Enzyme replacement therapy with galsulfase for mucopolysaccharidosis VI: clinical facts and figures

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Mucopolysaccharidosis VI (MPS VI) is an inheritable, clinically heterogeneous lysosomal storage disorder that develops due to a deficiency in the arylsulfatase B (ASB) enzyme. This deficiency impairs the stepwise degradation of glycosaminoglycans (GAGs) resulting in the accumulation of partially degraded GAGs in tissues and organs throughout the body. A relatively novel therapy for MPS VI is enzyme replacement therapy (ERT) with human recombinant ASB (galsulfase).

This manuscript gives an overview of all clinical trials that have evaluated the efficacy and safety of ERT with galsulfase in patients with MPS VI to date and discusses the outcome of these trials.

Key words: clinical trial, enzyme replacement therapy, mucopolysaccharidosis VI, review, treatment outcome.

Mucopolysaccharidosis VI (MPS VI), or Maroteaux-Lamy syndrome, is a rare autosomal recessive metabolic disease that belongs to the group of mucopolysaccharidoses[1]. Its incidence has been estimated at 0.15 to 0.3 per 100,000 births but may vary considerably between countries and even between different populations living in the same country[2]. The mucopolysaccharidoses are lysosomal storage disorders that manifest in patients with a deficiency in one of the enzymes involved in the degradation of glycosaminoglycans (GAGs). The affected enzyme in MPS VI patients is *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B, ASB). Its deficiency results in the accumulation of dermatan sulfate and chondroitin 4 sulfate in lysosomes and a wide range of tissues, which can lead to progressive tissue and organ dysfunction and premature death in most instances[3]. There are rapidly progressing (onset before 2 or 3 years of age) and slowly progressing (attenuated) forms of MPS VI disease, and patients can present with a vast array of clinical phenotypes[4]. Patients with MPS VI commonly demonstrate dysmorphic facial features, dysostosis multiplex, corneal clouding, impaired vision and hearing, hepatosplenomegaly, cardiopulmonary disease, and neurological problems such as carpal tunnel syndrome and spinal cord compression[3]. Skeletal abnormalities and associated joint disease (dysostosis multiplex) often result in dysmorphism and growth deceleration. Death generally occurs in the second or third decade of life in patients with rapidly progressive disease and in the fourth or fifth decade in slowly progressing patients. It usually results from infection, cardiac disease or complications secondary to surgery.

Mucopolysaccharidosis VI is typically associated with an abnormally high level of urinary GAG. A cross-sectional survey in 121 untreated MPS VI patients has suggested an association between urinary GAG levels and clinical morbidity[5]. A high GAG level (>200 μg/mg creatinine) is generally associated with a rapidly progressing phenotype and a GAG value below 100 μg/mg creatinine with a slowly progressing form of the disease.

Due to the presence of multiple disease manifestations, patients with MPS VI require an integrated program of care. Surgical, medical and physical therapy can considerably

alleviate symptoms of MPS VI, but do not affect the underlying cause of the disease, i.e. accumulation of GAG in cells and tissues. The regular degradation of GAG in the body can only be restored by therapies that are based on the replacement or delivery of the missing or defective enzyme. Currently available MPS VI-specific therapies include haematopoietic stem cell transplantation (HSCT), where ASB is delivered by transplanted donor cells, and enzyme replacement therapy (ERT), which involves infusion with recombinant enzyme. Although HSCT has been shown effective in some MPS types[6], its use is limited by an increased morbidity and mortality risk and the need for healthy stem cell donors[7]. ERT with recombinant human ASB (galsulfase, Naglazyme®, BioMarin Pharmaceutical Inc, Novato, CA, USA) for intravenous administration has become available for MPS VI only recently. Its efficacy and safety have been assessed in several clinical trials.

This paper provides a review of all currently available published clinical trial data on the efficacy and safety of galsulfase in MPS VI patients.

