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The effect of idursulfase on growth in patients with Hunter syndrome: Data from the Hunter Outcome Survey (HOS)

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ABSTRACT

Hunter syndrome (mucopolysaccharidosis type II) is a rare and life-limiting multisystemic disorder with an X-linked recessive pattern of inheritance. Short stature is a prominent feature of this condition. This analysis aimed to investigate the effects of enzyme replacement therapy with idursulfase on growth in patients enrolled in HOS — the Hunter Outcome Survey which is a multinational observational database. As of Jan 2012, height data before treatment were available for 567 of 740 males followed prospectively after HOS entry. Cross-sectional analysis showed that short stature became apparent after approximately 8 years of age; before this, height remained within the normal range. Age-corrected standardized height scores (z-scores) before and after treatment were assessed using piecewise regression model analysis in 133 patients (8–15 years of age at treatment start; data available on ≥1 occasion within +/−24 months of treatment start; growth hormone-treated patients excluded). Results showed that the slope after treatment (slope = −0.005) was significantly improved compared with before treatment (slope = −0.043) (difference = 0.038, $p = 0.004$). Analysis of covariates (age at treatment start, cognitive involvement, presence of puberty at the start of ERT, mutation type, functional classification), showed a significant influence on growth of mutation type (height deficit in terms of z-scores most pronounced in patients with deletions/large rearrangements/nonsense mutations, $p < 0.0001$) and age (most pronounced in the 12–15-year group, $p < 0.0001$). Cognitive involvement, pubertal status at the start of ERT and functional classification were not related to the growth deficit or response to treatment. In conclusion, the data showed an improvement in growth rate in patients with Hunter syndrome following idursulfase treatment.

1. Introduction

Hunter syndrome (or mucopolysaccharidosis type II [MPS II]; OMIM# 309900)[1] is a rare and life-limiting X-linked recessive disorder that affects approximately 1 in 77,000 newborn boys [1,2]. Girls are rarely affected. The condition arises as a result of a deficiency in the lysosomal enzyme iduronate-2-sulfatase (I2S; EC 3.1.6.13) that is responsible for breaking down heparan and dermatan sulfate within the cells [3]. Insufficient levels of this hydrolytic enzyme lead over time to the accumulation of these two glycosaminoglycans (GAGs) in tissues throughout the body. Disease-related manifestations develop progressively following birth and are multisystemic in nature [3]. Organs affected include the heart, lungs, bones, muscles, gut, skin and brain; however, there is considerable heterogeneity in disease presentation. Although disease expression represents a continuum, two broad forms of the condition are typically identified: a severe form associated with progressive neurological impairment and characterized by the presence of cognitive impairment, and an attenuated form in which the patient remains cognitively intact [4–7]. Both forms reduce life expectancy [8].

Short stature is a prominent and consistent feature of Hunter syndrome [6,9–11], that generally becomes evident at approximately 8–10 years of age [6,10,12]. Growth failure probably begins some time before the height deficit becomes apparent. One study showed that growth rate starts to fall relative to that of healthy peers after

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[1] ERT, enzyme replacement therapy; GAGs, glycosaminoglycans; HOS, Hunter Outcome Survey; MPS II, mucopolysaccharidosis type II.

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about 3 years of age. Before this point, it is interesting to note that children with Hunter syndrome may actually be slightly taller than average, are heavier and also have a larger head circumference [10,12]. Data show that they are generally larger than healthy children at birth and grow faster during the first 3 years of life [10].

Although the psychosocial impact of short stature has not been studied specifically in patients with Hunter syndrome, several studies in other populations suggest that short stature during childhood may have a negative impact on quality of life and social functioning [13–15]. Furthermore, it has been reported that young adults with disorders associated with short stature, including those with Hunter syndrome, have difficulties finding a partner [9,16]. Thus, ameliorating short stature may be beneficial to patients and their parents.

Specific treatment for patients with Hunter syndrome is now available in the form of recombinant human I2S enzyme replacement therapy (ERT) (idursulfase, Elaprase®, Shire Human Genetic Therapies, Inc., Lexington, MA. USA). Idursulfase has been generally well tolerated and has been shown in clinical trials to improve measures of pulmonary function and to improve walking capacity [17,18]. Treatment has also been found to decrease urinary GAG levels and liver and spleen volumes [18,19], and to stabilize joint range of motion, particularly in the elbow and shoulder, with associated improvements in functional status [18]. Data on the impact of ERT on growth are limited [9,18]; however, observations in patients with the attenuated form of the disease suggest that, particularly if started before 10 years of age, treatment may have a positive impact on height [9]. The aims of this analysis were to confirm previous reports of short stature and to assess the effects of ERT on growth in a larger cohort of patients with attenuated and severe forms of Hunter syndrome enrolled in HOS — the Hunter Outcome Survey.

