Galsulfase: enzyme-replacement therapy for mucopolysaccharidosis Type VI (Maroteaux–Lamy syndrome)

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Since enzyme-replacement therapy has been successfully introduced for patients with Gaucher disease, Fabry disease and mucopolysaccharidosis Type I, the principle of this treatment has also been taken into consideration for individuals who are affected by mucopolysaccharidosis Type VI (Maroteaux–Lamy disease), a rare lysosomal storage disorder with multiple organ and tissue involvement. After enzyme-replacement therapy with recombinant human arylsulfatase B in a feline model of mucopolysaccharidosis VI showed a reduction in storage vacuoles in Kupffer cells and connective tissue, clinical trials were intitiated. A Phase I/II trial showed that regular infusions of recombinant arylsulfatase B were able to reduce urinary glycosaminoglycan excretion. In all patients, general endurance and shoulder range of motion improved. These results were confirmed by a following open-label Phase II study with ten patients who had more rapidly advanced disease. After a Phase III (double-blind, placebo-controlled) study had demonstrated the clinical efficacy of weekly infusion of recombinant human arylsulfatase B, this enzyme preparation was approved by the US Food and Drug Administration for the treatment of patients with mucopolysaccharidosis Type VI. The efficacy and safety of the enzyme preparation is discussed in this review.

Keywords: arylsulfatase B, enzyme-replacement therapy, galsulfase, lysosomal storage disorder, mucopolysaccharidosis Type VI

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Mucopolysaccharidosis (MPS) Type VI (Online Mendelian Inheritance in Man [OMIM] 253200) is one of the distinct MPS disorders caused by deficiencies in specific glycosaminoglycan (GAG)-degrading enzymes. In MPS VI the deficient enzyme is *N*-acetylgalactosamine 4-sulfatase (also known as arylsulfatase B [ASB]), which is resonsible for breakdown of the GAG dermatan sulfate. The lack of ASB activity leads to the accumulation of dermatan sulfate in a variety of tissues, and subsequently to impairment of function in multiple organs, such as the skeleton, heart valves, airways, eyes and skin. MPS VI is a progressive disorder and is comparable to other MPS disorders as the first symptom is often a skeletal deformity in terms of a gibbus that may be observed within the first year of life. Umbilical and inguinal hernias are very common in early childhood. Later on, deceleration of growth becomes evident, leading to a disproportionately short stature. In severely affected patients, painful bone and joint disease occurs that, in part, is most likely due to secondary inflammatory cytokine release [1]. With the progress of disease, coarseness of the face develops, which is characterized by an enlarged tongue, prominent eyes, flat nasal bridge and macrocephaly. Liver and spleen size also increases. Impaired vision is caused not only by corneal clouding, but also by glaucoma and optic nerve disease. Conductive and/or inner ear hearing impairment is very common in MPS VI, and most patients develop moderate-to-severe deafness. The infiltration of the upper and lower airways by storage material causes obstructive airway disease and represents the most debilitating complication, leading to recurrent pulmonary infections and sleep apnea. Manifestations of the heart include valvular disease, cardiomyopathy and cardiac arrhythmia. Joint contractures, together with obstructive (and also restrictive) airway disease and cardiac involvement, are the origin of reduced endurance. Several neurologic complications arise from the accumulation of GAGs and subsequent thickening of ligaments that surround the nerves. Compression of the spinal cord in the craniocervical region may cause paraplegia and compression of the ligamentum carpi transversum leads to carpal tunnel syndrome. Hydrocephalus is not uncommon; however, in general, patients with MPS VI have normal intelligence.

As with all the MPS disorders, MPS VI is a clinically heterogeneous disease in terms of the extent and rate of progression of organ impairment in affected individuals.

