appetite (n = 1)
Age at baseline	Mean 11.5 y; median 11.3 y; range 0.5 - 23.1 y $\leq 4$ y: n = 9 5-9 y: n = 5 $\geq 10$ y: n = 21
ERT dose	Laronidase i.v. infusions at 100 U/kg body weight weekly
Years of follow-up	Mean 6.1 y; median 6 y; range 1-10 y (1 y: n = 1; 2 y: n = 2; 3 y: n = 1; 4 y: n = 7; 5 y: n = 1; 6 y: n = 7; 7 y: n = 7; 8 y: n = 2; 9 y: n = 3; 10 y: n = 4)

ENT, ear, nose, and throat; i.v., intravenous.