Guidelines for the Investigation and Management of
Mucopolysaccharidosis type VI

These guidelines have been prepared (to assist commissioning of services for MPS VI) by a multidisciplinary group consisting of:

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The clinicians from Cambridge, London and Manchester are involved in ongoing studies into the treatment and management of mucopolysaccharide disease and have extensive experience of enzyme replacement therapy for lysosomal storage disorders (LSDs). These centres have an ongoing commitment to managing patients in dedicated outpatient and inpatient facilities and are all designated NSCAG centres for the diagnosis and management of (LSDs).

The Society for Mucopolysaccharide disease provides an information and advocacy service for patients and families affected by mucopolysaccharide disease.
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MPS VI disease - a brief overview

Mucopolysaccharide storage (MPS) disorders are caused by deficiencies of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAGs). The accumulation of GAG substrates occurs in a variety of tissues and is dependent on the location of the affected substrates and their rate of turnover. N-acetylgalactosamine 4-sulfatase (also known as Arylsulfatase B, ASB) is a lysosomal enzyme that hydrolyzes the sulfate moiety of dermatan sulfate. Deficiency of ASB results in the accumulation of dermatan sulfate in many tissues and a chronic progressive disorder known as mucopolysaccharidosis VI (MPS VI, Neufeld and Muenzer 2001). In the absence of ASB, the stepwise degradation of dermatan sulfate is blocked, resulting in intracellular accumulation of the substrate in the lysosomes of a wide range of tissues. The accumulation causes a progressive disorder with multiple organ and tissue involvement. Infants with the disease appear normal at birth, but come to clinical attention at 6-24 months of age because of progressive deceleration of growth, skeletal deformities, coarse facial features, upper airway obstruction, and joint deformities. Progressive clouding of the cornea, communicating hydrocephalus, and heart disease may develop in MPS VI children. Death usually results from respiratory infection or cardiac disease. In contrast to many of the MPS disorders, MPS VI is not typically associated with progressive impairment of mental status, although physical limitations may impact learning and development. The disease is usually fatal by the teenage years for those with the most rapidly advancing form of the disease, although those with more slowly advancing disease may survive into their fourth decade. This variation in the development of clinical symptoms provides the basis for the large phenotypic heterogeneity of the disease.

Several publications provide estimates of MPS VI incidence. A 1990 British Columbia survey of all births between 1952 and 1986 published by Lowry et al. (1990) estimates an incidence of 1:1,300,000. An Australian survey of births between 1980 and 1996 (Meikle et al. 1999) found 18 MPS VI patients, for an incidence of 1:248,000. A survey in Northern Ireland by Nelson et al. (1997) estimated an incidence of 1:840,000. Finally, a survey in The Netherlands from 1970 to 1996 calculated a birth prevalence of 0.24 per 100,000 (1:416,000) (Poorthuis et al. 1999). Based on these surveys, it is estimated that there are approximately 1100 patients worldwide with MPS VI.

There is no satisfactory treatment for MPS VI, although a few patients have benefited from bone marrow transplantation (Krivit et al. 1984; Krivit 1992). Bone marrow transplantation is not universally available because of a lack of suitable donors and is associated with substantial morbidity and mortality. The European Group for Bone Marrow Transplantation reported a transplant-related mortality rate of 10% (HLA [human leukocyte antigen] identical) to 20%–25% (HLA mismatched) for 63 cases of transplantation in patients with LSDs (Hoogerbrugge et al. 1995). Most patients receive treatment for specific symptomatic problems as their only form of care.
1.1 A brief synopsis of ERT trials

Evidence on which these guidelines are based is limited at present. There have been two completed clinical trials in humans and a number of post-marketing clinical trials are in progress. Additional long term data is available from abstracts presented at various clinical meetings.

In both human studies recombinant ASB (rhASB) was given as a weekly infusion in a dose of 1.0 mg per kg per week.

a) A randomized, double-blind, Phase 1 / 2 study (ASB-00-01) designed to evaluate the safety, efficacy, and pharmacokinetic profile of rhASB given as enzyme replacement therapy in patients with MPS VI is ongoing. Patients were randomized in a double-blind fashion to two dose groups: 0.2 and 1.0 mg/kg. Study drug was given once per week as a 4-hour IV infusion.