2. Material and methods

2.1. Survey design

HOS is a global, multicenter, longitudinal, observational survey sponsored by Shire HGT that collects data on the natural history of Hunter syndrome and long-term safety and effectiveness of ERT with idursulfase. The survey is overseen by national, regional and global scientific advisory boards comprised of physicians experienced in the management of patients with Hunter syndrome. Participating sites obtained approval from their local Ethics Committee/Institutional Review Board before enrolling patients in HOS. Written informed consent for participation was provided by each patient, their parents or a legal representative. Data entry and analysis in HOS were conducted as described previously [12].

All data are obtained during routine clinical practice. Data collection and entry are at the discretion of the participating centers. All patients with a confirmed diagnosis of Hunter syndrome are eligible for enrolment in HOS. As well as collecting data on patients followed prospectively, data can be entered on patients who died before the initiation of HOS (followed retrospectively). Quality control checks are made at data entry and analysis; at the time of analysis the clinics are contacted and asked to confirm (or correct) any apparent outlying values.

2.2. Patient population and data collection

This analysis included only data from male patients who were followed prospectively in HOS (i.e. those who were alive at the time of entry into HOS). As of 23 January 2012, HOS contained information on over 902 patients with Hunter syndrome (892 males) from 116

Table 1
Baseline characteristics of patients with Hunter syndrome in HOS aged 8–15 years at the start of enzyme replacement therapy (ERT).

	Patients in HOS aged 8–15 years at start of ERT		
	Treated male patients alive at HOS entry	Patients in the study population[a]	Patients in the subgroup analysis[b]
N	564	133	93
Age at last visit in HOS (yrs) (n)			
Mean (SD)	13.2 (8.4)	14.7 (2.8)	15.1 (2.9)
Median (10th–90th percentile)	11.6 (4.3–24.1)	14.5 (11.4–18.1)	14.8 (11.9–18.8)
Age at onset of symptoms (yrs) (n)			
Mean (SD)	2.1 (1.9)	2.2 (1.8)	2.2 (1.7)
Median (10th–90th percentile)	1.5 (0.3–4.0)	2.0 (0.3–4.8)	2.0 (0.3–4.0)
Age at diagnosis (yrs) (n)			
Mean (SD)	4.0 (3.5)	4.6 (2.9)	4.5 (3.0)
Median (10th–90th percentile)	3.3 (1.1–7.0)	4.0 (1.5–8.3)	3.8 (1.4–8.5)
Proportion in age group at treatment start, n (%)	182	133	93
8–11 years	120 (66.0%)	92 (69.2%)	55 (59.1%)
12–15 years	62 (34.1%)	41 (30.8%)	38 (40.9%)
Cognitive involvement, n[c]	543	133	93
Yes, n (%)	242 (44.6%)	66 (49.6%)	50 (53.8%)
Puberty, n[b]	298	74	56
Prepubertal at treatment start, n (%)	210 (70.5%)	48 (65%)	34 (60.7%)
In puberty at treatment start, n (%)	88 (29.5%)	26 (35%)	22 (39.3%)
Ethnicity, n (%)			
Caucasian	438 (77.7%)	115 (86.5%)	77 (82.8%)
Black	28 (5.0%)	5 (3.8%)	4 (4.3%)
Asian	29 (5.1%)	0 (0.0%)	0 (0.0%)
Other	69 (12.2%)	13 (9.8%)	12 (12.9%)
Mutation classification, n[b]	351	99	66
Complete deletion/large rearrangement, deletion or nonsense, n (%)	117 (33.3%)	29 (29.3%)	25 (37.9%)
Missense, splice-site mutation, insertion or insertion/duplication, n (%)	234 (66.7%)	83 (70.7%)	41 (62.1%)

[a] The study population included all patients in HOS who were aged 8–15 years at the start of ERT and for whom data on height were available on one or more occasion within 24 months of the start of treatment.
[b] Patients in the study population with baseline height z-scores < -2.
[c] n is the number of patients with available data.

clinics in 24 countries; 747 of these patients (740 males) had been followed prospectively. Overall, 569 of the 747 patients (564 males) followed prospectively have received treatment with idursulfase on at least one occasion. Patients who had received growth hormone (GH) treatment at any time during enrolment in HOS were excluded from all analyses.

The first height data from all male patients for whom information on growth were available prior to the start of ERT were included in a cross-sectional analysis of height at baseline. The analysis to assess the impact of ERT on growth included patients in HOS who were aged 8–15 years at the start of ERT and for whom data on height were available on at least one occasion within 24 months before or after the start of treatment. 'At the start of ERT' was defined as the time of treatment start +/−3 months. Previous analysis of cross-sectional data from HOS showed that short stature became apparent after approximately 8 years of age; before this, height remained within the normal range. The age group used in this analysis was selected based on these findings: it was expected that patients would be old enough for short stature to be apparent, but young enough that height could still potentially be increased by treatment. Baseline demographics for the population studied are presented in Table 1 alongside data for all patients in HOS aged 8–15 years.