Efficacy and Safety of Galsulfase in MPS VI Patients

Thus far, three independent clinical trials have evaluated the efficacy and safety of galsulfase: one phase 1/2 study, one phase 2 study and one phase 3 study[8-10]. A total of 56 MPS VI patients between 5 and 29 years with a mean age of 12 years were included in these trials, and the majority of cases had a rapidly progressing form of the disease[8-10]. An open-label extension study, including all patients who completed these three clinical trials, evaluated the long-term efficacy of galsulfase in endurance and safety, and included follow-up data for a period of 97 to 260 weeks[11]. Additional data on the long-term efficacy of galsulfase on pulmonary function were collected during the 97 to 240 weeks of the extension study involving the same patients[12]. Table I gives a summary of the designs of the clinical trials. The following paragraphs summarize the outcome of these trials.

Table I. Overview of Clinical Trials with Galsulfase[8-11]

	Study design	Number of patients enrolled/ completed	Galsulfase dose (mg/kg)	Duration of therapy (weeks)	Duration of follow-up (weeks; efficacy/ safety)[11]	Mean age (range)	Sex (male/ female)	Endurance tests
Harmatz 2004[8]	Phase 1/2 randomized, double-blind, two dose trial*	7/5	0.2/1.0	48	240/260	12.0 (7-16)	4/3	6MWT
Harmatz 2006[9]	Phase 2 open-label trial	10	1.0	48	144/214	12.7 (6-22)	7/3	12MWT 3MSC
Harmatz 2006[10]	Phase 3 double-blind, randomized, placebo-controlled trial with open-label extension	39**/38	1.0	24†/24‡	96/159	13.7 (5-29)	13/26	12MWT 3MSC

6MWT: 6-minute walk test. 12MWT: 12-minute walk test. 3MSC: 3-minute stair climb.

*Study blind was removed after 24 weeks

**19 of these patients received galsulfase 1.0 mg/kg and 20 received placebo during the double-blind phase of the study (†). During the open-label phase (‡), all patients received galsulfase 1.0 mg/kg.

Impact on urinary GAG

All clinical trials reported a significant decrease in urinary GAG after ERT was started[8-10]. In

the phase 1/2 study, weekly infusions of 1.0 mg/kg galsulfase resulted in a more rapid and larger sustained relative reduction than weekly infusions of 0.2 mg/kg galsulfase (63% vs 51% reduction at 48 weeks) (Fig. 1)[8,13]. In the placebo-controlled part of the phase 3 study compared to galsulfase-treated patients, urinary GAG levels decreased significantly more in patients treated with galsulfase than in those treated only with placebo ($p<0.001$)[10]. In the open-label phase 3 extension study, urinary GAG levels remained on average 71% lower than baseline for patients who were switched from placebo at 24 weeks and treated with galsulfase up to the 96th week ($p<0.001$) compared to 72% lower than baseline for patients on galsulfase throughout the study to the same end-point ($p<0.001$)[11].

Impact on endurance

Physical endurance in MPS VI patients was measured in all clinical trials using 6- or 12-min walk tests (6MWT and 12MWT) and/or a 3-min stair climb (3MSC) test (Table I)[8-11]. In the placebo-controlled phase 3 study, distance walked in a 12MWT was the primary efficacy variable, whereas the number of stairs climbed in a 3MSC was a secondary efficacy variable. In the phase 1/2 and phase 2 clinical studies, most patients treated with galsulfase for 24 and 48 weeks performed significantly better in the walk test than they did before treatment was started[8,9]. All patients included in the phase 2 study performed better in the 3MSC test 24 weeks after treatment was started compared to baseline values, with continued improvement through 48 weeks[9]. In the phase 2 study, the investigators observed a mean improvement of 155 m (98%) in the 12MWT and a gain of 48 stairs (110%) in the 3MSC after 24 weeks compared to baseline mean values. After 48 weeks, the mean distance walked in a 12MWT increased by 211 m (138%), and the number of stairs climbed in a 3MSC increased by 61 stairs (147%) compared to baseline mean values [9]. In the phase 3 study, the mean distance walked in a 12MWT and the mean number of stairs climbed per min were higher in patients treated with galsulfase than in the placebo group after 24 weeks ($p=0.025$ and $p=0.053$, respectively)[10]. Figures 2a and 2b show the mean performance change from baseline in the 12MWT and 3MSC, respectively, for all patients included in the phase 2 and phase 3

