Idursulfase for enzyme-replacement therapy in mucopolysaccharidosis II

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Hunter syndrome (mucopolysaccharidosis II) is a rare, X-linked disorder caused by the missing or deficient lysosomal enzyme, iduronate-2-sulfatase, which leads to tissue and organ accumulation of glycosaminoglycans, resulting in multisystem dysfunction with death occurring most commonly in the first or second decade of life. Enzyme-replacement therapy with idursulfase (recombinant human iduronate-2-sulfatase) has been shown in a Phase II/III clinical trial to statistically significantly improve the primary end point – the sum of ranked changes in 6-min walking test distance and ranked changes in percentage predicted forced vital capacity compared with placebo – with the improvement being larger in the group treated with weekly doses compared with those treated every other week. Significant reductions in spleen and liver volume were also observed. Suspected hypersensitivity reactions were observed during the infusions in some patients, but were successfully managed, and no patients discontinued therapy. Idursulfase is now approved in the USA and EU and may offer the opportunity to affect the progression of Hunter disease in treated patients.

Mucopolysaccharidosis II (MPS II/Hunter syndrome) was first described by Charles Hunter [1], and is one of approximately 40 heritable lysosomal-storage diseases (LSDs) that are each caused by a missing or deficient distinct lysosomal enzyme. These deficiencies are commonly caused by a mutation involving the enzyme itself, although, in some cases, mutations of other proteins (e.g., activators or transporters) or extralysosomal enzymes (e.g., mucolipidosis II and IIIA [2]) are the cause. In MPS II, the missing or deficient enzyme is iduronate-2-sulfatase (I2S), which catalyzes a step in the catabolism of glycosaminoglycans (GAGs) – the cleaving of O-linked sulfate moieties [3]. MPS II is X-linked and nearly exclusively affects males, although the phenotypic expression in females, which occurs due to skewed X-chromosomal inactivation or chromosomal abnormality, has been reported [4,5]. The syndrome occurs in all ethnic groups with an estimated incidence of 1 in 100,000 male births [6–8]. The gene coding for I2S resides at position Xq28 [9], and many mutations responsible for I2S deficiency have been described, ranging from single-point mutations to complete deletions of the gene [10–14].

The signs and symptoms of MPS II are caused by the progressive accumulation of the GAG dermatan sulfate and heparan sulfate within various tissues and organs, including liver and spleen, heart, skin, central and peripheral nervous system, bones and joints [15]. The effects of this accumulation become apparent in the first decade of life, with the most common presenting signs being coarseness of facial features [16,17] or the appearance of whitish papules or nodules creating a 'pebbly' appearance to the skin of the chest and scapular regions [18,19]. Oropharyngeal GAG deposition results in abnormal dentition, macroglossia and enlargement of the tonsils and adenoids. These obstructions, coupled with GAG deposition within the respiratory system, commonly cause acute respiratory difficulties and sleep apnea [20,21]. The heart is also affected, with GAG deposition causing myocardial enlargement and valvular dysfunction [22,23]. Hepatosplenomegaly is a common finding, resulting in gross abdominal distension [15,17]. Linear growth may be normal until 6–8 years of age, but slows profoundly thereafter [16,17]. Skeletal malformations, collectively known as dysostosis multiplex, are nearly universal, and most patients have progressive joint stiffness accompanied with lack of mobility. Hearing loss appears to be universal [15].

The phenotypic expression of MPS II is quite variable with respect to the presence and severity of the signs and symptoms listed above. Two forms of MPS II, mild or attenuated and severe [16,17], have been historically recognized, but it is becoming commonly accepted that these designations represent the extremes of what is a continuous spectrum of phenotypic expression. In the most

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severe form, the onset occurs between the ages of 2 and 4 years and is characterized by severe neurological involvement leading to impaired intelligence [15,16]. In these patients, death occurs in the first or second decade of life, with the most common causes being progressive neurological involvement, obstructive respiratory disease and/or cardiac failure [15]. By definition, patients with the attenuated form of MPS II demonstrate normal intellectual development with minimal neurological difficulties, but still exhibit multisystemic somatic involvement [15]. Although some patients with the attenuated form of MPS II survive into the fifth or sixth decade of life, death usually occurs in early adulthood, with airway obstruction and cardiac failure being the most common causes [15]. Some have suggested that different mutations may explain the variability of expression of MPS II, but the results of these analyses have been inconclusive [9,12,24].

Management of MPS II

Management of MPS II is palliative and focused on symptoms. For example, surgery has been used to relieve airway obstruction [20]. Surgery to reduce obstruction combined with continuous positive airway pressure is reported to successfully treat sleep apnea [21]. Others have attempted to treat the underlying metabolic defect with bone marrow [25–28] or unrelated cord blood transplantation [29], with the hope that successfully transplanted cells would produce sufficient I2S to act systemically. The results of these small studies have been mixed, and long-term follow-up is limited. Because of these disappointing results and the substantial morbidity risk associated with the transplant procedures, their use remains controversial [25].

Enzyme-replacement therapy

Advances in biotechnology have resulted in the ability to produce large quantities of human proteins that have been used for enzyme-replacement therapy (ERT) in the treatment of other LSDs. Examples include glucocerebrosidase for Gaucher disease [30], α-galactosidase A for Fabry disease [31,32], α-L-iduronidase for MPS I [33] and *N*-acetylgalactosamine-4-sulfatase for MPS VI [34]. The greatest experience with ERT is in the use of glucocerebrosidase for non-neuronopathic (type 1) Gaucher disease. More than 3200 patients have been treated with glucocerebrosidase and have experienced reversal of anemia, thrombocytopenia and organomegaly, as well as a reduction in frequency and severity of painful bone crises [35]. To date, ERT has not been reported to improve the central nervous symptom manifestations of LSDs. The experience with ERT in the other LSDs listed above is not as extensive, but in each case, a reduction in plasma and/or urine substrate levels in addition to clinical benefits have been reported. In the remainder of this review, the development and clinical testing of idursulfase (recombinant human I2S, Elaprase™, Shire Human Genetic Therapies, Inc.) for ERT in MPS II will be discussed. Idursulfase was approved for marketing by the US FDA on July 24, 2006 for the treatment of MPS II. Marketing authorization in the EU for the use of idursulfase for the long-term treatment of patients with MPS II was granted by the European Commission on January 8, 2007. The approved dose is 0.5 mg/kg infused intravenously every week.