HOS collects information on height measurements made at baseline and during subsequent routine clinic visits. It is recommended that height is measured using a standard technique. Data on concomitant medications (including GH therapy) are collected at the same time points as other measurements.

The extent of disease was determined based on (1) the presence/absence of cognitive involvement, (2) the type of mutation and (3) the functional classification.

Cognitive involvement was defined based on the answer to a yes/no question. Patients for whom 'yes' had been recorded on any clinic visit were deemed to have cognitive involvement for the purposes of this analysis.

Type of mutation was determined based on data on amino acid and/or genomic sequence collected in HOS. Data entered on each sequence were compared with the full gene sequence using a program developed by Professor Andreas Gal (Hamburg, Germany) for use within the outcome surveys. This enabled the sequences to be verified as true mutations. Known mutations were automatically categorized into one of six groups: complete deletion or large rearrangement, deletion, nonsense, missense, splice-site, and insertion or insertion/duplication. Mutations that could not be classified automatically were categorized manually. For the purposes of this analysis, patients were separated into two groups: patients with mutations predicted to be associated with a severe phenotype (complete deletion, large rearrangement, deletion or nonsense mutation) and those predicted to be associated with a less-severe phenotype (all other mutation types). These classifications were based on the experience of the authors. Functional classification was defined for each individual as normal, borderline/educable/trainable or profound impairment.

2.3. Data analysis

The first height data at baseline were plotted against normal height data for boys from the USA [20]. These growth charts have been used in previous studies of patients with Hunter syndrome [9,17].

A z-score (the number of standard deviations from the reference population mean) was calculated for each height measurement using the 2000 Centers for Disease Control growth data; a z-score < -2 is generally considered to be indicative of short stature.

A piecewise regression model was used to analyze age-corrected standardized height scores (z-scores) or actual height measurements made according to time before and after the start of ERT (± 24 months of the start of treatment). Individual analyses were conducted to assess covariates selected by the authors as likely to impact on growth [age at start of ERT (8–11 versus 12–15 years), cognitive involvement (at any time; present versus absent), in puberty at the start of ERT (yes versus no), type of mutation (mutations associated with a severe versus less-severe phenotype)], last-reported functional classification by clinical impression (normal, borderline/educable/trainable or profound impairment). Covariates for the final model were selected based on the results of these individual analyses; significant variables were selected for inclusion in the final model.

A subgroup analysis using height z-scores for those patients with baseline height z-scores < -2 was performed.

2.4. Role of the funding source

Data collection and analysis in HOS are supported by Shire HGT, a business unit within the Shire group of companies. Data review and analysis were conducted by Shire HGT under the direction of the clinical expert members of the HOS Natural History Working Group. Medical writing support was provided by Harriet Crofts and Helen Bremner of Oxford PharmaGenesis™ Ltd and was funded by Shire HGT. The sponsor had no role in the decision to publish the manuscript.

3. Results

3.1. Patient population

As of 23 January 2012, height data before treatment were available for 573 of the 740 males followed prospectively after HOS entry. Six of these patients had received GH treatment and so were excluded from the analysis. There were 137 male patients aged 8–15 years old at treatment start for whom one or more data point was available within 24 months of the start of ERT. Four of these patients had received GH treatment and so were excluded from further analysis. Among the 133 patients eligible for this analysis, ERT was started at a mean (SD) age of 11.3 (2.2) years. Mutation data were available from 99 patients in this group; 29 patients had mutations considered associated with a severe phenotype (a complete deletion, large rearrangement, deletion or nonsense mutation). Cognitive involvement was recorded as present in 66 of the 133 patients. Data on functional classification by clinical impression were available from 96 patients in this group; function was classified as normal in 45 patients, profoundly impaired in 34 patients, and borderline/educable/trainable in 17 patients. At baseline, 93 of the 133 patients were considered to have short stature relative to that expected for their age based on a z-score < -2 (subgroup analysis population).

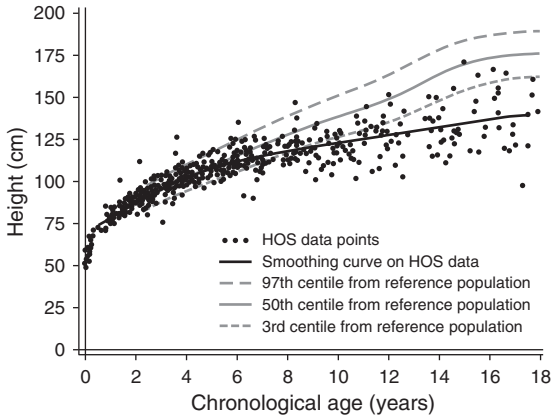

Fig. 1. First height measurement recorded before the start of enzyme replacement therapy in boys enrolled prospectively in the Hunter Outcome Survey (HOS). Patients who had received growth hormone treatment were excluded. Data are plotted relative to reference data from an age-matched population from the USA [20].

