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ORIGINAL ARTICLE

Treatment of mucopolysaccharidosis type II (Hunter syndrome) with idursulfase: the relevance of clinical trial end points

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Abstract The current treatment of mucopolysaccharidosis type II (MPS II, Hunter syndrome) is enzyme replacement therapy with recombinant idursulfase (Elaprase®). The efficacy of ERT was established based primarily on reduction in urine glycosaminoglycans:creatinine (GAG:Cr) ratio and improvement in a composite score of predicted forced vital capacity (FVC% predicted) and 6-min walk-test distance (6MWT). We retrospectively reviewed these parameters in 11 boys with MPS II treated with idursulfase between April 2007 (or the time of diagnosis) and February 2010. Some results were inconsistent with published trial data, and there was only a small number of analyzable results obtained for the FVC% predicted and 6MWT. A major drawback was the high prevalence of neurological involvement and young age of patients in the study cohort compared with the clinical trials. This study emphasizes the limitations of the current tools utilized to monitor ERT efficacy and MPS II disease burden in clinical practice.

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Introduction

Mucopolysaccharidosis type II (MPS II, Hunter syndrome) (MIM #309900) is an X-linked lysosomal storage disorder (LSD) caused by deficiency in the enzyme iduronate 2-sulfatase (I2S), the role of which is to remove O-linked sulfates from the glycosaminoglycans (GAGs) dermatan and heparan sulfate. Subsequent tissue accumulation occurs to a variable extent, primarily in the airway, skeleton, viscera and – in some – central nervous system (CNS). The efficacy of enzyme replacement therapy (ERT) with idursulfase was established based primarily on change from baseline in urine GAG:creatinine (Cr) ratio in the phase I/II trial (Muenzer et al 2007) and improvement in a composite score of percentage of predicted forced vital capacity (FVC% predicted) and 6-min walk test (6MWT) in the phase II/III trial (Muenzer et al 2006) (Table 1). Clinical trial end points should be relevant to the disease process, reliable, accurate, and responsive to change in disease state (International Conference on Harmonisation 1998). Understanding the relevance to everyday clinical practice of the end point chosen is important for evaluating treatment efficacy. The objectives of this study were to evaluate the response to idursulfase in a cohort of MPS II patients, specifically assessing the relevance of these published end points to everyday clinical practice.

Methods

This was a retrospective study. The study group consisted of all patients diagnosed with MPS II at Great Ormond Street Hospital (GOSH) and treated with idursulfase between April 2007 and February 2010. The criteria for treatment were based on the UK guidelines for management

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Table 1 Summary of the study design and patient selection for the phase I/II and II/III clinical trial compared with this study

	Phase I/II	Phase II/III	This study
Number	12 patients	96 patients	11 patients
Inclusion and exclusion criteria	Age >5 years; height: 119-151 cm; cooperative; clinical diagnosis of MPS II	Age 5 to 31 years old; height 122-130.6 cm; able to reproducibly perform LFT; clinical diagnosis of MPS II; FVC <80% predicted: Exclusion criteria - tracheostomy, BMT or severe CNS disease	All patients with a clinical diagnosis of MPS II commenced on ERT from April 2007 to February 2010 (age mean 4 years, range 10 months to 8 years; height 103.9-122.8cm). Exclusion: involvement in clinical trial
Study design	Six-month RDBPCT placebo vs 0.15, 0.5, 1.5 mg/kg/week idursulfase; 6-month OLCS	53 week RDBPCT with three arms: placebo vs fortinightly vs weekly 0.5 mg/kg idursulfase	Retrospective review of notes, lab, and respiratory function tests; treatment 0.5 mg/kg/week of idursulfase
Primary end points	Urine GAG:Cr ratio % change from baseline to 5, 13 and 25 weeks	Composite score of change from baseline to 53 weeks in 6MWT and FVC% predicted	GAG:Cr ratio initially weekly, 2 weekly, then 3 and 6 monthly; 6 monthly FVC% predicted and 6MWT where able
Secondary end point	Echo, 6MWT distance, LFT, MRI, passive joint ROM; sleep study at baseline to 13 and 24 weeks for RPCT and 25 and 52 weeks for OLCS for: Echo, 6MWT, LFT, spleen and liver size measured by MRI and sleep study	Individual change from baseline to 18, 36 and 53 weeks for: 6MWT, FVC% predicted, absolute FVC, liver and spleen volumes measured by MRI, urine GAG:Cr ratio, passive joint ROM	Not applicable