Idursulfase chemical profile

Idursulfase was developed as a replacement for the missing or deficient enzyme I2S in the treatment of MPS II. Idursulfase is produced by genetic engineering in a continuous human cell line, which was produced by transfecting HT-1080, a well-characterized human cell line, with an expression plasmid encoding the human *I2S* gene. Idursulfase is a protein of approximately 76 kDa and is expressed as a single polypeptide chain of 550 amino acids that includes a 25-amino acid signaling sequence that is cleaved prior to secretion [36]. Thus, idursulfase has the same amino acid sequence as the native human enzyme. The enzyme contains eight N-linked glycosylation sites that are occupied by complex, hybrid and high mannose-type oligosaccharide chains; in particular, idursulfase contains mannose-6-phosphate (M6P) and sialic acid residues. The M6P residues are essential for receptor-mediated cellular internalization and trafficking of the enzyme to the lysosome, and the sialized glycans prolong the plasma half-life of idursulfase (see later). Because idursulfase is made in human cells, its glycosylation pattern is similar to that of the native human enzyme. Approximately 50% of the cysteine 59 is converted to formylglycine, a post-translational modification that is essential for enzymatic activity [36].

Glycosylation plays an essential role in determining the pharmacokinetics, biodistribution and biological activity of glycoproteins such as

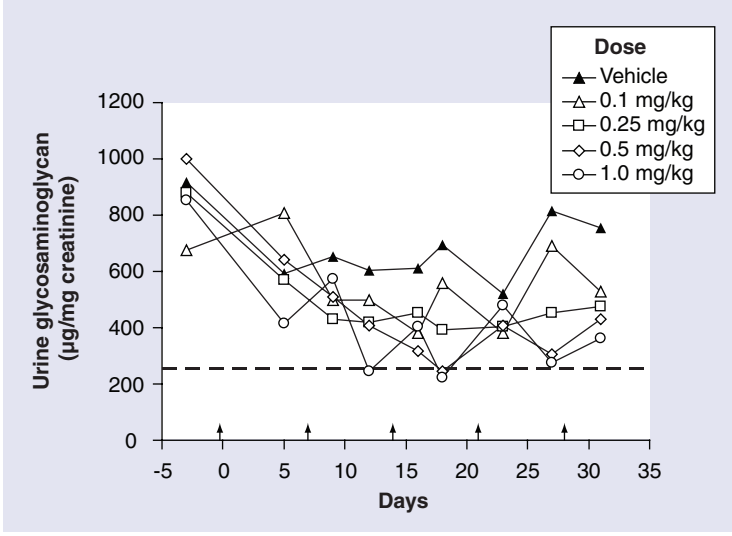
idursulfase. Sufficient sialic acid residues are necessary to prevent rapid scavenging by the liver via asialoglycoprotein receptors, and M6P moieties serve to direct idursulfase into cells and to the lysosomes. Cellular internalization of idursulfase is mediated by the binding of M6P moieties on idursulfase to cell-surface M6P receptors, providing a receptor-mediated uptake mechanism for the enzyme [37,38]. A similar M6P receptor-mediated process directs the enzyme to the lysosome [38]. As is true with most lysosomal hydrolases, idursulfase is inactive at neutral pH and requires the acidic environment of the lysosome for the pharmacodynamic activity of the enzyme [39].

Preclinical testing

Pharmacodynamics

All preclinical pharmacodynamic studies have been performed with male mice lacking the gene for I2S. This knockout mouse (*I2S*-KO) develops many of the characteristics of MPS II in humans, including coarse features, skeletal defects and elevations in urine and tissue GAG [40]. This model was used to evaluate the effect of idursulfase on urine GAG as well as on tissue GAG content. Urine and tissue extract GAG concentrations were quantified by a colorimetric assay using 1,9-dimethylmethylene blue dye [41,42].

Figure 1. Effect of idursulfase on urine glycosaminoglycan in a knockout mouse model of mucopolysaccharidosis II.



Dotted line represents the average urine glycosaminoglycan level in wild-type mice. Arrows indicate when mice were dosed with idursulfase. Each point represents the pooled urine of three to four mice.
Data from [43].

Urine GAG levels were reduced following two to three weekly doses of idursulfase at doses ranging from 0.1 to 1 mg/kg intravenously with the levels approaching those in the wild-type mice in the 0.5- and 1.0-mg/kg dosing groups (**Figure 1**) [43]. Following five weekly doses of idursulfase, liver and spleen GAG levels were reduced to those found in the wild-type mice at doses as low as 0.1 mg/kg (**Table 1**). Similar reductions were also found in the heart, kidney, lung, skin and skeletal muscle, with the greatest reductions in the mice treated with the highest dose (1.0 mg/kg) [43].

Experiments were conducted to determine the effect of dosing frequency on the reduction in urine GAG and tissue GAG levels. *I2S*-KO mice were treated with a single dose, weekly doses, every-other-week (EOW) doses or monthly doses of idursulfase at 1.0 mg/kg/dose for periods up to 6 months [43]. KO mice receiving a single or monthly infusions of idursulfase (1.0 mg/kg) demonstrated a reduction in urine GAG to levels seen in wild-type mice, but the levels returned to pretreatment values within 4 weeks. After 8 weeks of treatment, liver and spleen GAG levels were reduced by each treatment regimen compared with vehicle-treated control KO mice, but only mice treated with weekly or EOW idursulfase saw tissue levels drop to near those in wild-type mice. Through 3 months, the reduction in tissue GAG levels was greater in the weekly than in the EOW dosing groups, but by 6 months no significant difference between weekly and EOW dosing was apparent. In addition to the effect on urine and tissue GAG levels, liver weight was significantly reduced at 6 months in the weekly and EOW dosing groups compared with vehicle-treated KO mice.