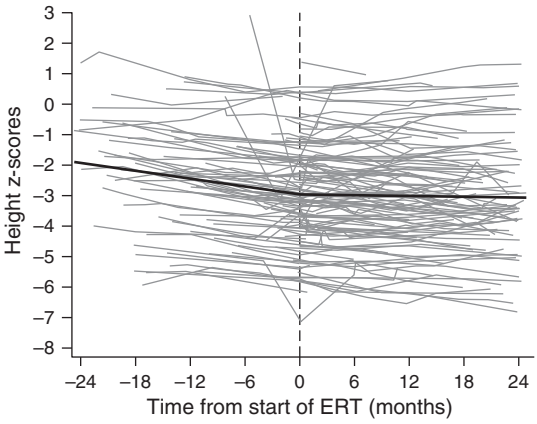

Fig. 2. Regression plot from the raw model without covariate adjustment showing height z-scores before and after the start of enzyme replacement therapy in the study population of 133 patients aged 8–15 years at treatment start in HOS. Gray lines show regression lines for individual patients. The slope of the regression was significantly improved after treatment compared with that before treatment (difference in z-score, 0.038; $p = 0.004$).

3.2. Growth/height in untreated patients in HOS

Cross-sectional analysis of the first baseline height measurement recorded for 567 boys enrolled in HOS showed that height remained within the normal range expected based on age and gender until 8–9 years of age (Fig. 1). Short stature was apparent from this age onwards in most untreated patients with Hunter syndrome. Furthermore, there appeared to be no pubertal growth spurt.

3.3. Effect of ERT on growth

3.3.1. Analysis of height z-scores

Overall analysis from the raw model (without covariate adjustment) using height z-score data from all 133 patients aged 8–15 years at the start of ERT showed that the slope of the regression over time after treatment (in months) was significantly improved compared with before treatment (estimated slopes before and after treatment were −0.043 and −0.005, respectively: difference in the slope, 0.038; $p = 0.004$) (Fig. 2).

3.3.1.1. Covariates. Individual analysis of the potential covariates showed a significant influence on growth of mutation ($p = 0.002$) and age ($p < 0.0001$). There were no differences between groups when stratified according to puberty at the start of ERT, cognitive impairment, or functional classification by clinical impression (Fig. 3).

3.3.1.1.1. Impact of age at start of ERT. Patients with Hunter syndrome aged 8–15 years were shorter on average than their peers. The height deficit was most pronounced in patients aged 12–15 years of age at the start of treatment, as indicated by a lower z-score relative to patients aged 8–11 years at the start of treatment (difference in z-score at the start of ERT, −1.63; $p < 0.001$) (Fig. 3a).

There was no difference in growth velocity (slope) between patients aged 12–15 years at the start of treatment versus those aged 8–11 years. Before treatment, estimated slope difference between the older and the younger age groups was 0.013 ($p = 0.584$), and it was 0.006 ($p = 0.483$) after treatment. The angle of the slope was modified by ERT to a similar degree in both groups (Fig. 3a).

3.3.1.1.2. Puberty at start of ERT. The height deficit in terms of z-score seemed to be slightly more apparent in patients who started treatment during puberty than in patients who were prepubertal at the start of ERT, although this was not statistically significant (difference in z-score at the start of ERT was −0.535; $p = 0.156$). There was no difference in slope in those who had already begun puberty at start of ERT versus those who had not. Before treatment, estimated slope difference was 0.036 ($p = 0.257$), and it was −0.0003 ($p = 0.974$) after treatment. The angle of the slope was modified by ERT to a similar degree in both groups (Fig. 3b).

3.3.1.1.3. Type of mutation. Overall, the height deficit in terms of z-scores was more pronounced in patients with mutations associated with severe phenotypes than in patients with mutations associated with less severe phenotypes; z-scores were significantly lower in those with mutations associated with severe phenotypes than in those with other mutations (difference in z-score at the start of ERT, −1.251; $p = 0.0005$); however, there was no statistically significant difference in slope in those with mutations associated with severe phenotypes versus those with other mutations. Before treatment, estimated slope difference was 0.029 ($p = 0.298$), and it was −0.015 ($p = 0.145$) after treatment (Fig. 3c).

3.3.1.1.4. Presence of cognitive involvement. The deficit in height in terms of z-scores was similar in patients with and without cognitive involvement. There was no difference in z-score for patients with cognitive involvement compared with those without (difference in z-score at the start of ERT, −0.160; $p = 0.579$) (Fig. 3d).

z-Score declined progressively before the start of treatment in patients with or without cognitive involvement. There was a small change in the trajectory of the slope following the initiation of ERT in both groups but there was no difference between the two groups.

3.3.1.1.5. Functional classification. The deficit in height in terms of z-scores was similar in those with normal, borderline/educable/trainable, or profound functional classifications (Fig. 3e). There was no significant change in the trajectory of the slope following the initiation of ERT in the three groups.