Six patients exhibiting disease characteristics varying from moderately to rapidly advancing disease were initially enrolled in the study. One patient dropped out of the study (at Week 3) for personal reasons and was replaced. A pre-specified interim analysis was conducted following the completion of 24 weeks of treatment by the remaining 6 patients. Data from the Week 24 interim analysis showed that rhASB was well tolerated, the 1.0 mg/kg dose produced a greater reduction in urinary GAG excretion than the 0.2 mg/kg dose, and the two doses had comparable safety profiles. Patients in the low-dose group were offered continued treatment at the 1.0 mg/kg dose. One patient elected to discontinue the study for personal reasons at Week 32 prior to switching to the higher dose. The remaining 2 patients from the low-dose group initiated treatment at the high dose after Week 48 (1 at Week 59 and 1 at Week 69). Patients treated through Week 96 have received the majority of the planned rhASB infusions. No patient has missed more than a total of two infusions during this period.

Evaluation of biochemical markers of rhASB activity, urinary excretion of GAGs as well as urinary excretion of dermatan sulfate, showed dose-related decreases from baseline levels through Week 24, with continued declines through Week 96 following transition to the higher dose by the 0.2 mg/kg group. The extent of reduction in GAG excretion during the first 24 weeks of treatment was largest in the 1.0 mg/kg group, with a mean reduction from baseline of 70% in the 1.0 mg/kg group and 55% in the 0.2 mg/kg group. Excretion of dermatan sulfate also showed a greater decline at 24 weeks in the high-dose group. Examination of the time course of the change in urinary excretion of GAGs as a function of weeks on treatment showed a more pronounced drop in total urinary GAGs in the 1.0 mg/kg versus 0.2 mg/kg group by 6 weeks. These data confirm that the higher dose produced a larger change in urinary excretion of both GAGs and dermatan sulfate. By Week 96, all patients, regardless of their initial assigned dose level, had experienced significant declines (63%–86%) in urinary GAGs.
The distance walked in the 6-minute walk test served as the primary clinical measure of endurance. The 2 patients unable to walk >100 meters at baseline, both randomized to the higher dose group, had large improvements in the total distance walked by 24 weeks. All but 1 patient (who developed C1–C2 cord compression) showed improvement in distance walked by Weeks 48 and 96. Modest improvements in a number of other efficacy parameters were seen during the 96 weeks of treatment, including shoulder range of motion (ROM), measures of respiratory function, visual acuity, and hepatomegaly.

No deaths or discontinuations because of adverse events (AEs) were reported during the initial 96 weeks of the study. A total of 17 SAEs were reported in 4 patients. One of these events, dermatitis (urticaria), was considered to be related to study drug administration. The remaining events were considered to be related to MPS VI disease or intercurrent illness. Data from this clinical trial has been published (Harmatz et al 2005a, Harmatz et al 2005b).

b) A 24-week, Phase 3, multi-center, double-blind, placebo-controlled trial involving 39 patients has also completed and entered an extension phase. Patients were randomized on a one-to-one basis into a RhASB treatment group or a placebo control group and received a weekly intravenous infusion of either 1.0 mg/kg of RhASB or placebo solution. During the 24-week period, 19 patients received weekly intravenous infusions of RhASB and 20 patients received weekly placebo infusions. One patient in the placebo group dropped out of the trial for reasons unrelated to treatment. All 38 patients who completed the trial elected to receive RhASB in an ongoing open-label extension study. Inclusion criteria for this study included:

- The patient must be at least 7 years of age
- The patient must have a diagnosis of MPS VI, confirmed by clinical signs and symptoms of MPS VI, and a documented fibroblast or leukocyte ASB enzyme activity level of less than 10% of the lower limit of the normal range of the measuring laboratory.
- The patient must be able to walk independently at least 5 meters and no more than 270 meters in the first 6 minutes, or no more than 400 meters total in 12 minutes, in the screening 12-minute walk test.

After 24 weeks of treatment, patients receiving RhASB demonstrated a statistically significant improvement (p=0.025) in endurance compared to patients receiving placebo as measured by the change relative to baseline in the distance walked in 12 minutes. The RhASB-treated group showed greater mean increase in distance walked in 12 minutes compared to the placebo group. The model-derived mean difference measured as a change from baseline between patients receiving RhASB and patients receiving placebo after 24 weeks was 92 +/- 40 meters. Following an additional 24 weeks of treatment with RhASB in the extension study, for a total of 48 weeks, patients demonstrated further improvement in endurance as measured by the change in distance walked in 12 minutes, relative to baseline. From week 24 to week 48, patients receiving
RhASB since week one of the trial improved their mean walk distance an additional 36 +/- 97 meters.