GAG glycosaminoglycans, *Echo* echocardiography, *6MWT* 6-minute walk test, *LFT* lung function test, *MRI* magnetic resonance imaging, *ROM* range of motion, *MPS II* mucopolysaccharidosis type II, *BMT* bone marrow transplant, *CNS* central nervous system, *ERT* enzyme replacement therapy, *GOSH* Great Ormond Street Hospital, *FVC* forced vital capacity, *RDBPCT* randomised double blind placebo controlled trial, *RPCT* randomized placebo controlled trial, *OLCS* open label crossover study

of MPS II (http://www.specialisedservices.nhs.uk/index.php/key-documents/lysosomal-storage-disorders/). Notes, lung function tests (LFT) and urine GAG:Cr ratios were reviewed. Urine GAG:Cr ratios were performed initially weekly, fortnightly, then 3 monthly for the first year, followed by 6 monthly. The 6MWT was performed as per the American Thoracic Society (ATS) guidelines (2002), and FVC% predicted was based on ATS and European Respiratory Society (ERS) standards for spirometry, adapted for children (Kirkby et al 2008). Attempts at 6MWT and lung function were made at baseline and yearly thereafter.

Statistical methods

The change from baseline GAG:Cr ratio was calculated at 8, 52, and 120 weeks (or the nearest available measurement) following commencement of treatment. These dates were chosen because 53 weeks was used in the phase II/III clinical trial (Muenzer et al 2006), and the study duration was completed in most patients by 120 weeks. Where the exact date was not available, an average of the two nearest GAG:Cr was used. Patients on treatment <52 weeks were excluded from these calculations. A two-tailed, paired *t* test was used to determine whether there was a significant difference in change from baseline GAG:Cr ratio between eight and 52 weeks and between 52 and 120 weeks. The change in normal reference range for age must be taken into account when interpreting the relevance of this data.

Antibodies

Samples were taken for immunoglobulin G (IgG) antibodies and neutralizing IgG antibodies at regular intervals. The tests were performed by Shire Pharmaceuticals using an enzyme-linked immunosorbent assay (ELISA)-based assay called confirmation-specific assay (CSA) that detects antibodies to Elaprase®. Specific IgG and IgE antibodies were looked for. Positive results were confirmed with a radioimmune precipitation (RIP) assay as per the phase II/III trial (Muenzer et al 2006).

Results

Fourteen boys were identified. Of these, three were included in the phase II/III trial, there was insufficient data available, and they were therefore excluded from the study. The age at commencement of ERT ranged from 1 months to 8 years and 8 months. The mean period of follow-up was 22.1 months, with a range of 5–35 months. The height range was 103.9-122.8 cm and the age range is seen in Table 2. The height range was 103.9-122.8 cm. Evidence of CNS disease based on clinical assessment from the primary

Table 2 Summary of the 11 patients identified with mucopolysaccharidosis type II (MPS II) at the Great Ormond Street Hospital (GOSH) treated between April 2007 and February 2010. A 6-min walk-test (6MWT) distance, and percent predicted forced vital capacity (FVC% predicted) data was only available for four of the 11 patients. Neutralizing antibody data from Shire Pharmaceuticals was available for five of the 11 patients

Patient	Age (commenced ERT)	Period of follow-up	CNS disease	6MWT and FVC% predicted data	Neutralizing antibody
1	21 months	6 months	Yes	N/A	N/A
2	4 years	2 year 5 months	Yes	N/A	Negative
3	8 years 8 months	1 year 9 months	No	Yes	Negative
4	3 years 7 months	2 years	Yes	Attempt with parent	Positive (84.2%)
5	4 years 4 months	5 months	Yes	N/A	Positive (67.8%)
6	5 years 11 months	2 years 5 months	Yes	Yes	Negative
7	7 years 5 months	2 years 10 months	No	Yes	Negative
8	5 years 4 months	2 years 10 months	No	Yes	Negative
9	13 months	2 years 11 months	No	N/A	N/A
10	14 months	2 years 6 months	Yes	Attempt with parent	N/A
11	10 months	2 years 6 months	Yes	N/A	N/A

ERT enzyme replacement therapy, *CNS* central nervous system, *N/A* not available

consultant, and in some cases formal assessment, was present in 7/11 patients (Table 2).