Clinical efficacy

Idursulfase has been evaluated in two double-blind, randomized, clinical trials, and continues to be administered in two ongoing, open-label extensions to these studies. The initial clinical study was a Phase I/II trial designed to evaluate the safety and explore the clinical activity of idursulfase in patients with MPS II and to determine the appropriate dose to be used in the pivotal Phase II/III study [44]. The second clinical trial was a Phase II/III study designed to evaluate the clinical efficacy and safety of idursulfase in MPS II [36].

Phase I/II clinical trial

Patients who were at least 5 years old, cooperative and with both a clinical and biochemical diagnosis of MPS II were eligible to enroll in this double-blind, placebo-controlled trial [44]. Patients with neurological involvement were not explicitly excluded from the study, although all patients were required to be able to cooperate with the functional testing of the trial. All patients were considered to have an attenuated form of MPS II, but 11 out of 12 patients had some evidence of neurological involvement at baseline, ranging from headaches to low receptive language skills to lack of a deep tendon reflex at the knee (Data on file, Shire Human Genetic Therapies). The age of the patients ranged from 6–20 years, with an average age of 14 years. At baseline, all patients had hepatomegaly based on physical examination. Three groups of four patients were sequentially enrolled and, within each group, three patients were randomized to treatment with idursulfase and one to placebo. Three doses of idursulfase were used: 0.15, 0.5 and 1.5 mg/kg administered by intravenous infusion EOW for a period of 6 months. The lowest dose was used for the initial group of patients, with subsequent groups receiving the next highest dose. After 6 months, the study continued as an open-label extension study, with the placebo-treated patients being switched to the idursulfase dose of their original group. After all patients had completed at least 48 weeks of treatment with idursulfase, the patients in the high- and low-dose groups were switched to 0.5 mg/kg EOW. All patients enrolled in this extension study.

All 12 patients successfully completed the 6-month study. Pharmacokinetics were assessed during and after the initial infusion (Data on file, Shire Human Genetic Therapies). C_{max} occurred at the end of the infusion and was proportional to dose. Mean clearance half-lives after 0.5 and 1.5 mg/kg were 80 and 193 min, respectively. This nonlinearity was similar to that seen in preclinical testing and suggested that the M6P-mediated transport of idursulfase was saturated at a dose of 1.5 mg/kg. No idursulfase was detected in serum 24 h after dosing, indicating that idursulfase would not accumulate in serum, even with daily dosing.

Urinary GAG levels were reduced by all three idursulfase doses after 6 months of treatment, with more rapid decreases occurring in the 0.5- and 1.5-mg/kg groups ($p = 0.0092$ for mean change from baseline for the combined idursulfase groups) [44]. No change in the placebo-treated patients was observed during the first 6 months. During the 6-month double-blind study, a reduction in liver volume determined by magnetic resonance imaging (MRI) was demonstrated by eight out of nine idursulfase-treated patients, but the magnitude of the decrease was not dose related. Similarly, seven out of nine idursulfase-treated patients demonstrated a decrease in spleen volume (MRI) during the double-blind study, but again, no dose response was observed. In the 12-month open-label analysis, reductions in mean spleen and liver volume were seen in all dosing groups, with the reductions being statistically significant for the pooled idursulfase-treated patients. Evidence of clinical benefit was provided by the results of the 6-min walk test (6MWT), which measured how far each patient could walk in 6 min at baseline and throughout the study. After 12 months of treatment, no change in 6MWT distance was observed in the 0.15-mg/kg group, but the mean 6MWT distance increased by

Table 1. Reduction of tissue glycosaminoglycans storage with idursulfase in iduronate-2-sulfatase-knockout mice.

Dose (mg/kg)	Liver (percentage change in volume)	Spleen (percentage change in volume)
Vehicle	155.5 ± 30.4	65.4 ± 7.4
0.1	25.7 ± 2.6*	45.3 ± 2.9*
0.25	21.7 ± 3.2*	34.6 ± 1.6*
0.5	25.5 ± 4.7*	43.8 ± 1.4*
1.0	19.6 ± 2.4*	45.9 ± 2.2*
Wild-type	20.1 ± 2.8	43.4 ± 2.7

Iduronate-2-sulfatase-knockout mice were treated with idursulfase intravenously once weekly for 5 weeks. Organs were harvested 2 days after the final treatment.

**$p < 0.05$ compared with vehicle-treated group.*

Data from [43].

10.9 ± 7.13% in the 0.5-mg/kg group and by 27.9 ± 15.1% in the 1.5-mg/kg group. When the results of the three dosing groups were pooled, average walking distance significantly improved from 398 ± 117 to 445 ± 124 m after 12 months on idursulfase (p = 0.013, t-test). During the first 12 months of treatment, nine out of 12 patients demonstrated an increased in forced vital capacity (FVC) compared with baseline, but the mean change was not significant. No consistent changes in joint range of motion testing were found.

Phase II/III clinical study

This Phase II/III study of idursulfase in MPS II was the largest and longest placebo-controlled trial used to support registration of an ERT in a LSD [36]. In this pivotal study, 96 MPS II patients between the ages of 5 and 31 years with percentage predicted FVC (%FVC) less than 80% were equally randomized to one of three groups, stratified by age and disease severity: placebo or idursulfase 0.5 mg/kg intravenously infused either weekly or EOW for a period of 1 year. As was true in the Phase I/II trial, patients with neurological involvement were not explicitly excluded from the study, and neurologic involvement was evident to varying degress in many patients (Data on file, Shire Human Genetic Therapies). The three groups were well balanced with respect to age, baseline pulmonary function and mobility (**Table 2**).