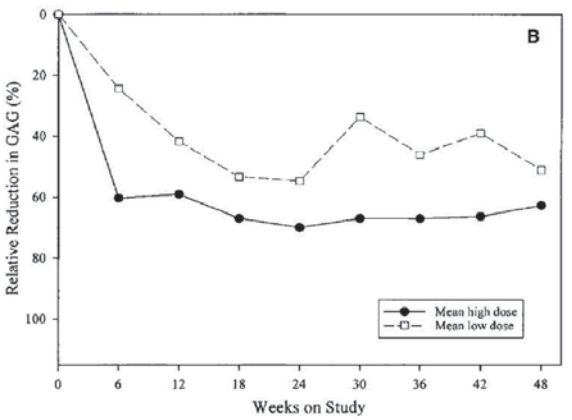

Fig. 1. Weekly infusions with galsulfase significantly reduced urinary glycosaminoglycan (GAG) excretion, with the effect being larger in patients receiving a high dose (1.0 mg/kg) of galsulfase than in those receiving a low dose (0.2 mg/kg). Reprinted from Harmatz P, et al.[11], with permission from Elsevier.

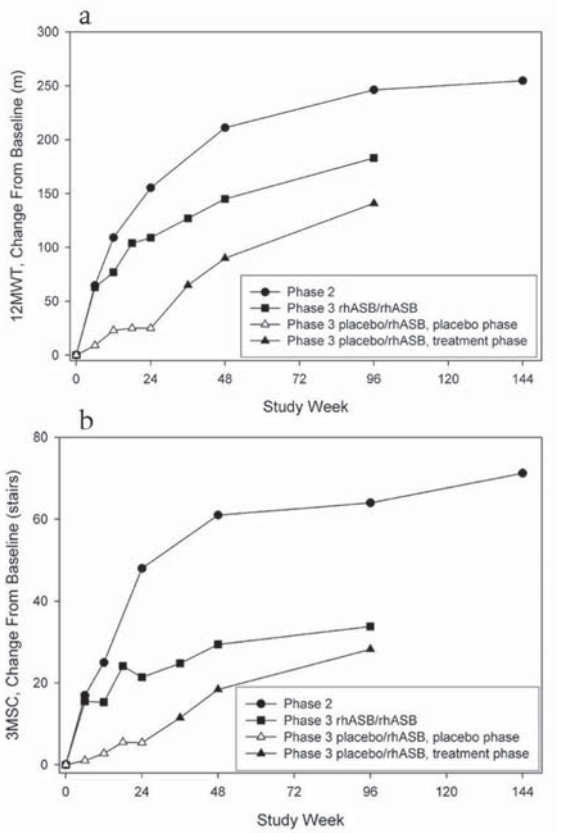

Fig. 2. Weekly infusions with galsulfase caused a sustained increase in (a) the distance walked in a 12-minute walk test (12MWT) and (b) the number of stairs climbed in a 3-minute stair climb (3MSC) test. Reprinted from Harmatz P, et al.[11], with permission from Elsevier.

studies over a period of 144 and 96 weeks, respectively. Sustained improvements were seen for the entire study period[11]. Endurance improved in all patients after starting ERT and was sustained for at least 2 to 5 years in most patients as supported by these clinical trials.

Other clinical evaluations

All clinical trials evaluated the impact of ERT on several clinical variables other than endurance. Additional clinical evaluations in the phase 1/2 and phase 2 studies included joint range of motion, joint pain and stiffness, pulmonary function, functional status, ophthalmology, electrocardiogram, liver volume, bone density, and polysomnography[8,9]. Tertiary efficacy variables of the phase 3 study included (1) joint pain, joint stiffness, and physical energy level, (2) joint range of motion, and (3) hand dexterity as measured by a coin pick-up test[10].

The phase 1/2 study reported improvements in shoulder range of motion in five of six patients after 48 weeks of ERT ($p=0.04$ for both shoulders)[8]. Although improvements in joint range of motion were also observed in the phase 2 and phase 3 studies, the mean improvements were modest ($<10°$) or not significantly different between the galsulfase and placebo groups[9,10] . The phase 1/2 and phase 2 studies also reported improvements in joint pain and stiffness, measured using modifications of the Health Assessment Questionnaire (HAQ) and the Childhood Health Assessment Questionnaire (CHAQ). In the phase 2 study, (C)HAQ scores decreased significantly from baseline by more than 50% within 24 weeks and were maintained up to 48 weeks[9]. In the phase 3 study, joint pain and stiffness did not significantly differ between the placebo and galsulfase treatment groups.