Urine GAG:Cr ratio

Urine GAG:Cr ratios were available for all patients (Fig. 1). Patients 1 and 5 were excluded from statistical analysis, as they were on treatment for <52 weeks. A trend toward rapid reduction was seen in the first 8 weeks of treatment. This was then followed by a relative stabilization. A significant change from baseline continued to occur between 8 and 52 weeks (P=0.015). There was no significant difference in change from baseline between 52 and 120 weeks (P=0.096).

Lung function and 6 -min walk-test distance

Analyzable LFT and 6MWT data were available for only four patients: the rest were either too young (four patients) or noncompliant due to CNS disease (three patients) (Figs. 2 and 3). Patient were <120 cm tall, on which normative spirometry data are based (Rosenthal et al 1993). By the end of the study, one patient (patient 6) had grown from 112 cm to 126 cm, which may adversely affect interpretation of results. A trend toward reduction in FVC% predicted was seen throughout the observation period in two of these four patients. An increase in 6MWT distance of between 35 and 97 m was seen (Table 3) (Fig. 3).

Table 3 Change in percent predicted forced vital capacity (FVC% predicted) and 6-minute walk test (6MWT) distance measured during treatment with idursulfase. Patients 3 and 7 did not have baseline lung function test (LFT) and 6MWT but were tested at approximately 20 and 50 weeks into treatment

Patient	Change in FVC% predicted	Change in 6MWT
3	−1%	+97 m
6	−13%	+35 m
7	−1%	+77 m
8	−8%	+70 m

Antibodies

Antibody results were available for seven of 11 patients, two of whom were positive for neutralizing antibodies. All patients who had 6MWT and FVC% predicted data had results available, which were negative.

Discussion

This study retrospectively reviewed 11 patients diagnosed with MPS II and commenced on ERT after idursulfase became available for general use in England in April 2007. The ability to measure treatment outcomes accurately is crucial, as idursulfase is a potentially life-long and expensive therapy. In addition, many pharmaceutical funding bodies are now demanding this. The primary objective of this study was therefore to evaluate the relevance of the tools utilized in the clinical trials, namely FVC% predicted, 6MWT distance (Muenzer et al 2006), and GAG:Cr ratio (Muenzer et al 2007) to our clinical practice.

The greatest difference between the clinical trial and this study was patient characteristics. Inclusion criteria for the phase II/III trial resulted in a study population quite different from those encountered in everyday practice. Specifically, the patients were taller than 120 cm, older

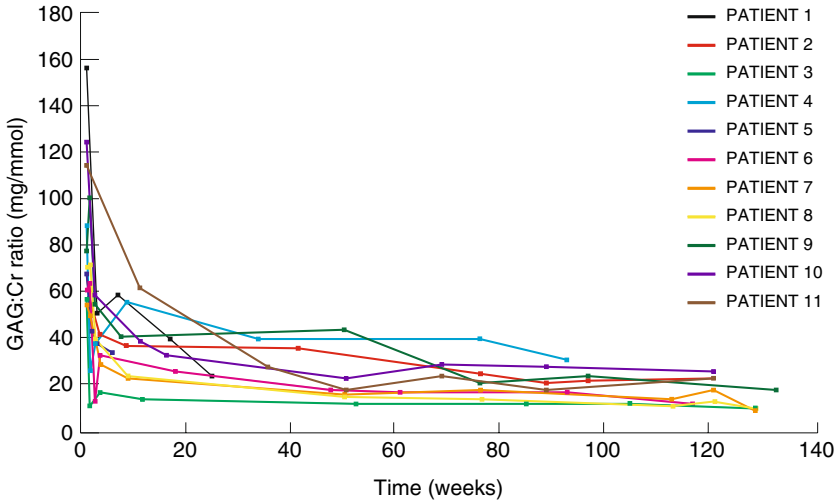

Fig. 1 Urinary glycosaminoglycans:creatinine (GAG:Cr) ratio recorded, in weeks, over time from commencement of idursulfase for 11 patients. Patients 4 and 5 were positive for neutralizing antibodies

than 5 years, and needed to be able to perform the tests required (Muenzer et al 2006). This last criterion essentially results in the exclusion of patients with significant CNS disease. In contrast, our cohort was younger (age range 10 months to 8.7 years compared with 11.8–16.2 years in the phase II/II trial cohort) and shorter (103–112 cm in five of 11 patients where data was available compared with 121.9–131.1 cm in the trial cohort). Eight of the 11 patients had CNS disease. Three of the eight patients who were old enough to perform 6MWT and spirometry had neurological involvement, which adversely affected compliance.