The primary efficacy assessment was the comparison between placebo and weekly idursulfase treatment of a composite variable comprising the sum of ranked changes in 6MWT distance and ranked changes in %FVC between baseline and week 53. Patients who received either dosing regimen of idursulfase showed a significant improvement in the adjusted mean treatment difference for the composite primary end point compared with placebo (**Figure 2**), with the improvement being greater for the weekly than for the EOW regimen. In the weekly group, the mean 6MWT distance increased by 44.28 m, which was significantly greater than the 7.28 m mean increase observed in the placebo group (p < 0.0131). The mean change in %FVC in the weekly group (3.45%) was greater than that observed in the placebo group (0.75%), with the adjusted mean difference approaching statistical significance (p = 0.0650). No difference was observed for %FVC between the placebo and the EOW group (p = 0.9531). Further evidence of clinical benefit was provided by the significant increase in absolute FVC (0.22 l) in the weekly dosing group compared with placebo (0.06 l; p = 0.0011) or the weekly group compared with the EOW idursulfase group (0.07 l; p = 0.0176). Liver and spleen volumes were significantly decreased in both idursulfase groups compared with placebo (p < 0.0001) (**Figure 3**). Urine GAG levels were significantly reduced in both idursulfase groups compared with placebo (p < 0.0001), with the decrease in the weekly dosing group being larger than in the EOW group (-189.2 ± 25.8 vs -155.0 ± 17.2 µg/mg creatinine; p = 0.0394).

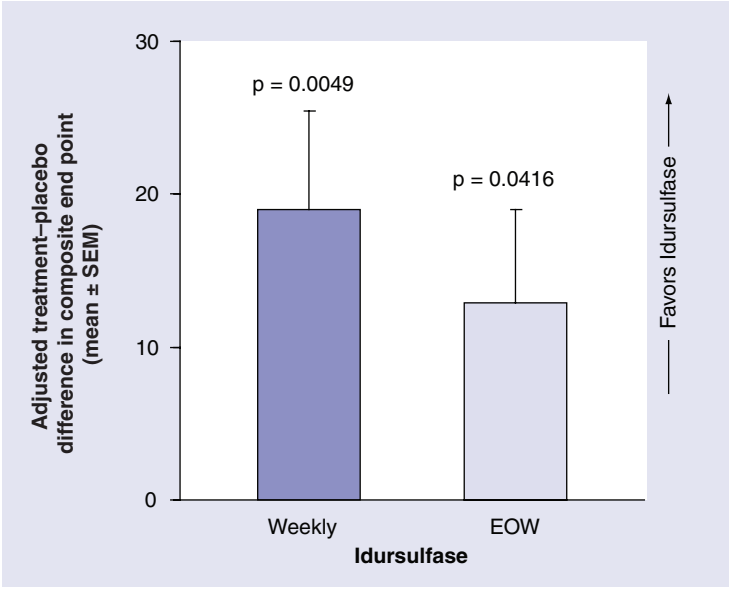
The results of this double-blind, placebo-controlled clinical trial of idursulfase in MPS II suggest that idursulfase may slow or reverse the progression of the disease by addressing the underlying enzyme deficiency. Weekly dosing appeared to offer a greater benefit based on the larger improvement in the composite efficacy end point, the larger increase in absolute FVC and the larger reduction in urine GAG levels seen in the weekly dosing group compared with the EOW group. The increased endurance shown by the change in 6MWT distance and the reduction in organomegaly represent real clinical benefits in these patients. All patients who completed this study have enrolled in an open-label extension that will address whether additional benefit may accrue with long-term dosing with idursulfase.

Table 2. Baseline disease characteristics of patients in the Phase II/III clinical trial of idursulfase in the treatment of mucopolysaccharidosis II.

Treatment group	Age (years)	FVC (%predicted)	6 MWT (m)
Placebo	13.1 ± 1.2	55.6 ± 2.2	392 ± 19
Idursulfase every other week	14.4 ± 1.2	55.1 ± 2.5	401 ± 18
Idursulfase weekly	15.1 ± 1.1	55.3 ± 2.8	392 ± 19

Values are mean ± standard error of the mean.
6 MWT: 6-min walk test; FVC: Forced vital capacity.
Adapted from [36].

Figure 2. Effect of idursulfase on primary end point in the Phase II/III clinical trial.



Primary end point was a composite of the sum of ranked changes in 6-min walk test distance and ranked changes in percentage predicted forced vital capacity. Patients were treated with idursulfase at 0.5 mg either weekly (dark bar; n = 32), EOW (light bar; n = 32) or placebo (n = 32) for 1 year.
EOW: Every other week; SEM: Standard error of mean.
Data from [36].