3.3.1.2. Final model. The covariates included in the final model were age, the associated age-related interaction terms and type of mutation (without the interaction terms).

The model confirmed that the overall slope of the regression after treatment was significantly improved compared with that before treatment. There was a significant influence of mutation type (height deficit in terms of z-scores more pronounced in patients with deletions/large rearrangements/nonsense mutations than in patients with other mutations, difference in z-score at the start of ERT, −1.22; $p < 0.001$), age (height deficit in terms of z-scores more pronounced in the 12–15-year age group than in the 8–11-year age group, difference in z-score at the start of ERT, −1.61; $p < 0.0001$).

3.3.2. Analysis of height

A similar analysis to that conducted on height z-scores was carried out on height data for all 133 patients aged 8–15 years at the start of ERT. The overall pattern of results was similar to that seen for height z-scores. The slope of the regression after treatment was significantly improved compared with that before treatment (estimated slopes before and after treatment were 0.103 and 0.346, respectively: difference in the slope, 0.243; $p = 0.002$) (Fig. 4).

3.3.2.1. Final model. The final model used for the height analysis was the same as the one used for the z-score analysis. The model confirmed that the overall slope of the regression after treatment was significantly improved compared with that before treatment. There was a significant influence of mutation type (height deficit was more pronounced in patients with deletions/large rearrangements/nonsense mutations than in patients with other mutations, difference in height at the start of ERT, −5.66 cm; $p = 0.008$), age (the 12–15-year age group is taller than the 8–11-year age group, difference in height at the start of ERT, −5.27 cm; $p = 0.005$). The difference in the slope between after and before the start of ERT was 0.257 ($p = 0.002$).

3.3.3. Subgroup analysis results using height z-scores

The same final model was used for the subgroup analysis on those patients with baseline height z-scores < -2 ($n = 93$) (Table 2). The model confirmed that the overall slope of the regression after