Clinical end points should ideally be disease specific (ICH Harmonised Tripartite Guideline Harmonisation 1998) and should be responsive and relevant to change in disease burden (Christensen 2008). Spirometry results reflect the obstructive and restrictive airway disease brought about by the mucosal and chest-wall manifestations of MPS II. The 6MWT is a submaximal exercise test that reflects the integrated function of all systems utilized in day-to-day exercise. Normal values for children are available (Lammers et al 2008), and it is an established tool for monitoring disease burden in children with pulmonary and cardiac disease, juvenile arthritis, and spina bifida (Hassan et al 2010). Performance and interpretation of FVC% predicted and 6MWT distance is dependent on cognitive ability, practice effect, cooperation, and the patient's ability to form a seal around and/or avoid obstructing the spirometry mouthpiece, which MPS II patients can find difficult due to thickening of the tongue and lips. This was highlighted in our study where there was no reliable data in seven of 11 patients. Another problem was the short stature that is a feature of this condition. The majority of data available in this cohort was in patients who did not reach the minimum height threshold on which normative data for spirometry is based (Rosenthal et al 1993). Unlike previously seen in the phase II/III trial (Muenzer et al 2006), the FVC% predicted decreased or did not change in all patients. However, a trend toward improvement in 6MWT distance was seen, with an average improvement of 69.7 m (Table 3) compared with 44.3±12.3 m in the clinical trial (Muenzer et al 2006). Use of FVC% predicted instead of absolute FVC attempts to take into account any growth that may occur over the study period. However, this confounding factor is not addressed in the 6MWT. The average growth in the study period was 9.8 cm, which may provide part of the explanation for this improvement. Interpretation of the significance of this data is difficult given the small numbers.

Urine GAG:Cr ratio was initially established as a diagnostic and screening tool for mucopolysaccharidoses (Gallegos-Arreola et al 2000, Byers et al 1998). There is no

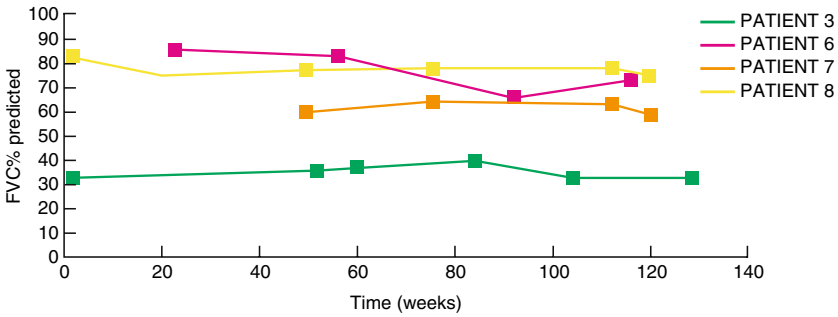

Fig. 2 Percent predicted forced vital capacity (FVC% predicted) over time, in weeks, from commencement of idursulfase for patients 3, 6, 7, and 8

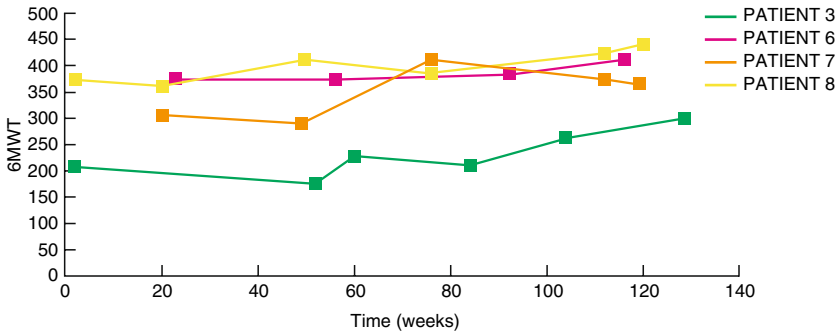

Fig. 3 Six-minute walk-test (6MWT) distance in meters over time from commencement of idursulfase in weeks