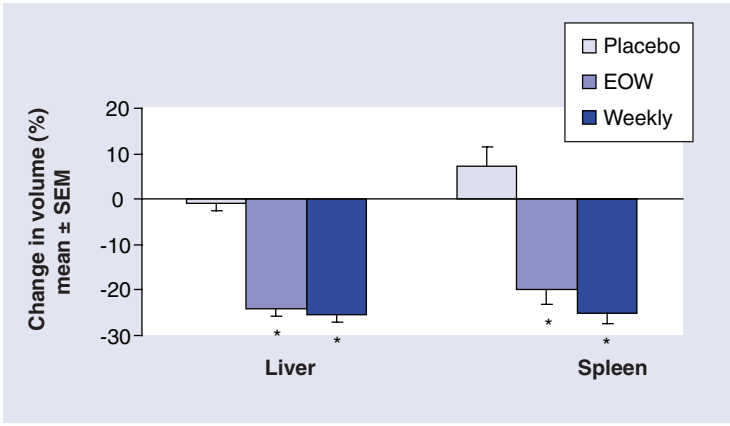
Clinical safety & tolerability

The safety profile of idursulfase in both clinical trials was similar to that reported for other ERTs [30–34]. During the first year of treatment, the emergent adverse events (AEs) were consistent with those expected to be seen in an untreated MPS II population [36,44], with the exception of infusion-related AEs. Fever, headache, cough, pharyngitis, upper respiratory tract infection, nasal congestion, nausea, vomiting, abdominal pain and diarrhea were the most commonly reported AEs in the Phase II/III clinical trial [36]. Most AEs were mild or moderate in severity in all groups. Infusion-related AEs, typically involving flushing, fever, chills, and/or headache, were experienced by some patients in both studies. In the Phase I/II study, three of four patients in each of the 0.5- and 1.5-mg/kg dosing groups experienced infusion reactions that were successfully managed by increasing the infusion time from 1 to 3 h and by premedication with oral antihistamines or corticosteroids [44]. No patients treated with 0.15 mg/kg had an infusion reaction. In the Phase II/III study, all infusions were given over a 3-h period. Infusion-related AEs occurred in a similar number of patients in each treatment group (placebo: 21; idursulfase EOW: 22; idursulfase weekly: 22), with most of these events occurring during the first 6 months of the study, suggesting that tolerance was occurring [36]. One 20-year-old patient in the Phase I/II trial with a history of airway obstruction requiring a tracheostomy, night-time ventilation and supplemental oxygen at baseline experienced severe infusion-related respiratory distress with hypoxia, hypotension, angioedema and seizure [44]. Ten other patients in the clinical trials had suspected hypersensitivy reactions during one or more infusions [45]. Subsequent infusions were managed by treating these patients with antihistamines and/or corticosteroids prior to or during infusions, slowing the infusion rate, or by early stopping of an infusion if serious symptoms were observed. With these measures, no patient discontinued treatment permanently due to hypersensitivity reactions.

Because MPS II patients are deficient in I2S, idursulfase would likely be viewed as 'foreign', and it was expected that some patients would generate antibodies directed against idursulfase. Immunoglobulin (Ig)G anti-idursulfase antibodies were detected at one or more time points in three of four patients treated with 0.5 mg/kg and in three of four patients treated with 1.5 mg/kg in the Phase I/II study [44]. No anti-idursulfase IgG antibodies were detected in any patient in the 0.15-mg/kg group. After 12 months, one of these six IgG-positive patients had reverted back to antibody-negative status. In the Phase II/III study, IgG anti-idursulfase antibodies were detected in 46.9% of patients in each idursulfase dosing group [36]. At the end of the 1-year study, only 31.7% remained IgG positive. No IgE anti-idursulfase antibodies were detected during either study. This rate of seroconversion is less than has been reported for other forms of ERT for LSD [33,46]. The reduction in the fraction of patients who were IgG positive over time suggests that immunological tolerance was occurring, as has been described in ERT for Gaucher disease [47] and Fabry disease [48].

The presence of IgG antibodies appeared to attenuate the reduction in urine GAG levels in the Phase II/III trial and was associated with an increased incidence of infusion-related AEs, including hypersensitivity reactions [45]. IgG antibodies were not otherwise associated with AEs or reduced clinical efficacy (Data on file, Shire Human Genetic Therapies). This

Figure 3. Effect of idursulfase on liver and spleen volume in Hunter syndrome patients.



Values shown represent changes from baseline to week 53 of treatment.
N = 32 in each group. The changes in liver or spleen volume seen in the two dosing regimens were not significantly different.
*p < 0.0001 compared with placebo.
EOW: Every other week; SEM: Standard error of mean.
Data from [36].

minimal influence on enzymatic activity is important because MPS II is a chronic disease and ERT is expected to be life-long.

Two deaths occurred during the Phase II/III study. One patient in the idursulfase weekly group developed respiratory insufficiency and cardiac arrest 5 days after his first dose of idursulfase. However, his death was determined not to be associated with idursulfase treatment. A second patient who was in the placebo group developed *Streptococcus pneumoniae* after his 34th weekly infusion and was subsequently diagnosed with sepsis and disseminated intravascular coagulation. He died of pulmonary hemorrhage followed by fatal cardiac arrest. This death was also determined to be not associated with study treatment.

The US Elaprase label includes a boxed warning with information on the potential for hypersensitivity reactions.

Conclusion & future perspective

MPS II patients treated with idursulfase for 1 year demonstrated clinical benefits, including correction of organomegaly and improved endurance. However, it is not yet known whether continued ERT will result in progressive improvement in pulmonary function that was first seen in the Phase II/III study, or whether significant improvements in joint mobility will emerge during long-term therapy. Evaluation of pulmonary function using changes in %FVC is problematic in MPS II patients because the formulae for predicted FVC [49,50] assume both normal growth and accurate measurement of height; neither assumption is correct for MPS II patients. A patient treated with idursulfase might be able to stand more erect because of improvement in joint flexibility, leading to a spurious increase in height and predicted FVC, despite the lack of linear growth. In such a patient, any improvement in %FVC would be underestimated. Thus, it seems appropriate that changes in absolute FVC should be used to evaluate the effect of long-term idursulfase treatment on pulmonary function.

The long-term experiences with ERT in Gaucher disease [35] and MPS I [51] clearly suggest that the clinical benefits of ERT will persist and may further improve with continuous long-term ERT. The open-label extension study noted above will help to address these issues in MPS II. In addition, the Hunter Outcome Survey has been initiated. Hunter Outcome Survey, which is sponsored by Shire Human Genetic Therapies, is a worldwide outcome survey that follows both treated and untreated MPS II patients. Similar surveys or patient registries have added to the knowledge of the natural history and the benefits of ERT in Gaucher disease [35] and Fabry disease [52,53] and are an essential tool when studying rare diseases.

The neurological signs and symptoms of MPS II remain difficult to treat with ERT. In one case report of eight patients with mild chronic neuronopathic (type 3) Gaucher disease, long-term (10 years) ERT appeared to slow the deterioration in neurological and mental function [54]. However, no placebo-controlled studies have been reported. Intrathecal administration of ERT has reduced lysosomal substrate storage in an animal model of MPS I [55], but it remains to be shown whether the neurological deterioration can be prevented or slowed by enzyme delivered by this nonconventional route of administration.

