Guidelines for the Investigation and Management of Mucopolysaccharidosis type I

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These guidelines have been prepared (to assist commissioning of services for MPS I) 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.

CONTENTS

MPS I 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. Alpha-L-iduronidase is a lysosomal enzyme that hydrolyzes the terminal α-L-iduronic acid residues of dermatan and heparan sulfate. Deficiency of α-L-iduronidase results in the accumulation of dermatan and heparan sulfate in many tissues and a chronic progressive disorder known as mucopolysaccharidosis I (MPS I).

Patients with MPS I are classified into three clinical syndromes – Hurler, Hurler-Scheie and Scheie. These three phenotypes cannot be distinguished by routine diagnostic procedures because all patients lack α-L-iduronidase activity and excrete excessive amounts of heparan sulfate and dermatan sulfate. Thus, patients are classified into a phenotype based on their symptoms and the severity of their symptoms. Hurler syndrome is the most severe clinical phenotype; Hurler-Scheie syndrome is an intermediate clinical phenotype; and Scheie syndrome is a milder clinical phenotype[1,2]. However, there is considerable heterogeneity in the severity and symptomatology within each clinical phenotype and there is substantial overlap of the symptomatology of the three syndromes[1, 3, 4].

Hurler syndrome

The symptoms of Hurler syndrome (MPS IH) present between 6 months and 2 years. They include inguinal or umbilical hernia, hepatosplenomegaly, coarse facies, skeletal deformities, short stature, enlarged tongue, prominent forehead, joint stiffness, acute cardiomyopathy associated with endocardial fibroelastosis, developmental delay followed by progressive degeneration, deafness, recurring upper respiratory tract and ear infections, obstructive airway disease, noisy breathing, persistent copious nasal discharge, corneal clouding, and communicating hydrocephalous associated with increased intracranial pressure[5, 6, 7, 8]

Obstructive airway disease, respiratory infection and cardiac complications are the most frequent causes of death. Death usually occurs by age 10 with a median of 5.19 years[9].

Hurler Scheie syndrome

The symptoms of Hurler-Scheie syndrome (MPS I H-S) include, but are not limited to, dysostosis multiplex, short stature, characteristic facies, corneal clouding, joint stiffness, deafness, and valvular heart disease.

Hurler-Scheie patients experience little or no intellectual dysfunction. The onset of symptoms in Hurler-Scheie patients is observed between ages three and eight. Death usually occurs during the second or third decade of life from cardiac and/or respiratory disease. A number of patients have died as a complication of anaesthesia[1, 3, 4].

Scheie syndrome

The symptoms of Scheie syndrome (MPS IS) include joint stiffness, aortic valve disease, mild hepatosplenomegaly, and corneal clouding. Scheie patients have little or no neurological involvement, are usually of normal stature and can have a normal life span although most have increasing physical disability and many will die in middle age predominantly of cardiac disease though a number many develop fatal cervical cord compression. The onset of symptoms is usually after five years, with a diagnosis between 10 and 20 years[1, 10, 11].

Treatment

Currently, no specific treatment exists for MPS I. Allogeneic bone marrow transplantation is the treatment of choice for selected MPS IH patients, but the outcomes vary widely and the procedure has associated risks, including increased morbidity and mortality[12, 13]. BMT, however, has been shown to slow or reverse some of the features of the disease.

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 iduronidase (rhIDUA) was given as a weekly infusion in a dose of 100 units per kg per week (0.58 mg/kg/week).

An open label study in 10 patients[14] showed that hepatosplenomegaly decreased significantly in all patients, and the size of the liver was normal for body weight and age in eight patients by 26 weeks. The rate of growth in height and weight increased by a mean of 85 and 131 percent, respectively, in the six prepubertal patients. The mean maximal range of motion of shoulder flexion and elbow extension increased significantly. The number of episodes of apnea and hypopnea during sleep decreased by 61 percent. New York Heart Association functional class improved by one or two classes in all patients. Urinary glycosaminoglycan excretion decreased after 3 to 4 weeks of treatment; the mean reduction was 63 percent of base-line values.