Analysis of pooled pulmonary function data from the three clinical studies using a longitudinal linear mixed-effects model indicated that pulmonary function (>10% gain in forced vital capacity [FVC] and forced expiratory volume in 1 s [FEV1]) changed little from baseline during the first 24 weeks of treatment, but both variables increased after 96 weeks by 17% ($p=0.009$) and 11% ($p=0.014$), respectively, and continued to improve thereafter (up to 240 weeks)[12]. Changes in FVC and FEV1 were accompanied by a 5.5% increase in height in patients <12 years. In older patients (≥12 years), these changes also occurred despite a smaller increase in height (2.4%). In the phase 3 study, the maximum voluntary ventilation (MVV) was evaluated as a measure for rib-cage excursion as a result of increased strength or flexibility. Improvements in MVV by 15% over baseline were seen within 24 weeks of treatment ($p=0.021$) and appeared to continue through 240 weeks of treatment[12].

Of the functional status measures evaluated in the phase 2 study, the greatest improvements were reported for the coin pick-up test (time in seconds to pick up 10 coins and put them into a cup); at week 48 all 10 patients performed the test faster than at baseline (mean improvement 17 seconds, $p=0.004$)[9]. The phase 3 study did not show a significant difference in outcome for this test between the placebo and galsulfase treatment groups[10]. In the phase 2 study, the mean total time to perform the Expanded Timed Get-Up and Go test, a test originally developed to quantify functional mobility in the geriatric population[14], decreased from 31 seconds at baseline to 26 and 23 seconds at weeks 24 and 48 ($p=0.002$ and $p=0.003$ vs. baseline, respectively).

Reductions in liver and spleen size were observed in all five patients with hepatosplenomegaly included in the phase 2 study[9].

No changes were reported on echocardiogram, bone density examinations, or visual examination in any of the studies[8-10].

Safety

Enzyme replacement therapy (ERT) was withdrawn in three of the 56 patients participating in the clinical trials. None of the withdrawals was related to treatment. In the phase 3 study, the incidence of total adverse events (AEs), severe AEs and serious AEs in patients allocated to galsulfase was similar to that in patients treated with placebo, with most AEs being a result of pre-existing medical problems due to MPS VI[10]. Long-term follow-up safety data from the three clinical trials reported that 14% of AEs were considered related to treatment and only 2% of these were described as severe[11]. Infusion-related reactions occurred in over half of the patients and were usually mild or moderate.

Anaphylactoid reactions, occurring in 16% of patients, could be managed by decreasing the study drug infusion rate, interrupting the infusion or by adding antihistamines or anti-inflammatory agents such as ibuprofen and corticosteroids[11]. IgG antibodies against galsulfase developed in almost all patients, but did not have a neutralizing effect in most cases[8-10]. The effect of galsulfase on urinary GAG levels was not associated with antibody development.

Discussion

The clinical trials described in this paper show that intravenous ERT with galsulfase causes a rapid and significant reduction of urinary GAG, suggesting a better degradation of GAG. Within 24 weeks of treatment, most patients treated with ERT demonstrated significant and sustained improvements in performance in 6- and 12MWT and 3MSC tests. Long-term safety data show that the therapy has an acceptable safety profile.

The combination of the walk and stair-climb tests provides a robust approach for assessing the impact of ERT on endurance in MPS VI patients[9]. The ability to perform a walk or climb test can depend on several factors such as cardiorespiratory function, joint and muscle function, pain, orthopedic complications, and neurological function, which may differ considerably from patient to patient. Analysis of pooled data from the three clinical studies indeed indicated that long-term treatment with galsulfase improves the pulmonary function of patients with MPS VI, irrespective of age[12]. The impact of galsulfase on other individual manifestations of MPS VI remains unclear. Although the phase 1/2 and phase 2 clinical trials suggested improvements in joint stiffness and pain, performance in a coin pick-up test, and functional mobility[8,9], no significant effect of galsulfase could be seen for any of these variables when compared with placebo in the phase 3 study up to 24 weeks of treatment. A possible explanation for this lack of effect is that the impact of galsulfase was limited in this study by access to better medical care or that a treatment period longer than 24 weeks is required to achieve significant changes in some of these variables[10]. The observation in the phase 2 study that galsulfase has a positive impact on liver and spleen size in patients with hepatosplenomegaly seems to be confirmed by observations beyond clinical trials[15]. However, the impact of ERT on these variables was not evaluated against placebo in the phase 3 study and needs further investigation before definitive conclusions can be drawn.