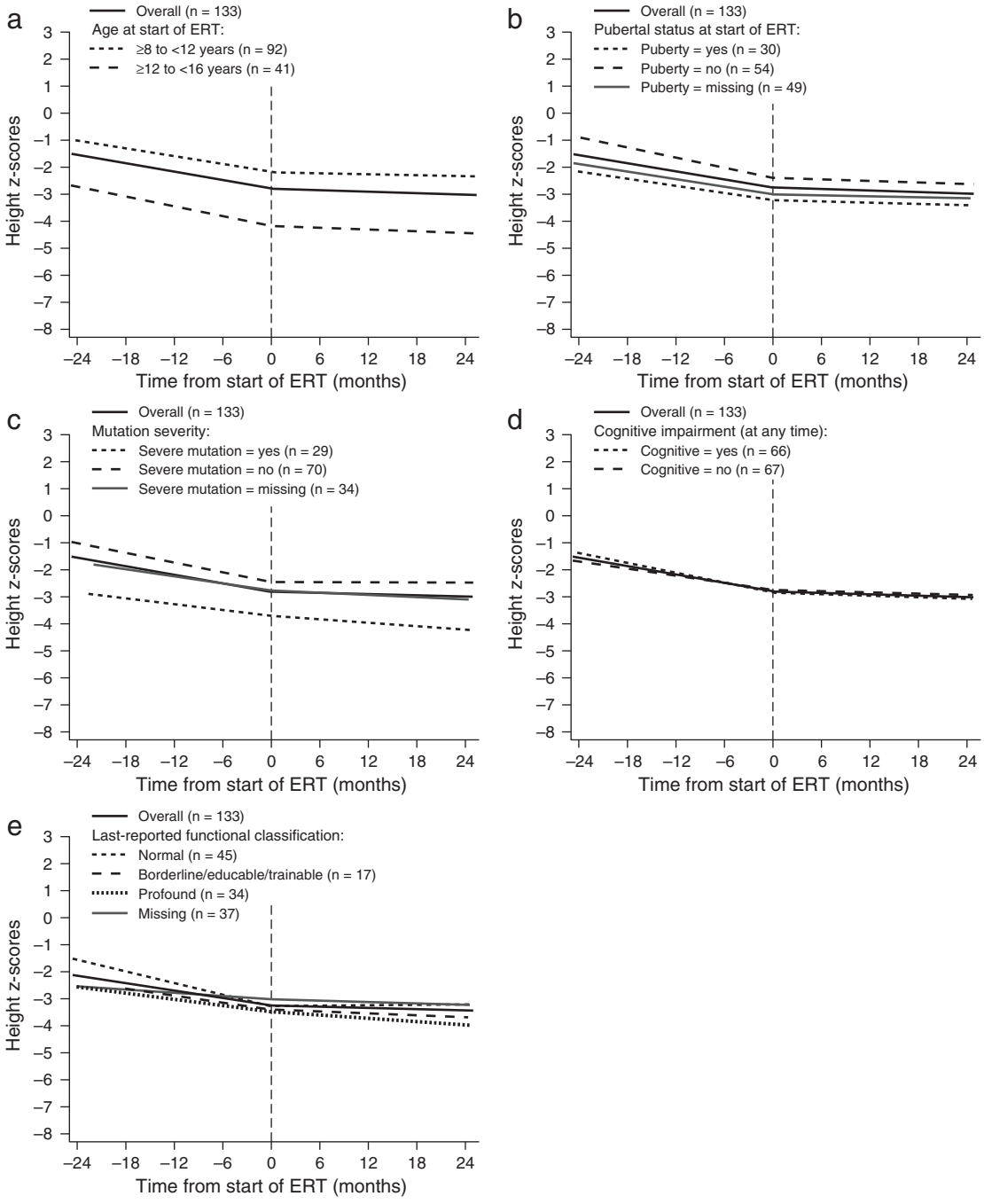

Fig. 3. Regression plot showing height z-scores before and after the start of enzyme replacement therapy for each of the covariates assessed in the study population of 133 patients aged 8–15 years at treatment start in HOS. Data for patients where information on individual variables is missing are labeled as missing. (a) Age at start of ERT. (b) Puberty at start of ERT. (c) Type of mutation. (d) Cognitive impairment (at any time). (e) Last-reported functional classification.

treatment was significantly improved compared with that before treatment. There was a significant influence of mutation type (height deficit in terms of z-scores more pronounced in patients with deletions/large rearrangements/nonsense than in patients with other mutations, difference in z-score at the start of ERT, −0.709; $p = 0.008$) and age (height deficit in terms of z-scores more pronounced in the 12–15-year age group than in the 8–11-year age group, difference in z-score at the start of ERT, −0.860; $p = 0.0001$).

4. Discussion

Growth impairment is a widely recognized manifestation in patients with Hunter syndrome that so far has received limited attention in the literature. Using data from HOS, we can now start to look at growth over an extended time period in a large group of patients with this rare condition and to assess the effects of ERT on this manifestation. Results from the present study support findings from smaller-scale studies showing the extent of growth impairment and also provide evidence that, in addition to other known effects [17,18], ERT may have a positive effect on growth rate in patients with Hunter syndrome. There is also the potential for further long-term follow-up as the HOS patient population increases.

Overall, the results of this analysis support previous reports that short stature first becomes apparent in untreated patients with Hunter syndrome after about 8 years of age [6,10,12]. Visual inspection of cross-sectional data also suggests that the expected pubertal growth

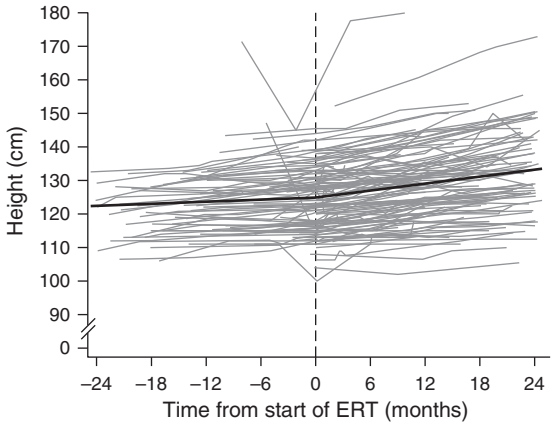

Fig. 4. Regression plot from the raw model without covariate adjustment showing height data before and after the start of enzyme replacement therapy in the study population of 133 patients aged 8–15 years at treatment start in HOS. Gray lines show regression lines for individual patients. The slope of the regression was significantly improved after treatment compared with that before treatment (difference in z-score, 0.243; p = 0.002).

spurt may be absent, although this requires confirmation. It is, however, important to note that there is greater variability in height and growth between patients after 8 years of age, with most individuals having severe short stature but others having normal stature during their mid-teenage years.

Looking at the effect of treatment, it is apparent that ERT had a positive impact on growth rate in these patients with MPS II. This was reflected in the significant change in growth velocity as indicated by the slope of the regression after treatment that showed the degree of deviation in height relative to the reference population was decreased by therapy. This effect was apparent to a similar degree in both of the age groups studied. This effect appeared not to be related to the timing of treatment relative to puberty, as this variable was not associated with differences in height deficit or response to treatment. Thus, although ERT improved growth rate, the benefits were greatest in those who started treatment at an earlier age. This finding is similar to observations in GH-treated children, where better growth responses were observed in those receiving GH from an earlier relative to a later age [21]. Improvements in growth observed in the current study are similar to those obtained during the first 24 months in children treated with GH [22–24]. One recent study of data from an observational database, for example, showed changes in mean height standard deviation scores (z-scores) ranging from 0.5 to 0.85 after 12 months and 0.82 to 1.20 after 24 months of GH therapy in a range of patient groups aged 6.4–11.2 years at baseline [24] (predicted difference in height z-score after 12 months and 24 months in the current study was 0.47 [95% confidence interval, 0.02–0.79] and 0.94 [95% confidence interval, 0.30–1.58], respectively).