One method of addressing the treatment of neurological complications of MPS II may involve the use of small molecule chemical chaperones. These molecules bind to and stabilize proteins in the endoplasmic reticulum, preventing misfolding that commonly occurs in mutated enzymes. By chaperoning the transit of these mutant enzymes to the lysosome, some enzymatic activity may be preserved. Chemical chaperones have been reported to

reduce substrate accumulation in cultured fibroblasts of Fabry disease patients [56] and to improve cardiac function in a patient with the cardiac variant of Fabry disease [57]. No chemical chaperones for mutant I2S have yet been reported, and it seems doubtful that this approach would work in MPS II since many of the mutations are deletions or rearrangements that result in protein with little or no enzymatic activity. When and if chemical chaperones for mutant I2S are discovered, they would have to cross the blood–brain barrier to have any possibility of affecting the neurologic pathologies of MPS II.

Substrate reduction has also been proposed as a mechanism for treatment of LSDs. The aim of this approach is to reduce the rate of biosynthesis of the material stored in the lysosome to match the rate of its impaired lysosomal catabolism [58,59]. Substrate-reduction therapy with miglustat, an imino sugar that inhibits ceramide glucosyltransferase, a key enzyme in the synthetic pathway of glycosphingolipids, has been developed for treatment of patients with type 1 Gaucher disease in whom ERT is unsuitable [58].

The accumulation of heparan sulfate and dermatan sulfate begins early in life and is progressive and life-limiting. Therefore, one could hypothesize that ERT started early in childhood might offer the greatest chance of slowing the course of the disease. This hypothesis is supported by results of ERT in an animal model of MPS VI. Auclair and colleagues reported that, in MPS VI cats, ERT with recombinant human *N*-acetylgalactosamine-4-sulfatase started at birth resulted in more pronounced neurological and skeletal benefits than observed in cats in which treatment was delayed until 3–5 months of age [60]. The results of a clinical trial of idursulfase in MPS II patients under the age of 5 years, which is currently in the planning stages, may address this issue.

Disclosure

The author is a consultant for, and has received travel grants from, Shire Human Genetic Therapies. In addition, he was an investigator in the Phase II/III study of idursulfase. Shire HGT paid for the editorial assistance provided by Edward Weselcouch. Shire HGT reviewed the manuscript to ensure the accuracy of all statements regarding company-sponsored preclinical and clinical studies.

Executive summary

Mucopolysaccharidosis II (Hunter syndrome)

- Mucopolysaccharidosis (MPS) II is an X-linked lysosomal storage disease that is caused by the missing or deficient enzyme, iduronate-2-sulfatase.
- The accumulation of dermatan sulfate and heparan sulfate within tissues and organs is responsible for signs and symptoms of MPS II, which include organomegaly, respiratory difficulties, reduction in joint motion, slow neurological development and a reduced lifespan.

Idursulfase

- Idursulfase is a recombinant form of iduronate-2-sulfatase that is produced in a human cell line. It has the same amino acid sequence and similar glycosylation pattern as the native enzyme.
- Idursulfase has been approved for the treatment of patients with MPS II in both the USA and the EU. The US label includes a boxed warning with information regarding the potential for hypersensitivity reactions.

Clinical efficacy

- In clinical studies involving 108 patients, idursulfase has been shown to significantly reduce urine glycosaminoglycan levels and liver and spleen size.
- In a Phase II/III randomized, double-blind clinical trial, patients treated with either weekly or every-other-week idursulfase (0.5 mg/kg) for a 1-year period demonstrated significant improvement in the primary end point, a composite comprising the sum of ranked changes in 6-min walking test distance and ranked changes in percentage forced vital capacity.
- Idursulfase was generally well tolerated, with the most common treatment-related adverse event being infusion reactions, which declined in frequency with long-term therapy. Significant hypersensitivity reactions occurred during a small fraction of infusions.
- Anti-idursulfase immunoglobulin (Ig)G antibodies were seen in approximately 50% of patients with a decreasing prevalence with long-term therapy. No anti-idursulfase IgE antibodies were observed in any patients.