A pivotal phase III, placebo-controlled, double-blind, multi-centre and multinational study of ERT was performed in 45 patients over 5 years of age with MPS I. This trial is now in an extension phase (publication in preparation). Patients treated with rhIDUA compared to placebo showed a statistically significant increase of 5.9 percentage points in % predicted FVC (p=0.016), corresponding to an 11% improvement over baseline FVC. rhIDUA treated patients showed a mean 38.1 meter improvement in 6 minute walk test compared to placebo that approached statistical significance (p=0.066) and achieved statistical significance by pre-specified exploratory ANCOVA (p=0.039). Other significant treatment effects included reduction in hepatomegaly (p<0.001) and urinary glycosaminoglycan excretion (p<0.001). An extension study was commenced at the end of the trial in (June 2001 and completes in June 2005). These improvements have been maintained in the extension phase of the study and similar responses were seen in placebo patients who swapped over to active product after the end of the initial 26 week trial period[15].

Changes in the Disability Index as measured by CHAQ/HAQ (Childhood Health Assessment Questionnaire/Health Assessment Questionnaire) did not differ between the treated and placebo group.

1.2 Other evidence

The Aldurazyme Clinical Development Program includes further trials which are still in progress:

a. Patients under 5 years of age presenting with severe forms of MPS I
b. Patients with severe MPS I who are about to undergo or who have already received bone marrow transplantation
c. A dose ranging study to compare the effects of different dosage regimens both in terms of dose amount and frequency of administration.
d. A study in female patients who become pregnant whilst on Aldurazyme to see whether or not the drug is secreted into breast milk (the lactation study).

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

A number of abstracts have been presented which increase our knowledge of the potential long term benefits of Aldurazyme. These include:

a. 72 week extension phase III clinical trial data[16]. Analysis of data at this time point confirms sustained improvements in the clinical end points of the phase III study (endurance as measured by six minute walk test (6MWT) distance and respiratory function).

b. Effect of Aldurazyme on joint mobility[17]. Analysis of this data confirms that in patients with the more severe degrees of limitation of joint range of motion (JROM) that improvements continue to occur with ongoing therapy.
c. Several abstracts describing the use of Aldurazyme in patients with variable disease presentation from various countries. These are referenced for completeness but add little to the information already obtained from the clinical trials[18,19]
d. Presentations of ERT and HSCT (Haematopoetic Stem Cell Transplant0 combined[20,21,22]

2.0 Confirmation of diagnosis

All patients with MPS I as defined by a deficiency /absence of α-L-Iduronidase 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 I 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.

Patients with MPS I who have little or no cognitive impairment with any of the following symptoms should be considered for immediate treatment:

1. Signs of upper airways obstruction such as obstructive sleep apnea diagnosed by formal sleep study and defined as an apnea-hypopnea index >5 in adults (age over 18 years) or >1 in children or an overnight oxygen saturation <85% in adults or <92% in a child. (The Apnea-hypopnea index is the average number of apneas or hypopneas per hour of sleep)[23].

   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. Myocardial dysfunction as indicated by a reduction in ejection fraction to less than 56% (Normal Range 56-78%).
4. Evidence of impaired endurance as measured by the 6 minute walk test (6MWT) distance. This test was used in the pivotal clinical trial as a primary efficacy endpoint but normal ranges for this test depends on height and stride length and there are no normative data for children. Independent community ambulation, defined as the ability to walk at near normal speed of 80 m/min for 332 m is considered to be functionally important for activities such as crossing a street or performing an errand in the neighbourhood and therefore it is suggested that a 6MWT distance of less than 300 metres should be considered an indication for treatment. The mean baseline 6 MWT distance for patients in the phase III study was 319 metres.
5. Patients with symptoms and signs suggestive of raised intracranial pressure such as recurrent headaches and papilledema.

Patients with non-neurological MPS I 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 MPS IH

Treatment in this group should be confined to those patients awaiting HSCT in whom a donor has been identified and ERT is used to improve the patient's general condition prior to the treatment.

4.0 Exclusion criteria

1. Patients with MPS IH who are not proceeding to HSCT
2. Pregnant or lactating patients.
3. Patients deemed too sick.
4. 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 as part of the Physical Performance Testing for MPS I[24].
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

Aldurazyme

100U/kg/week in 100 mls normal saline <20 kgs
100U/kg/week in 250 mls normal saline >20 kgs

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) are repeated unless there is a clinical need to repeat them more frequently.

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.

There is an absence of quality of life (QoL) data from the various studies. There was no disease- specific QoL instrument available and it was felt that the generic tools available did not adequately in reflect changes in treated MPS I patients. Some disease specific tools tests have been developed, for example the Physical Performance Scale[24]. Where available these should be used as they are more likely to accurately reflect changes in function as a result of therapy.

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.

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