Once established, certain disease manifestations of MPS VI, such as skeletal dysplasia and coarse facial features, will not be reversed or stabilized with ERT. As ERT slows down the accumulation of GAG in cells and tissues, it is thought that early treatment might prevent or delay the development of irreversible disease manifestations and limit or prevent growth deceleration. Indeed, animal studies have established that early onset of ERT maximizes the impact on skeletal dysplasia[16-18]. However, no conclusions can currently be made on the efficacy and safety of ERT with galsulfase in human babies and infants as the clinical trials only included patients between 5 and 29 years old (mean age around 12-14 years). More insight in this matter can be expected from the ongoing multinational infant study (http://clinicaltrials.gov/ct2/show/NCT00299000) and several ongoing case studies. One recently published case control study assessed the impact of galsulfase in two siblings: one treated from the age of 8 weeks, one from 3.6 years[19]. After 3.6 years of treatment with galsulfase, the youngest child had a lack of scoliosis and preserved joint movement, cardiac valves and facial morphology, unlike the older sibling at the same age. The older sibling had improvements in joint mobility and cardiac valve disease after 3.6 years of treatment with galsulfase. Despite treatment, both siblings developed corneal clouding and progressive skeletal changes. New data can also be expected from the Clinical Surveillance Programme (CSP). The CSP, a voluntary, multi-national observational program for patients with MPS VI, aims at tracking specific clinical outcomes in patients with MPS VI over a period of ≥15 years. According to a first data analysis, 101 patients with MPS VI, 60 from European centers and 41 from United States centers, have been included since September 2005[20]. The median age of the enrolled patients was 14 years (range: 0-60 years) and the majority (N=95) were receiving or had been receiving ERT. ERT was started at a median age of 10

years. Overall, the first results of the CSP appear to confirm the effects of ERT on urinary GAG levels and endurance that were reported in the clinical trials. In addition, an increase in both height and weight was observed[20]. No improvement or deterioration was seen for cardiac, ophthalmologic or auditory data. Safety data confirmed that ERT with galsulfase is generally well tolerated[20].

Enzyme replacement therapy (ERT) usually has no or only limited effects in the eyes, central nervous system and joints. This is likely due to the inability of the enzyme to cross the blood-brain and blood-retina barrier and the inaccessibility of articular cartilage[21,22]. The limited effect of ERT on joint disease and the central nervous system probably explains why some patients do not show sustained improvement in walk and stair-climb tests despite an initially positive effect. Other administration routes for ERT, i.e. intrathecal and intraarticular, are being examined in order to prevent progression of complications such as spinal cord compression and skeletal dysplasia. Intrathecal ERT involves the infusion of recombinant enzyme into the spinal fluid, whereas intraarticular ERT involves the direct injection of enzyme into the intra-articular space. Studies in MPS animal models and a few case reports in humans have shown promising results for both techniques[23-25].

Conclusion

The introduction of ERT with galsulfase has been a milestone in the treatment of MPS VI patients. This therapy opens the door to a more proactive approach of managing the disease, i.e. slowing down the accumulation of GAG rather than alleviating the resulting clinical manifestations. Clinical trials have shown that intravenous ERT with galsulfase is well tolerated and improves endurance in most cases. Therefore, international guidelines now recommend weekly intravenous infusions with galsulfase, when available, as first-line treatment for MPS VI[4]. Obviously, ERT should be used in the framework of integrated care, along with physical therapy, and medical and surgical management of individual disease complications. More research is warranted to assess the impact of ERT on individual disease manifestations of MPS VI and its efficacy and safety in very young children.

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