In order to establish demographics, urinary GAG levels and clinical progression of the disease, a cross-sectional survey of 121 MPS VI patients ranging from 4 to 56 years of age was conducted [2]. Centers from 15 countries, primarily in North America, South America, Europe

and Australia, participated in this study. Investigations included complete physical examination, measurement of GAG excretion and assessment of other parameters such as pulmonary function, joint range of motion and quality of life (QoL). For evaluation of endurance a 6-min walk test was performed [3]. Not unexpectedly, a wide variation in clinical presentation was observed. From a total of 16 subjects who required ventilatory assistance, seven had tracheotomies, five needed continuous positive airway pressure (CPAP) during sleep, one used a ventilatory mist, one was on ventilator day and night and two used oxygen nasal prongs. A total of 59 patients had an electrocardiogram (ECG) abnormality (e.g., tachycardia, right or left axis deviation and atrial enlargement). From a subset of 68 subjects, 65 had evidence of valvular stenosis and/or regurgitation. Many of the patients (23%) used one or more devices, such as a walking aid (wheelchair, crutches, cane). Visual acuity was compromised in 21 individuals. Analysis of clinical and laboratory data disclosed an association of age, height/weight and morbidity with urinary GAG levels. High GAG values (>200 µg/mg creatinine) correlated with short stature, low body weight, compromised pulmonary function and reduced joint range of motion, indicating a more rapidly progressing disease. Almost all patients over the age of 20 years had GAG values of less than 100 µg/mg creatinine, suggesting that longer term survival is associated with urinary GAG levels below a threshold of 100 µg/mg creatinine. However, one has to take into consideration that these data were derived by a cross-sectional study, and a longitudinal study of many years' duration will be required to reach to a definitive conclusion regarding the relationship of GAG excretion and the severity of clinical manifestation.

Genetics

MPS VI (Maroteaux–Lamy syndrome) is an autosomal-recessive disorder. The gene coding for ASB, the enzyme that is deficient in MPS VI, has been localized to the region 5q11–q13 [4]. Although the precise size of the gene is not known, it consists of eight exons [5]. By sequencing genes from 89 MPS VI patients, 170 alleles have been identified [6,7]. Of these, 36 were missense mutations, 12 deletions and seven intronic mutations. Results from clinical investigations and mutation analysis suggest that there are correlations between genotype, cell biology and clinical phenotype. For example, patients who have nonsense mutations or small insertions or deletions and therefore would not produce functional enzyme activity, are severely affected, whereas in patients with missense mutations the clinical severity varies greatly depending on the location of the amino acid substitution [6,7].

There is little information concerning the incidence of MPS VI. It belongs to the less frequent mucopolysaccharidoses in most populations – the incidence has been found to be between 1:667,000 in The Netherlands [8] and 1: 248,000 in Australia [9]. In Brazil, MPS VI is more frequent than in other countries [10] – this could possibly be explained by a founder effect [11].

Treatment

Until recently, no specific treatment was available for patients with Maroteaux–Lamy disease, and management mainly consisted of supportive care and treatment of complications. Due to the progressive nature of the disease, regular investigations of the clinical status of the patients are necessary, and must include evaluation of vision, hearing, joint function and neurologic status. Physical therapy may have some benefits in preserving joint function; however, it cannot prevent the development of joint stiffness. A large number of MPS VI patients require a hearing aid. Several factors such as valvular disease, cardiomyopathy and systemic and pulmonary hypertension may contribute to congestive heart failure and sudden cardiovascular collapse [12]. Mitral and aortic valve regurgitation or stenosis often requires valve replacement. Bacterial endocarditis prophylaxis is recommended in all MPS VI patients with cardiac abnormalities. With regard to heart failure, patients with MPS VI should receive treatment according to the same principles as patients from the general population.

There is a broad spectrum of surgical procedures that may be required in affected individuals. In the first years of life, umbilical and inguinal hernia repair must often be performed. In order to prevent recurrent infections of the ears and upper airways, tonsillectomy/adenoidectomy and grommet insertion are recommended. If increased intracranial pressure occurs, a ventriculoperitoneal shunt placement becomes necessary [13]. The development of cervical myelopathy can be avoided by timely surgical release of the compressed spinal cord, perhaps combined with cervical spinal fusion. Hip replacement is often required, even in young

adults, due to severe joint pain. Cornea transplantation may be a valuable treatment option for visually rehabilitating such patients.

Bone marrow transplantation, which is associated with high morbidity and mortality, has been shown to provide some benefit for the MPS VI patient. For example, Herskhovitz and colleagues reported that in four patients who received a bone transplantation, the facial features became less coarse and the cardiac manifestations improved or at least remained stable [14]. There was also an improvement of joint mobility, whereas skeletal changes progressed.