Conclusion

- Idursulfase offers the potential to correct the underlying enzymatic deficiency in MPS II and to benefit patients by reducing organ size and improving respiratory function.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Hunter C: A rare disease in two brothers. *Proc. Royal Soc. Med.* 10, 104–116 (1917).
• **Initial description of Hunter syndrome.**
2. Kudo M, Brem MS, Canfield WM: Mucolipidosis II (I-cell disease) and mucolipidosis IIIA (classical pseudo-hurler polydystrophy) are caused by mutations in the GlcNAc-phosphotransferase α/β subunits precursor gene. *Am. J. Hum. Genet.* 78(3), 451–463 (2006).
3. Bach G, Eisenberg F Jr, Cantz M, Neufeld EF. The defect in the Hunter syndrome: deficiency of sulfoiduronate sulfatase. *Proc. Natl Acad. Sci. USA* 70(7), 2134–2138 (1973).
4. Tuschl K, Gal A, Paschke E, Kircher S, Bodamer OA: Mucopolysaccharidosis type II in females: case report and review of literature. *Pediatr. Neurol.* 32(4), 270–272 (2005).
5. Sukegawa K, Matsuzaki T, Fukuda S *et al.*: Brother/sister siblings affected with Hunter disease: evidence for skewed X chromosome inactivation. *Clin. Genet.* 53(2), 96–101 (1998).
6. Meikle PJ, Hopwood JJ, Clague AE, Carey WF: Prevalence of lysosomal storage disorders. *JAMA* 281(3), 249–254 (1999).
• **Provides estimates of the incidence of Hunter syndrome.**
7. Poorthuis BJ, Wevers RA, Kleijer WJ *et al.*: The frequency of lysosomal storage diseases in The Netherlands. *Hum. Genet.* 105(1–2), 151–156 (1999).
• **Provides estimates of the incidence of Hunter syndrome.**
8. Baehner F, Schmiedeskamp C, Krummenauer F *et al.*: Cumulative incidence rates of the mucopolysaccharidoses in Germany. *J. Inherit. Metab. Dis.* 28(6), 1011–1017 (2005).
• **Provides estimates of the incidence of Hunter syndrome.**
9. Wilson PJ, Suthers GK, Callen DF *et al.*: Frequent deletions at Xq28 indicate genetic heterogeneity in Hunter syndrome. *Hum. Genet.* 86(5), 505–508 (1991).
10. Lissens W, Seneca S, Liebaers I: Molecular analysis in 23 Hunter disease families. *J. Inherit. Metab. Dis.* 20(3), 453–456 (1997).
11. Kim CH, Hwang HZ, Song SM *et al.*: Mutational spectrum of the iduronate-2-sulfatase gene in 25 unrelated Korean Hunter syndrome patients: identification of 13 novel mutations. *Hum. Mutat.* 21(4), 449–450 (2003).
12. Timms KM, Bondeson ML, Ansari-Lari MA *et al.*: Molecular and phenotypic variation in patients with severe Hunter syndrome. *Hum. Mol. Genet.* 6(3), 479–486 (1997).
13. Vafiadaki E, Cooper A, Heptinstall LE *et al.*: Mutation analysis in 57 unrelated patients with MPS II (Hunter's disease). *Arch. Dis. Child.* 79(3), 237–241 (1998).
14. Li P, Bellows AB, Thompson JN: Molecular basis of iduronate-2-sulphatase gene mutations in patients with mucopolysaccharidosis type II (Hunter syndrome). *J. Med. Genet.* 36(1), 21–27 (1999).
15. Neufeld EF, Muenzer J: The mucopolysaccharidoses. In: *The Metabolic and Molecular Bases of Inherited Disease.* Scriver CR (Ed.). McGraw-Hill, NY, USA 3421–3452 (2001).
• **Overview of the phenotypic expression of Hunter syndrome.**
16. Young ID, Harper PS: The natural history of the severe form of Hunter's syndrome: a study based on 52 cases. *Dev. Med. Child. Neurol.* 25(4), 481–489 (1983).
• **Overview of the phenotypic expression of Hunter syndrome.**
17. Young ID, Harper PS: Mild form of Hunter's syndrome: clinical delineation based on 31 cases. *Arch. Dis. Child.* 57(11), 828–836 (1982).
• **Overview of the phenotypic expression of Hunter syndrome.**
18. Demitsu T, Kakurai M, Okubo Y *et al.*: Skin eruption as the presenting sign of Hunter syndrome IIB. *Clin. Exp. Dermatol.* 24(3), 179–182 (1999).
19. Knoell KA, Tunnessen WW Jr: Picture of the month. Hunter syndrome (mucopolysaccharidosis IIA). *Arch. Pediatr. Adolesc. Med.* 154(1), 85–86 (2000).
20. Yoskovitch A, Tewfik TL, Brouillette RT, Schloss MD, Der Kaloustian VM: Acute airway obstruction in Hunter syndrome. *Int. J. Pediatr. Otorhinolaryngol.* 44(3), 273–278 (1998).
21. Orliaguet O, Pepin JL, Veale D *et al.*: Hunter's syndrome and associated sleep apnoea cured by CPAP and surgery. *Eur. Respir. J.* 13(5), 1195–1197 (1999).
22. Kettles DI, Sheppard M, Liebmann RD, Davidson C: Left ventricular aneurysm, aortic valve disease and coronary narrowing in a patient with Hunter's syndrome. *Cardiovasc. Pathol.* 11(2), 94–96 (2002).
23. Dangel JH: Cardiovascular changes in children with mucopolysaccharide storage diseases and related disorders – clinical and echocardiographic findings in 64 patients. *Eur. J. Pediatr.* 157(7), 534–538 (1998).
24. Froissart R, Moreira da Silva I, Guffon N, Bozon D, Maire I: Mucopolysaccharidosis type II – genotype/phenotype aspects. *Acta Paediatr. Suppl.* 91(439), 82–87 (2002).
25. Peters C, Krivit W: Hematopoietic cell transplantation for mucopolysaccharidosis IIB (Hunter syndrome). *Bone Marrow Transplant.* 25(10), 1097–1099 (2000).
26. McKinnis EJ, Sulzbacher S, Rutledge JC, Sanders J, Scott CR: Bone marrow transplantation in Hunter syndrome. *J. Pediatr.* 129(1), 145–148 (1996).
27. Vellodi A, Young E, Cooper A *et al.*: Long-term follow-up following bone marrow transplantation for Hunter disease. *J. Inherit. Metab. Dis.* 22(5), 638–648 (1999).
28. Coppa GV, Gabrielli O, Zampini L *et al.*: Bone marrow transplantation in Hunter syndrome. *J. Inherit. Metab. Dis.* 18(1), 91–92 (1995).
29. Mullen CA, Thompson JN, Richard LA, Chan KW: Unrelated umbilical cord blood transplantation in infancy for mucopolysaccharidosis type IIB (Hunter syndrome) complicated by autoimmune hemolytic anemia. *Bone Marrow Transplant.* 25(10), 1093–1097 (2000).
30. Barton NW, Brady RO, Dambrosia JM *et al.*: Replacement therapy for inherited enzyme deficiency – macrophage-targeted glucocerebrosidase for Gaucher's disease. *N. Engl. J. Med.* 324(21), 1464–1470 (1991).
•• **First clinical trial to demonstrate a benefit of enzyme-replacement therapy (ERT) in a lysosomal storage disease.**
31. Eng CM, Guffon N, Wilcox WR *et al.*: Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. *N. Engl. J. Med.* 345(1), 9–16 (2001).
32. Schiffmann R, Kopp JB, Austin HA 3rd *et al.*: Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA* 285(21), 2743–2749 (2001).
33. Wraith JE, Clarke LA, Beck M *et al.*: Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human α-L-iduronidase (laronidase). *J. Pediatr.* 144(5), 581–588 (2004).
34. Harmatz P, Giugliani R, Schwartz I *et al.*: Enzyme replacement therapy for mucopolysaccharidosis VI: a Phase III,

randomized, double-blind, placebo-controlled, multinational study of recombinant human *N*-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or RHASB) and follow-on, open-label extension study. *J. Pediatrics* 148, 533–539 (2006).