Patients with large deletions, small deletions, large rearrangements or nonsense mutations are generally thought to experience more severe disease on average than patients with missense, splice-site mutations or insertions and insertion/deletions. An interesting finding in the current study was that the overall height deficit before and after the start of treatment was more pronounced in patients with deletions/large rearrangements or nonsense mutations compared with those with other types of mutation; however, the change in the slope in this group in response to treatment was similar to those with other mutations. Thus, this study found no relationship between height deficit or response to treatment and the presence/absence of cognitive involvement or the functional classification as defined in HOS. Although we know that patients in HOS with cognitive involvement die at a younger age than patients without cognitive involvement [8], it is important to note that, unlike MPS I for example, somatic presentation does not necessarily correlate with cognitive involvement and profound functional impairment in patients with Hunter syndrome. However, it is also important to remember that we cannot currently categorize all known Hunter syndrome mutations accurately in terms of disease severity. Furthermore, we must consider that the subjective nature of the yes/no question on cognitive involvement in HOS introduces a bias that may limit the usefulness of this variable in defining clearly all patients with serious neurological involvement in the present study [8]. Thus, further investigation, including additional variables that may provide insight into cognitive impairment and functional status, is required before it is possible to exclude a relationship between these variables and short stature.

The improvement in growth observed in the current analysis is likely to be the result of multiple factors, including both direct effects on the bones and other more general changes in manifestations, although this has yet to be proven. Idursulfase treatment has been shown in clinical trials to improve mobility and to stabilize joint range of motion, particularly the elbow and shoulder, in patients with Hunter syndrome [17,18]. There have also been suggestions that soft tissue joint contractures may improve with ERT [25]. Other general improvements, such as better pulmonary function, may also have a beneficial impact on growth. Based on the results of a study of the effects of ERT in patients with MPS I in which there was substantial growth following 6 years of treatment [26], it will be interesting to evaluate whether there is a greater impact on growth in patients with Hunter syndrome after long-term treatment with idursulfase. It would also be interesting to evaluate further the psychosocial impact of short stature and its amelioration in patients with Hunter syndrome. Despite the many other manifestations of the disease that may affect social functioning and quality of life, for example facial dysmorphism, sleep apnea and difficulties with walking and eating, short stature remains a distinguishing feature of Hunter syndrome and increased final height may have a positive impact on patients' daily lives [9].

The registry-based nature of the current analysis presents limitations that must be considered. As an observational survey, patient enrolment and data entry and collection in HOS is at the discretion of participating physicians who include only information collected during routine clinical practice. As such, data collection is subject to

Table 2
Trend comparison from the final model.

	Patients in the study population[a] (n = 133)		Patients in the subgroup analysis[b] (n = 93)	
	Estimate of slope over time (months) Difference (P value)	95% CI	Estimate of slope over time (months) Difference (P value)	95% CI
Overall trend comparison	0.039 (0.006)	0.012–0.066	0.045 (0.014)	0.009–0.081
Aged 8–11 years at ERT start	0.042 (0.010)	0.010–0.074	0.055 (0.025)	0.007–0.104
Aged 12–15 years at ERT start	0.035 (0.112)	−0.008–0.079	0.034 (0.192)	−0.018–0.087

[a] The study population included all patients in HOS who were aged 8–15 years at the start of enzyme replacement therapy (ERT) and for whom data on height were available on one or more occasion within 24 months of the start of treatment.
[b] Patients in the study population with baseline height z-scores < −2. CI, confidence interval.

certain biases and the number of patients available for study varies depending on the parameter of interest and time frame studied. In addition, all clinical measurements are performed according to the standards of each center. Thus, an inherent limitation is that height may be measured using different methods at different centers. However, it is expected that within each center the same techniques will be used, resulting in accurate reporting of changes in height and growth rate. Despite such considerations, data collected in HOS provide important information about the manifestations of Hunter syndrome and the impact of treatment on patients with this rare condition.

As the number of children enrolled in HOS increases, it will be possible for future studies to follow long-term changes in growth both prior to and during treatment. This may help us to determine whether growth in response to ERT could be a guide to overall treatment outcome or even an endpoint for future studies.

5. Conclusions

In conclusion, the results of this study are consistent with previous smaller scale studies and provide evidence of an impairment in growth in untreated patients with Hunter syndrome and the beneficial effects on ERT on growth.

Conflicts of interest

SAJ has received honoraria for speaking engagements and assistance with travel to conferences from Shire HGT; he is also engaged in ongoing research projects with Shire HGT, Genzyme, BioMarin and Synageva BioPharma.

RP has received travel grants from Shire HGT, Genzyme and BioMarin, research grants from Shire HGT, and honoraria for speaking engagements from Shire HGT and Genzyme.