Overview of the market

There is no other drug on the market for enzyme-replacement therapy (ERT) for MPS VI patients. The effect of bone marrow transplantation is limited to improvement of soft tissue and does not appear to have a significant influence on skeletal involvement. Based on several studies, it is estimated that there are approximately 1100 patients worldwide who suffer from mucopolysaccharidosis VI. However, it cannot be discounted that a notable number of patients are not diagnosed or have been misdiagnosed.

Chemistry of galsulfase

ERT studies in several animal models of mucopolysaccharidoses have demonstrated a reduction, or even a resolution, of lysosomal storage in a variety of connective tissue. Shull and colleagues used a canine model of Hurler syndrome for their trials, in which three affected animals received weekly infusions of recombinant human α-L-iduronidase over a period of 3 months [15]. In biopsies of the liver and spleen taken after the trial, a normal enzyme activity was detected, whereas in the brain, heart cartilage and cornea almost no activity was found. Light and electron microscopy examinations revealed normalization of lysosomal storage only in the liver, spleen and kidney; however, this was not found in the heart, brain or cornea. The effects of long-term ERT were also investigated in mice affected by MPS Type VII [16]. The animals were treated either at birth or at 6 weeks of age with recombinant β-glucuronidase, and the effect of a combination of ERT early in life followed by bone marrow transplantation was analyzed. After treatment for at least 185 days a decrease in lysosomal storage was observed in liver and spleen tissue. In mice treated at birth, the skeletal dysplasia was less severe when compared with animals who received the enzyme at 6 weeks of age. It should be mentioned that in none of these animal studies was an improvement in chondrocyte storage observed, suggesting that only minimal amounts of the enzyme had been taken up by these cells. This explains the progression of degenerative joint changes in MPS VI cats undergoing ERT [17]. To try to overcome this problem, Byers and colleagues used modified recombinant human (rh)ASB that should lead to higher enzyme concentrations in the cartilage cells [18]. For this purpose, the enzyme was coupled to either ethlyene diamine or to poly-L-lysine to yield a high net positive surface charge and promote diffusion through the extracellular cartilage matrix. It was shown that these modified enzymes retained activity and were taken up by feline MPS VI cells (fibroblasts and chondrocytes) in a mannose-6-phosphate-dependent manner. *In vitro*, modification of rhASB also improved diffusion of the enzyme into cartilage tissue that was gained from fetal sheep. However, *in vivo* studies in MPS VI cats have shown that the modified forms of rhASB exhibited a tissue distribution similar to that of the unmodified enzyme [18]. The majority of the enzyme was always taken up by the liver, whereas the 4-sulphatase activity found in cartilage was minimal, regardless of the physical properties of the enzyme. Based on these results, the unmodified ASB was used for further animal and clinical studies.

The first preclinical studies with rhASB were performed in a naturally occurring animal model of MPS VI, a cat that shows many clinical features comparable to those observed in humans [19]. Initial studies in three MPS VI cats have shown that regular infusions of the human recombinant enzyme, produced in a Chinese hamster ovary cell, resulted in the reduction of storage cells in liver Kupffer cells and connective tissues; however, not in chondrocytes [20]. One cat showed greater mobility under treatment.

After the first animal experiment yielded promising results, a further study was performed in nine cats, who received weekly infusions of recombinant human *N*-acetylgalactosamine 4-sulfatase at variable dose rates (0.2, 1 and 5 mg/kg), starting at between 14 and 58 h after birth [17]. This study revealed a dose–response effect at the clinical, biochemical and histopathologic level. The cats treated with the enzyme at 1 and 5 mg/kg every week were heavier and more flexible in comparison with the untreated controls, had greatly reduced or no spinal cord compression and had almost normal urinary GAG levels. In the heart valves, aorta, skin and liver a near normalization or even complete reversal of lysosomal storage was found. No reduction in lysosomal vacuolation was

observed in cartilage or cornea. There was a clear improvement of skeletal pathology visible by near normalization of bone density and trabecular pattern. Between 1 and 5 mg/kg, dose rate differences were not clearly distinguishable. However, the cat who was treated with 0.2 mg/kg showed the same disease progression as the untreated controls.