35. Weinreb NJ, Charrow J, Andersson HC *et al.*: Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am. J. Med.* 113(2), 112–119 (2002).
36. Muenzer J, Wraith E, Beck M *et al.*: A Phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis type II (Hunter syndrome). *Genet. Med.* 8, 465–473 (2006).

•• **Phase II/III clinical trial demonstrating a clinical benefit of weekly infusions of idursulfase in the treatment of Hunter syndrome.**

37. Bielicki J, Hopwood JJ, Wilson PJ, Anson DS: Recombinant human iduronate-2-sulphatase: correction of mucopolysaccharidosis-type II fibroblasts and characterization of the purified enzyme. *Biochem. J.* 289(Pt 1), 241–246 (1993).
38. Hille-Rehfeld A: Mannose 6-phosphate receptors in sorting and transport of lysosomal enzymes. *Biochim. Biophys. Acta* 1241(2), 177–194 (1995).
39. Bielicki J, Freeman C, Clements PR, Hopwood JJ: Human liver iduronate-2-sulphatase. Purification, characterization and catalytic properties. *Biochem. J.* 271(1), 75–86 (1990).
40. Muenzer J, Fu H: Targeted disruption of the mouse iduronate sulfatase gene. *Am. J. Genet.* 65, A427 (1999) (Abstract).
41. de Jong JG, Wevers RA, Laarakkers C, Poorthuis BJ: Dimethylmethylene blue-based spectrophotometry of glycosaminoglycans in untreated urine: a rapid screening procedure for mucopolysaccharidoses. *Clin Chem.* 35(7), 1472–1477 (1989).
42. de Jong JG, Wevers RA, Liebrand-van Sambeek R: Measuring urinary glycosaminoglycans in the presence of protein: an improved screening procedure for mucopolysaccharidoses based on dimethylmethylene blue. *Clin Chem.* 38(6), 803–807 (1992).
43. Garcia AR, DeCosta JM, Pan J, Muenzer J, Lamsa JC: Preclinical dose ranging studies for enzyme replacement therapy with idursulfase in a knock-out mouse model of MPS II. *Mol. Genet. Metab.* (2007) (In Press).
44. Muenzer J, Gucsavas-Calikoglu M, McCandless SE, Schuetz TJ, Kimura A: A Phase I/II clinical trial of enzyme replacement therapy in mucopolysaccharidosis II (Hunter syndrome). *Mol. Genet. Metab.* 90, 329–337 (2007).

•• **First clinical trial of idursulfase. Established the safety of ERT in Hunter syndrome and was used to determine the dose to be used in the Phase II/III trial.**

45. Elaprase™ (idursulfase) Prescribing Information. Shire Human Genetic Therapies, Inc., MA, USA (2006).
46. Wilcox WR, Banikazemi M, Guffon N *et al.*: Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. *Am. J. Hum. Genet.* 75(1), 65–74 (2004).
47. Rosenberg M, Kingma W, Fitzpatrick MA, Richards SM: Immunosurveillance of alglucerase enzyme therapy for Gaucher patients: induction of humoral tolerance in seroconverted patients after repeat administration. *Blood* 93(6), 2081–2088 (1999).
48. Schiffmann R, Ries M, Timmons M, Flaherty JT, Brady RO: Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting. *Nephrol. Dial. Transplant.* 21, 345–354 (2006).
49. Hankinson JL, Odencrantz JR, Fedan KB: Spirometric reference values from a sample of the general U.S. population. *Am. J. Respir. Crit. Care Med.* 159(1), 179–187 (1999).
50. Polgar G, Promadhat V: *Pulmonary Function Testing in Children: Techniques and Standards*. WB Saunders and Company, PA, USA (1971).
51. Wraith JE: The first 5 years of clinical experience with laronidase enzyme replacement therapy for mucopolysaccharidosis I. *Expert Opin Pharmacother.* 6(3), 489–506 (2005).
52. Hoffmann B, Garcia de Lorenzo A, Mehta A *et al.*: Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey). *J. Med. Genet.* 42(3), 247–252 (2005).
53. Ramaswami U, Whybra C, Parini R *et al.*: Clinical manifestations of Fabry disease in children: data from the Fabry Outcome Survey. *Acta Paediatr.* 95(1), 86–92 (2006).
54. Erikson A, Forsberg H, Nilsson M, Astrom M, Mansson JE: Ten years' experience of enzyme infusion therapy of Norrbottnian (type 3) Gaucher disease. *Acta Paediatr.* 95(3), 312–317 (2006).
55. Kakkis E, McEntee M, Vogler C *et al.*: Intrathecal enzyme replacement therapy reduces lysosomal storage in the brain and meninges of the canine model of MPS I. *Mol. Genet. Metab.* 83(1–2), 163–174 (2004).
56. Yam GH, Bosshard N, Zuber C, Steinmann B, Roth J: Pharmacological chaperone corrects lysosomal storage in Fabry disease caused by trafficking-incompetent variants. *Am. J. Physiol. Cell Physiol.* 290(4), C1076–C1082 (2006).
57. Frustaci A, Chimenti C, Ricci R *et al.*: Improvement in cardiac function in the cardiac variant of Fabry's disease with galactose-infusion therapy. *N. Engl. J. Med.* 345, 25–32 (2001).
58. Cox TM: Substrate reduction therapy for lysosomal storage diseases. *Acta Paediatr.* 94(Suppl. 447), 69–75 (2005).
59. Aerts JM, Hollak CE, Boot RG, Groener JE, Maas M: Substrate reduction therapy of glycosphingolipid storage disorders. *J. Inherit. Metab. Dis.* 29(2–3), 449–456 (2006).
60. Auclair D, Hopwood JJ, Brooks DA, Lemontt JF, Crawley AC: Replacement therapy in mucopolysaccharidosis type VI: advantages of early onset of therapy. *Mol. Genet. Metab.* 78(3), 163–174 (2003).