evidence that it is useful for monitoring total body burden of disease, as urinary GAG excretion is likely to predominately represent renal storage. It is affected by height, body mass, and age, and so the normal range changes, at times abruptly, between age groups. Other factors affecting GAG:Cr ratio include tissue damage/turnover and renal function (Mabe et al 2004). These factors complicate the interpretation of change from baseline data. In lieu of another useful biomarker, however, it is commonly measured, as urine is easy to collect and relatively simple to process. Urine GAG:Cr ratios were available for all patients from commencement of ERT. A trend toward the normal followed by relative stabilization just above this range was seen in all patients. This trend has been reported previously, but in the phase II/III trial, 40.6% achieved the normal range by 53 weeks (Muenzer et al 2006). In our cohort, normal values were reached in only two of 11 patients. In some patients, it reduced more slowly; the reason for this was not immediately apparent. Once this plateau was reached at approximately 52 weeks post treatment, there was no significant change from baseline to 120 weeks. Neither the phase I/II nor II/III trials studied patients beyond 53 weeks. The lack of change suggests either that disease manifestations stabilize with time, or (and in our opinion, more likely) the GAG:Cr ratio is unhelpful as a long-term monitoring tool for assessing the burden of disease caused by ERT sanctuary sites.

In interpreting the outcome of ERT, the possible effect of antibodies should be considered. It has been shown, for example, that in patients with Fabry disease treated with agalsidase beta, that development of high titers of IgG antibodies may impair the effects of treatment (Bénichou et al 2009). Similar effects may well be encountered in treating other storage diseases. Two of our patients developed neutralizing antibodies (Table 2). Patient 4 had the highest titres of the two and failed to reach the normal GAG:Cr range over a 2-year period of treatment. He also had the highest GAG:Cr levels of all patients in the cohort (Fig. 1). Patient 5 was followed with GAG:Cr ratios for only five months before treatment was withdrawn due to progressive CNS disease. The very small numbers makes the significance of these antibody results and the impact they have on our conclusions difficult to interpret.

Despite the imperfections of the tools used in this study and the clinical trials, there have been few alternative clinical end points or outcome measures suggested for MPS II. One of the first signs of efficacy is improved well-being, energy, and ability to partake in activities of daily living (Wraith et al 2008). The 6MWT is used in an attempt to objectively quantify this. Gait is also thought to be a good measure of complex processes and therefore should reflect change in multisystem diseases, such as MPS II. One study looked at the use of GAITRite™ in six boys with MPS II. This is an electronic pressure-sensing walkway that reliably measures the qualitative and quantitative aspects of gait. Three out of six patients were <5 years of age, and all three had CNS disease. The results were reproducible even in these patients, suggesting it may be a useful tool in this cohort (Wood et al 2009). White-matter N-acetylaspartate, choline, glutamate, and myoinositol peaks on brain magnetic resonance (MR) spectroscopy (Davison et al 2010) and reduction in brain-tissue volumes using automated volumetric analysis of brain MR imaging (Fan et al 2010) have been shown to reflect changes in clinical CNS disease burden. As per the authors conclusions, in each of these studies, none are as yet validated tools for monitoring disease burden in MPS II but may be promising if larger, multicenter cohorts can be evaluated.

In summary, the objective of this retrospective study was to assess the relevance of clinical trial endpoints to monitoring disease burden for MPS II patients in clinical practice. It is difficult to make conclusions about absolute results due to the small numbers in this cohort. It does appear that some data obtained in clinical trials and our clinical practice differed, particularly with respect to GAG:Cr ratio and FVC% predicted. However, the results obtained from our cohort for 6MWT were similar. The different patient demographics and possibly the presence of neutralizing antibodies could explain result discrepancies. In addition, although the majority of patients with MPS II have some degree of neurological symptoms (Wraith et al 2008), such patients were excluded from the clinical trials.

The presence of CNS disease in this cohort impacted on the ability to obtain interpretable FVC% predicted and 6MWT data. This study demonstrates the need for more population-appropriate, validated clinical outcome measures to assess the efficacy of this important and potentially life-long therapy in everyday practice, particularly in patients <5 years of age and in those with CNS disease.

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