After 24 weeks of treatment, patients receiving RhASB demonstrated an improvement (p=0.053) in stair-climbing ability compared to patients receiving placebo as measured by the change relative to baseline in the number of stairs climbed per minute. The RhASB-treated group showed greater mean increase in the rate of stairs climbed in three minutes compared to the placebo group. The model-derived mean difference measured as a change from baseline between patients receiving RhASB and patients receiving placebo after 24 weeks was 5.7 +/- 2.9 stairs per minute. Following an additional 24 weeks of treatment with RhASB in the extension study, from week 24 to week 48, patients receiving RhASB since week one of the trial improved their mean number of stairs climbed per minute by an additional 3 +/- 7 stairs.

After 24 weeks of treatment, patients receiving RhASB experienced a statistically significant reduction (p<0.001) of GAGs excreted in the urine, compared to patients receiving placebo. The average urinary GAG reduction in patients receiving RhASB after 24 weeks was 75.5 percent. This initial reduction in urinary GAG levels was maintained following an additional 24 weeks of treatment in the extension study.

While in the extension study, patients who receive placebo solution during the initial 24-week trial demonstrated an improvement in endurance following 24 weeks of treatment with RhASB as measured by the change in distance walked in 12 minutes, relative to baseline. From week 24 to week 48, the original placebo group demonstrated a mean increase of 65 meters relative to week 24 values. These patients also demonstrated an average improvement in stair-climbing ability as measured by stairs climbed in three minutes, relative to baseline, of 5.7 stairs per minute following 24 weeks of treatment with RhASB. Additionally, patients initially receiving placebo demonstrated a reduction in urinary GAG levels following 24 weeks of treatment with RhASB comparable to that observed for those treated in the initial 24-week, double-blind portion of the trial.

Data from the Phase 3 clinical trial and extension study indicate that RhASB was generally safe. The most common adverse events observed in clinical trials in RhASB-treated patients were headache, fever, arthralgia, vomiting, upper respiratory infections, abdominal pain, diarrhea, ear pain, cough, and otitis media. Over 95 percent of the infusion-related adverse events were considered mild or moderate and were easily managed. Infusion-related adverse events commonly included fever, chills/rigors, headache, rash, and mild to moderate urticaria. Severe reactions included angioneurotic edema, hypotension, dyspnea, bronchospasm, respiratory distress, apnea, and urticaria. No patients discontinued RhASB infusions for adverse events and all patients that completed the double-blind portion of the trial continue to receive weekly infusions of
RhASB. Nearly all patients developed antibodies as a result of treatment, but the level of the immune response did not correlate with adverse events or impact the improvements experienced in endurance. Evaluation of airway patency should be considered prior to the initiation of treatment. Consideration to delay RhASB infusion should be given when treating patients who present with an acute febrile or respiratory illness. RhASB is marketed by Biomarin as Naglazyme.

1.2 Other evidence

The Naglazyme Clinical Development Program includes further trials which are to be started:

a. Patients under 1 year of age presenting with severe forms of MPS VI

These studies may provide additional evidence of efficacy in specific patient groups.

2.0 Confirmation of diagnosis

All patients with MPS VI as defined by a deficiency /absence of ASB enzyme activity measured in an appropriate tissue such as leukocytes or cultured skin fibroblasts.

3.0 Inclusion Criteria for Treatment

As impairments in respiratory function, cardiac disease, endurance and mobility are significant problems in MPS VI these have been used (along with other criteria) to determine suitability for ERT and improvements will be used to guide opinion on efficacy in an individual patient. The inclusion criteria are not the same as the entry criteria for the trial because if these alone were used many patients with significant disease burden would be excluded. The additional suggested criteria were not used in the clinical trial as they were felt not to be objective enough. Some patients with clinical evidence of severe disease will be too young to carry out formal pulmonary function tests or the 6MWT. These patients should still be regarded as eligible for immediate access to treatment. If there is any doubt about whether such patients are eligible they should be discussed at the NSCAG Expert Meeting.
Patients with MPS VI have little or no cognitive impairment and if they present with any of the following symptoms they should be considered for immediate treatment:

1. Signs of upper airways obstruction such as obstructive sleep apnoea diagnosed by formal sleep study. Other symptoms and signs include a history of difficult intubation or the use of continuous positive airways pressure (CPAP) or BiPAP would also signify significant upper airways obstruction and would constitute eligibility for treatment.

2. Symptomatic or asymptomatic airway disease including restrictive respiratory failure when detected and confirmed by pulmonary function tests indicating a forced vital capacity (FVC) of less than 80% of predicted.

3. Where it is possible to measure myocardial dysfunction by a reduction in ejection fraction, a value less than 56% (Normal Range 56-78%) should be regarded as an indication to start treatment with ERT. If ejection fraction is unreliable then significant impairment of systolic function should be demonstrated.