Bielicki and colleagues questioned whether the species-specific enzyme would be more efficacious in the cat model, rather than using the human analog [21]. Thus, two MPS VI cats received recombinant feline ASB at a dose of 1 mg/kg per week. The therapy was commenced within 24 h of birth. After 170 days of therapy, the cats showed a reduction in urinary GAG excretion and correction of lysosomal storage in almost all tissues, with the exception of cartilage, cornea and white blood cells. Comparing these results with those obtained in a similar study using the recombinant human enzyme [17], it was found that a dose of 1 mg of species-specific ASB had a more pronounced effect on reducing storage material in several tissues, such as in the aorta or heart valves, than the same dose of the human enzyme.

Further studies in the cat model were performed by Crawley and colleagues in order to investigate the clinical and biochemical response to different dose regimens [22]. They administered 20 mg/kg of recombinant feline ASB to three MPS VI cats in the first month of life and thereafter 1 mg/kg for a further 9 weeks (high-dose group). The low-dose group received 1 mg/kg from birth onwards. High-dose-treated cats had less rounded facial features and a more normal body shape compared with the low-dose-treated animals. In both groups, a clearance of storage material from lysosomes was observed in a range of soft tissues, such as the liver Kupffer cells. However, no reduction in storage was observed in the cornea or articular cartilage at either dose. Total urine GAG levels in high-dose-treated cats at approximately 25 days of age were nearly normalized, compared with the low-dose-treated cats, consistent with the higher enzyme dose rate administered in the first 28 days of age. However, at days 55 and 90 the level of urinary GAG was similar in both the high- and low-dose animals. In conclusion, this experiment showed that the initial high-dose therapy reduced storage load in the animals; however, it had no lasting clinical benefit over continuous low-dose therapy.

Galsulfase, the enzyme that is used for treatment in humans, is produced in a suspension bioreactor by genetically engineered Chinese hamster ovary cells. The harvested cell culture fluid from the bioreactor is purified by several cycles of the blue sepharose chromatography column. Further purification includes copper-chelating sepharose and phenyl sepharose chromatography, which are known to be capable of removing viruses. Virus removal is also provided by two subsequent filtration steps using a DNA-removing anion-exchange filter and a 0.02 µm size-exclusion removal filter. Several model viruses that may have the potential to contaminate the source material were used for the evaluation of clearance capability in the manufacturing process. Safety calculations for the xenotropic murine leukemia virus (XMulV), for example, revealed that the viral clearance capability of the purification process results in the probability of one retroviral particle/dose to be $10^{-7.4}$ or less, which is less than one particle in 25 million doses.

The purified product galsulfase is a glycoprotein with a molecular weight of approximately 56 kD. It consists of 495 amino acids and contains six asparagine-linked glycosylation sites, four of which carry a bis mannose-6-phosphate mannose oligosaccharide for specific cellular recognition. The catalytic amino acid residue C_{α}-formylglycine is generated by post-translational modification of Cys53, which is required for the enzyme activity of all sulfatases [23]. Galsulfase has a specific activity of approximately 70 U/mg protein content (1 U is defined as the amount of enzyme required to convert 1 µmole substrate/min at 37°C). The drug is supplied as a sterile, nonpyrogenic solution (5 mg/5 ml/vial) that must be diluted in 0.9% sodium chloride prior to administration. Pretreatment with antihistamines, and possibly antipyretics, is recommended before the start of infusion. For the first hour, the initial infusion rate should be 6 ml/h, and if the drug is well tolerated, the rate may be increased to 80 ml/h. The total infusion volume should not be given over less than 4 h.

From the stability data it can be delineated that galsulfase is stable at the recommended temperature (5 ± 3°C) for at least 30 months.

Pharmacokinetics & metabolism

From the animal model (MPS VI cat) it was concluded that the dose of 1 mg/kg/week of species-specific enzyme would be as efficient as 5 mg/kg/week of cross-species enzyme. Therefore, recombinant human enzyme at a dose of 1 mg/kg/week was used in the first clinical trial [24]. Additionally, a dose of 0.2 mg/kg/week

was selected to establish a pharmacokinetic and biologic dose–response correlation. A total of seven MPS VI patients were included in a randomized, double-blind study – four received 0.2 mg/kg/week human recombinant enzyme, while three were treated with a dose of 1.0 mg/kg/week. After safety and efficacy were evaluated at week 24, the study was unblinded; however, all patients remained on their assigned dose until evaluation at week 48. One patient from the low-dose group withdrew from the study at week 3 for reasons unrelated to the trial. The two patients remaining in the low-dose group were switched to the high dose at week 59 and 69.

Blood samples were drawn for analysis at weeks 1, 2, 12, 24, 83, 84 and 96. Plasma rhASB levels that were determined by an enzyme-linked immunosorbent assay (ELISA) were expressed in ng/ml. The pharmacokinetic parameters were calculated using non-compartmental methods, the C_{max} and time to C_{max} (T_{max}) were taken directly from the data. In this trial, the following results were obtained: approximately 90 min after starting the infusion, rhASB became measurable and reached maximum concentrations between 120 and 240 min; within 10 min following completion of the enzyme infusion, rhASB was no longer detectable.

In patients who received a dose of 0.2 mg/kg/week, the mean value of C_{max} was 75.1 ng/ml at week 1 and was relatively consistent until week 24. T_{max} was 90.5 min at week 1 and 240 min at week 24. The values for the area under the plasma concentration-time curve (AUC_{0-t}) did not differ significantly between week 1 ($AUC_{0-t} \cong 10{,}000$ min × ng/ml) and week 24 ($AUC_{0-t} \cong 13{,}000$). In the cohort that was treated with the higher dose (1.0 mg/kg/week), values for C_{max} increased from 572 ± 60.2 ng/ml at week 1 to 1651 ± 5.0 ng/ml at week 24, thereafter the values did not change significantly anymore until week 96. In the high-dose group (1.0 mg/kg/week) T_{max} was 120 min at week 1, 181 min at week 2 and remained stable until week 83. The AUC_{0-t} increased from 94,476 ± 13,785 min × ng/ml at week 1 to 251,907 ± 201,747 min × ng/ml. Evaluation of individual subject values revealed that the increase in the mean, as well as the large standard deviation of AUC_{0-t} at week 24 was due to the development of high serum antibody titer, measured by ELISA, in one patient. Later (week 83) the antibody titer declined; the AUC_{0-t} value decreased and was consistent with those of the other patients.

In summary, pharmacokinetic parameters for rhASB at week 83 were comparable to those from week 2, indicating consistency in pharmacokinetics after weekly infusion for approximately 18 months. However, there were enormous differences between the patients receiving 0.2 and 1.0 mg/kg/week. At week 2, the AUC_{0-t} was approximately 10,000 min × ng/ml in the low-dose group, and approximately 200,000 min × ng/ml in the high-dose group. These differences are much higher than that of the applied dose, indicating that the pharmacokinetics of rhASB are not linear over this dose range.

The optimum dose interval is a crucial issue in ERT in general, the recommended dosing interval for agalsidase-α and agalsidase-β (used for Fabry disease) is every 2 weeks, and weekly for laronidase (MPS I). For patients with Gaucher disease, an individualized dose regimen is proposed. As data for the optimal dosing interval for rhASB are lacking in humans, the parameter necessary for determining the dosing frequency was delineated from animal studies. Using cross-species rhASB in a normal cat, Crawley and colleagues estimated the tissue half-life to be 2 to 4 days and after 1 week almost no enzyme was detectable [20]. These results from the animal model support the hypothesis that weekly enzyme application might reveal better results.

Clinical efficacy

Phase I/II studies

As mentioned above, a clinical trial of enzyme replacement was initiated on the basis of the studies previously conducted in cats [25]. A total of seven MPS VI patients (7–16 years of age) were randomized to weekly infusions of either high (1.0 mg/kg) or low (0.2 mg/kg) doses of rhASB. Of the seven patients, two withdrew from the study due to personal reasons and five completed 48 weeks of treatment. At week 48, there was a considerable decrease in the GAG excretion and the difference between urinary GAG at baseline and that at week 48 (relative reduction) for the total population was significant ($p = 0.04$). In comparison with the low-dose group, a more rapid and larger sustained relative reduction was seen in the high-dose group (63 vs 51%) at week 48. Functional capacity was assessed by the 6-min walk test, which has primarily been used to measure cardiac or pulmonary disease [3]. A significant

improvement (p = 0.04) in the walking distance was observed in the patients, particularly in two who at baseline walked less than 100 m.

The patients in the Phase I/II study described above showed a great variation in severity. Therefore, a Phase II open-label trial was initiated that included patients (6–22 years of age), who were relatively uniform with regard to impaired endurance [26]. Furthermore, this study assessed clinically important measures of endurance, mobility and joint function that can be attributed to the enzyme application. Inclusion criterion of this trial was that the patient could walk at least 1 m, but not more than 250 m in 6 min. A total of ten patients with MPS VI were enrolled who received 48 weekly infusions of rhASB (1.0 mg/kg) and underwent clinical assessments at regular intervals. Results of the Phase I/II study suggested that some patients might not walk faster, but much further at the same speed after treatment. Therefore, it was decided to increase the measurement time to 12 min instead of 6 min to better capture the maximum walking distance – given the possibility, not that the walking velocity might change, but rather the walking range at the same speed. Furthermore, a 3-min stair climb test, as described by Balfour-Lynn and colleagues, was performed [27]. Range of motion of the shoulders was assessed with a goniometer – forced vital capacity (FVC) and forced expiratory volume at 1 min (FVC_1) was measured by standard spirometry techniques. Additional investigations in this trial included sleep studies, ophthalmologic evaluation, electrocardiogram, echocardiography, measurement of liver and spleen volume and assessment of bone density by computed tomography. For the evaluation of joint pain and stiffness, an analog scale was used based on the Health Assessment Questionnaire (HAQ) or the Childhood Health Assessment Questionnaire (CHAQ).

The patients received weekly infusions of rhASB at a dose of 1 mg/kg body weight. After 24 and 48 weeks of treatment, significant biochemical and clinical improvements were observed. There was a 71% decrease in urinary GAG excretion at 24 weeks and of 76% at 48 weeks. In the walk test, a greater mean improvement in walking distance (in meters) was observed at the 12-min time point in comparison with the 6-min time point (138 vs 80%) after 48 weeks of treatment. The results of both time points as a function of weeks of treatment, were statistically highly significant compared with baseline values. Furthermore, a significant increase in the number of stairs the patients could climb within 3 min was observed. Analysis of the CHAQ/HAQs revealed a pain decrease of 55 ± 54% (p = 0.015) and a stiffness decrease of 63 ± 22% (p < 0.001) at week 48. However, there were only minor gains (<10%) in shoulder range of movement. Considerable improvements (>10%) in FVC were observed in five patients. In all patients who had hepatosplenomegaly at baseline, a reduction of the liver and spleen size was observed.

Phase III study

Based on the experiences gained in the foregoing trials, a Phase III, randomized, double-blind, placebo-controlled clinical study was initiated [28]. In six centers from six countries (USA, Brazil, England, France, Germany and Portugal), 39 patients were enrolled, ranging in age from 5 to 29 years. Of these 29 patients, 19 received 1 mg/kg of recombinant human *N*-acetylgalactosamine 4-sulfatase (rhASB) and 20 received a placebo as weekly infusions. After 24 infusions, the group treated with the enzyme demonstrated a significant improvement (p = 0.025) in the 12-min walk test as compared with the placebo group. Moreover, patients receiving rhASB demonstrated a significant reduction (75%; p < 0.001) in urine GAGs. Improvements were also seen in the 3-min stair climb test. After completing the Phase III trial all patients entered into an open-label extension study, where the placebo group aslo received the enzyme [29]. This study confirmed the positive results of the Phase III study regarding the endurance (measured by the 12-min walk test and the stair climb test) and decrease of urinary GAG levels.

Postmarketing surveillance

After approval of the drug in the USA and Europe, an international registry will be established for postmarketing surveillance.

Safety & tolerability

In general, rhASB was well tolerated. Most of the adverse events that have been reported in the clinical trials reflected the underlying disease. Under placebo-controlled conditions, infusion-associated reactions such as dyspnea, rigors, pyrexia, chest pain, conjunctivitis, abdominal pain, rash and urticaria were observed. In the Phase III trial, nine patients had recurrent infusion-associated reactions that were managed by slowing down the

infusion at individual rates and administering additional antihistamines, antipyretics or steroids. No patients discontinued the study due to adverse events. A total of 37 of the 38 patients receiving 24 weeks of rhASB developed immunoglobulin (Ig)G antibodies; however, it was not tested whether they were neutralizing or not. Nevertheless, the antibodies did not have an impact on endurance nor were they associated with infusion-associated reactions. Development of antibodies during ERT is very common. In a large study of patients with Gaucher disease, 12.8% developed antibodies under treatment; however, 90% of these subjects became tolerant over time [30]. Similarly, five of ten MPS I patients treated with laronidase had an elevated antibody titer with high reactivity. However, by week 26 of the study, antibody titers were decreasing, and by week 103 all patients had titers in the same range as normal controls [31].

Regulatory affairs

On May 31, 2005, the enzyme preparation galsulfase (Naglazyme™, Biomarin Pharmaceutical, Inc.) was approved by the US Food and Drug Administration (FDA) for the treatment of individuals with MPS VI. Naglazyme achieved orphan drug status and has been granted marketing approval only in the USA; however, Biomarin has also filed marketing license applications in the European Union, and it is expected that the drug will receive approval in Europe from the European Agency for the Evaluation of Medicinal products (EMEA) at the end of 2005.

Conclusion

Enzyme replacement appears to be a very promising therapy for patients with MPS VI and enables physicians, for the first time, to offer more than symptomatic relief. However, it has to be taken into consideration that long-term experience of this new therapeutic option is still lacking, and it is not yet known which symptoms are reversible and which complications can eventually be prevented by early onset of treatment.

Expert commentary

Until now, ERT with galsulfase has only been administered in a small number of patients who participated in the clinical trials. Therefore, the experience with this drug remains very limited. This is also true for the duration of treatment time. Children under the age of 5 have not yet been treated, thus it is not known whether some complications could be prevented by the early start of infusions with galsulfase. Animal studies have shown that by enzyme replacement just after birth, even severe bone disease can be prevented [17]. Therefore, a screening program that makes the diagnosis of a lysosomal storage disorder possible in the presymptomatic stage appears to be essential, particularly as ERT is available for Gaucher disease, Fabry disease, MPS I and soon for MPS II [32] and Pompe disease [33].

Thus far, all clinical trials have demonstrated a favorable risk–benefit profile for galsulfase. However, most of the patients developed antibodies that did not have any impact on efficacy or tolerability. Infusion-associated reactions have been observed in some patients that should be managed by adequate premedication. No patient has had to discontinue treatment due to adverse events. In comparison with bone marrow transplantation, which is associated with high morbidity and mortality, ERT appears to have a better benefit–risk ratio. However, both therapeutic options do not have any influence on skeletal deformities.

As discussed above, the dose and dose interval for galsulfase has been deduced from animal experiments; however, it would be very difficult to perform dose-finding studies in a large number of patients due to the low incidence of MPS VI. It is likely that each patient will require an individualized dose, as for Gaucher disease. The urinary GAGs may serve as a marker, since it has been shown that GAG excretion correlates very well with dose [24]. Many questions regarding dose and dose interval will most likely be answered in the coming years when information from a database will be available, which should include patients who are on enzyme replacement as well as patients who have not yet been treated. In this database, variables should be collected such as GAG excretion, the 6-min walk test, lung function and measurement of QoL.

ERT with galsulfase offers, for the first time, the possibility of therapy rather than palliative care and is not associated with any unacceptable risk. As there is no alternative (except bone marrow transplantation), it is recommended for all patients with MPS VI and from a theoretical point of view, the infusions should start as soon as the diagnosis is made. As yet, there are no studies in children under 5 years of age that include assessment of the skeletal system. The effect of galsulfase on pregnancy and lactation also remains to be tested. However, the use of this enzyme preparation under such conditions should not be a major concern as ERT has been

used during pregnancy in other lysosomal storage disorders such as Gaucher disease [34], MPS I [35] and Fabry disease [36] without any complications. There is only one major concern about the application of galsulfase in a large number of patients – the price of the drug, which may particularly be a problem in countries that have a limited health budget. However, the cost of galsulfase does not differ too much from other enzyme preparations and expensive treatments.

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Highlights

- Mucopolysaccharidosis Type VI is a rare lysosomal storage disorder that affects the skeleton, joints, heart, eye and other organs. It is caused by a deficiency of the lysosomal enzyme arylsulfatase B.
- Until now no effective treatment was availabe besides bone marrow transplantation.
- Animal studies with cats have been conducted that have demonstrated the efficacy of regular infusions of recombinant arylsulfatase B.
- On the basis of experiments with cats, clinical trials with mucopolysaccharidosis Type VI patients were performed that confirmed the results of the animal studies.
- The positive results of the clinical trials have lead to the approval of the enzyme preparation galsulfase (Naglazyme™) in the USA.
- It is expected that galsulfase will also gain approval in Europe.

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