PH has provided consulting support to and received grant support and honoraria for speaking engagements from Shire HGT and BioMarin.

RG is an investigator on Shire-sponsored clinical trials and has received financial reimbursement for travel expenses and speaker fees from Shire, Genzyme, Amicus, Actelion and BioMarin.

JF is a full-time employee of Shire HGT.

NJM has received financial reimbursement for travel expenses from Shire and BioMarin; she has provided consulting support to Genzyme and is also engaged in ongoing research projects with Shire HGT, Genzyme and BioMarin.

Appendix A. List of HOS investigators

Argentina	
Buenos Aires:	H Amartino
	C Riccheri
Cordoba:	N Guelbert
Austria	
Graz:	M Brunner-Krainz
Salzburg:	F Lagler
Belgium	
Brussels:	L De Meirleir
Brazil	
Fortaleza:	E Ribeiro
Maceio:	E Santana Santos
Porto Alegre:	R Giugliani
	L Jardim
Rio de Janeiro:	R Boy
	M Ribeiro
Salvador:	A Xavier Acosta
Sao Paulo:	AM Martins
Bulgaria	
Sofia:	R Tincheva
Canada	
Calgary:	R Casey
Edmonton:	A Chan
Toronto:	JTR Clarke
	J Raiman
Vancouver:	L Clarke
Croatia	
Zagreb:	I Barišić
	I Barić
Czech Republic	
Prague:	J Zeman
Denmark	
Copenhagen:	A Meldgaard Lund
France	
Lyon:	N Guffon
Paris:	V Valayannopoulos
	B Héron
Marseille:	B Chabrol
Germany	
Berlin:	J Hennermann
Hamburg:	N Muschol
Magdeburg:	S Klose
Mainz:	M Beck
	W Kamin
	C Kampmann
	A Keilmann
	C Lampe
Hungary	
Budapest:	Z Almássy
Ireland	
Dublin:	E Crushell
Italy	
Ancona:	O Gabrielli
Bari:	F Papadia
Bologna:	A Cicognani
Catania:	A Fiumara
Catanzaro:	D Concolino
Firenze:	A Donati
Rome:	C Feliciani
Padova:	M Scarpa
Genova:	M Di Rocco
Monza:	R Parini
Napoli:	G Andria
Netherlands	
Rotterdam:	A van der Ploeg
Poland	
Warsaw:	A Tylki-Szymańska
Portugal	
Lisbon:	A Gaspar
Porto:	E Leão Teles
	E Martins
Russia	
Moscow:	LS Namazova-Baranova
Spain	
Almeria:	J Aguirre
Barcelona:	M del Toro
Esplugues de Llobregat	V Delgadillo
Badalona:	G Pintos-Morell
Badajoz:	E Galán
Huelva:	R Mateos
Las Palmas:	J Carlos Cabrera
Linares:	P Munguira
Madrid:	L González Gutiérrez-Solna
	L López Marín
Murcia:	R Domingo
	E Guillén-Navarro
Ourense:	G Novoa
Palma de Mallorca:	B de Azua
Salamanca:	A Hernández
Santiago:	ML Couce
Sevilla:	D Lluch
	A González-Meneses
Valencia:	J Dalmau
Valladolid:	C Alcalde
Zaragoza:	MA Torralba
Sweden	
Gothenburg:	N Darin
Halmstad:	N Nilsson

(continued on next page)

Lund:	D Papadopoulou
Stockholm:	K Naess
	I Dahlman
Switzerland	
Bern:	M Gautschi
Taiwan	
Taipei:	S-P Lin
United Kingdom	
Birmingham:	S Vijay
London:	A Vellodi
Manchester:	JE Wraith
	S Jones
	C Hendriksz
	R Sharma
United States of America	
Atlanta, GA:	S Shankar
Baltimore, MD:	G Maegawa
Boston, MA:	K Sims
Chapel Hill, NC:	J Muenzer
	J Loehr
Charlottesville, VA:	W Wilson
Chicago, IL:	B Burton
Cincinnati, OH:	N Leslie
Columbus, OH:	K McBride
Denver, CO:	J Thomas
Greenville, SC:	C Rogers
Hartford, CT:	R Greenstein
Houston, TX:	C Eng
Iowa City, IA:	V Sheffield
Jackson, MS:	O Abdul-Rahman
Kansas City, MO:	L Smith
Miami, FL:	P Jayakar
Minneapolis, MN:	N Mendelsohn
	C Whitley
New York, NY:	G Pastores
Norfolk, VA:	V Proud
Oakland, CA:	P Harmatz
Omaha, NE:	W Rizzo
	R Lutz
Orange, CA:	R Wang
Paterson, NJ:	J Ibrahim
Philadelphia, PA:	C Ficicioglu
Phoenix, AZ:	K Aleck
Portland, OR:	R Steiner
Salt Lake City, UT:	D Viskochil
Seattle, WA:	CR Scott
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