4. Evidence of impaired endurance as measured by the 6 minute walk test (6MWT) distance. The tests used in the phase III study the 12 minute walk test and the stair climb did not offer any significant advantages over the 6MWT and as this test is now so well known it is suggested that this is used to assess eligibility for treatment and to monitor the effects of therapy. Patients who walk less than 350 m in 6 minutes should be considered eligible for treatment.

5. Patients with symptoms and signs of raised intracranial pressure such as recurrent headaches and papilledema. These patients may also require surgical treatment.

Patients with MPSVI who fail to meet these criteria should be followed up in a systematic way with annual assessments designed to detect deterioration in clinical condition. In this way patients may be identified as suitable for treatment with ERT at a later date.

Patients with severe MPS VI presenting in infancy who are too young to carry out any of the assessments:

Treatment in this group should be started immediately as this group of patients always go on to develop the more rapidly progressive forms of MPS VI. As soon as they are old enough to comply attempts should be made to do all of the baseline assessments.
4.0 Exclusion criteria

1. Pregnant or lactating patients.
2. Patients deemed too sick or who have severe learning difficulties.
3. The presence of another life-threatening disease where prognosis is unlikely to be influenced by enzyme replacement therapy.

5.0 Baseline investigations

Patients may not be able to complete all these investigations. Essential studies have been indicated in bold print. In compliant, older patients (>5 years) e and f should also be regarded as essential.

5.1 Clinical including other specialist and radiological assessment

a) **medical history**
b) **clinical examination including head circumference measurement**
c) **vital signs – pulse, respiratory rate, BP, oxygen saturation in air**
d) **ENT assessment of upper airway with sleep study**
e) Pulmonary function tests
f) 6 minute walk test
g) **ECG and ECHO**
h) Ophthalmology assessment with ERGs, VEPs and a measure of intraocular pressure
i) Nerve conduction velocities to exclude carpal tunnel syndrome
j) Physiotherapy assessment to measure joint range of motion at shoulders, elbows, knees and hips
k) MRI scan of head and cranio-cervical junction
l) Skeletal survey- cervical spine in flexion/extension, lumbar spine, hips and pelvis

5.2 Laboratory Tests

a) **Urine glycosaminoglycans**

6.0 Treatment

Naglazyme

1.0 mg/kg/week in 250 mls normal saline

Infusion is initially given over 4 hours. Pre-medication with antihistamines and antipyretics at prescriber’s discretion. The length of time of infusions can be slowly reduced after the 8th infusion to 2 hours assuming there are no infusion associated reactions.
7.0 Follow up

Patients will be reviewed every 3 months in out-patients.

Each visit:

Clinical examination and vital signs
Urine glycosaminoglycans
Other baseline investigations may need to be repeated if clinically indicated

12 months (and annually thereafter):

All baseline investigations (with the exception of routine radiology and MRI scan) are repeated unless there is a clinical need to repeat them more frequently. MRI scan should be performed every 12-24 months; frequency to be left to discretion of treating clinician.

8.0 Efficacy end points

In the absence of any natural history studies it is unclear at what point the disease becomes irreversible. Consequently, our recommendations for commencing treatment and assessing efficacy are limited to what is available in the literature plus our clinical experience with affected patients.

The definition of effective treatment is:

8.1 “An improvement in or a prevention of progression of disease activity as indicated by a stabilisation in clinical condition associated with an improvement in the abnormalities present at baseline.”

8.2 Exit Criteria:

Patients or their parents must sign an agreement (a “patient contract”) to abide by the requirements regarding compliance and treatment discontinuation.

a) Treatment will be discontinued if the patient develops a life-threatening complication unlikely to benefit from further ERT. This includes severe infusion-associated reactions not controlled by other means.

b) Failure to comply with recommended dose regimen or follow up clinic visits and/or investigations.
c) Evidence of disease progression despite regular therapy as indicated by a 10% reduction in %predicted FVC, ejection fraction or 6MWT distance in the absence of a disease specific complication amenable to surgery such as a cardiac valve lesion or cervical myelopathy. The figure of 10% is arbitrary and subject to review as there no specific data to support this value.

9.0 Safety end points

Safety will be monitored by physical examination and vital signs.

In addition antibody testing and surveillance will be the responsibility of the prescribing physician in conjunction with the drug manufacturer who provides an antibody testing service. A protocol to deal with possible immune-related problems will be developed if this becomes necessary.

10 Audit

It is a requirement that each treatment centre will perform their own audit of their own service including patient satisfaction surveys. Other audit activity will be national and based on input into the national registry when developed.

After taking informed consent patient data should be entered into the disease specific registry as this is a component of the drug’s licensing approval.
References:


