

Guidelines for the Investigation and Management of Mucopolysaccharidosis type II

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

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The clinicians from Cambridge, Manchester and London are involved in ongoing studies into the treatment and management of mucopolysaccharide diseases 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 Diseases provides an information and advocacy service for patients and families affected by mucopolysaccharide disease.

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MPS II - a brief overview

Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is an X-linked lysosomal storage disease caused by the missing or defective enzyme, iduronate-2-sulfatase (I2S), which cleaves O-linked sulfate moieties from dermatan sulfate and heparan sulphate [1]. MPS II is a rare disease with an estimated incidence of approximately 1:162,000 live births[2]. Although males are predominantly affected, a small number of affected females have been described[3]. The condition is always progressive and life-limiting [1].

Accumulation of these GAG species affects nearly all cell types, tissues, and organs of the body including the oropharynx, upper respiratory tract, heart, liver and spleen, bones and joints, meninges and central nervous system. The clinical manifestations of Hunter syndrome vary considerably from patient to patient. The onset of signs and symptoms typically occurs between 2.5 to 4.5 years of age. An earlier appearance of clinical symptoms generally, but not always, predicts a more severe clinical course[1].

The most common clinical signs and symptoms include dysostosis multiplex with decreased range of joint motion, coarse facial features, enlarged tongue, hearing loss, abnormal dentition, upper airway obstruction with or without sleep apnoea, restrictive lung disease, hepatosplenomegaly, cardiomyopathy, skeletal deformities, and severe short stature[4;5].

There is a significant impact on quality of life. Individuals with MPS II suffer from chronic, significantly impaired endurance which is multifactorial. Early on, this may manifest as an inability to keep up physically with their peers. Later, their ability to walk even short distances may be lost and eventually many patients become wheelchair bound.

In parallel with this diminished endurance, patients also lose much of their ability to perform even simple day-to-day activities. Over time, the increasing size of the tongue causes difficulty with swallowing and may also impair articulation[4;5]. The progressive decrease in joint mobility and their broad, claw-like, short fingers may prevent patients from independently performing many self-care activities including self-dressing, toilet care, and personal grooming. Patients become increasingly dependent on others at an early age.

In the latter stages of the disease, continued accumulation of GAG leads to progressive end-organ failure and significantly shortened life span. In some cases, GAG accumulation in the central nervous system leads to progressive neurological decline, often exacerbated by communicating hydrocephalus and/or increased intracranial pressure. Death usually occurs in the second or third decade of life, most often from respiratory and/or cardiac failure[1].

There is considerable clinical overlap between MPS I and MPS II. There are, however, at least two important differences that are likely to impact on treatment decisions.

1. Whereas there are some very mildly affected MPS I patients, the same cannot be said of MPS II. All patients are severely affected by the second decade.

2. Some, but not all, patients may develop progressive cognitive decline. However, unlike in MPS I, it can be very difficult to predict this easily in children under the age of 5.

Treatment

The current treatment of MPS II is symptomatic. For example, surgery to reduce airway obstruction and continuous positive airway pressure (CPAP) have been used to treat sleep apnea[6;7]. Hematopoietic stem cell transplantation (HSCT) has been carried out in some patients[8]. However, the long-term results are unsatisfactory and the risk too great to support this form of therapy at present.

1.1 A brief synopsis of ERT trials

The preparation that has been used in clinical trials of ERT is known as idursulfase (Elaprase). Idursulfase is produced by recombinant DNA technology in a continuous human cell line. It is a purified form of the lysosomal enzyme iduronate-2-sulfatase. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow specific binding of the enzyme to the M6P receptors on the cell surface, leading to cellular internalisation and targeting to intracellular lysosomes of the enzyme, and subsequent catabolism of accumulated GAG.

Phase I/II Trial. Twelve patients were enrolled into a randomized, double-blind, placebo-controlled, dose-escalating trial for 24 weeks followed by an open-label extension study. The primary efficacy measurement was change from baseline in urinary excretion of glycosaminoglycans.

Results: Urinary glycosaminoglycans were reduced within 2 weeks of initiating idursulfase and remained low through 48 weeks ($P < 0.0001$). Both liver and spleen volume were decreased at 24 weeks ($P < 0.01$) and 48 weeks ($P < 0.001$). The 6-minute walk test distance increased an average of 48 meters after 48 weeks ($P = 0.013$). Six patients in the higher dose groups developed IgG antibodies that did not appear to influence the clinical activity of idursulfase.

Phase II/III Trial. A randomized, double-blind, placebo-controlled trial (TKT024) has been conducted at nine sites around the world. The primary goal of the study was to evaluate the safety and efficacy of 0.5 mg/kg of idursulfase administered weekly compared to placebo. Additionally, the trial evaluated 0.5 mg/kg of idursulfase every other week compared to placebo. Ninety-six patients were randomized to one of three groups with each patient receiving a total of 52 infusions of either idursulfase, idursulfase alternating weekly with placebo, or placebo. The primary efficacy endpoint of the trial was a composite of two clinical measures – forced vital capacity (FVC) and 6-minute walk test (6MWT).

Results-efficacy. Patients receiving the weekly dosing regimen of 0.5 mg/kg of idursulfase showed a statistically significant difference ($p=0.0049$) compared to placebo. Patients receiving the alternate week dosing regimen of idursulfase also showed a statistically significant difference ($p=0.0416$) compared to placebo.

Results-safety. Treatment with idursulfase was generally well-tolerated. The most common adverse events observed were associated with the clinical manifestations of MPS II. Of the adverse events considered possibly related to idursulfase, infusion related reactions were the most common and were generally mild. There were two patient deaths during the study, both of which were considered unrelated to treatment with idursulfase. IgG and IgM antibodies were observed in the idursulfase treated patients at some point during the course of the study. No IgE antibodies were observed. No patient withdrew from the trial due to an adverse event considered related to idursulfase. All patients with the exception of the two who died during study TKT024 continued into an open label extension study (TKT024EXT) which is currently ongoing.

2.0 Confirmation of diagnosis

All patients must have a documented deficiency /absence of iduronate sulphatase enzyme activity measured in an appropriate tissue such as leukocytes or cultured skin fibroblasts.

3.0 Inclusion Criteria for Treatment

Since all patients with MPS II develop severe disease at least by the second decade, the case for commencing ERT at an early age in all patients is a strong one.

However, the issue of whether or not to treat patients with significant cognitive impairment is a difficult one. On the one hand, ERT is likely to confer significant visceral benefit. On the other hand, as there is little evidence that intravenously administered enzyme crosses the blood-brain barrier, it is likely to have little or no impact on cognitive decline, once it sets in. However, in young children it can be very difficult to predict later cognitive decline.

We therefore propose the following inclusion criteria

1. A documented biochemical diagnosis of MPS II as above.
2. All patients under the age of five (male and female).
3. All patients over the age of five should also be offered treatment. However, if there is evidence of progressive and significant cognitive decline by this stage, then it is left to the discretion of the treating clinician, in discussion with the parents, to decide whether it is appropriate to commence treatment.

4.0 Exclusion criteria

1. Pregnant or lactating patients.

2. Patients deemed too sick or whose disease is so far advanced that there is little prospect of ERT having any benefit.
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 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

- a) **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 if indicated**
- e) Pulmonary function tests, specifically FVC.
- f) Six minute walk test.
- g) **ECG and echocardiogram**
- h) Ophthalmology assessment with ocular electrophysiology and an estimate 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 brain and cranio-cervical junction
- l) Skeletal survey- cervical spine in flexion/extension, lumbar spine, hips and pelvis

5.2 Laboratory Tests

Urine glycosaminoglycans (GAG/Cr ratio)

6.0 Treatment

Treatment will be with Elaprase. Each single-use vial of Elaprase contains 3 ml of drug product (6 mg of idursulfase). The concentration of each vial is 2 mg/mL.

Patients will receive weekly infusions of 0.5 mg of idursulfase /kg of body weight. The total volume will be infused over 3 hours.

7.0 Follow up

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

At 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.

The definition of effective treatment is: “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.”

Exit Criteria:

- a) 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) Progressive cognitive decline, as assessed clinically, following parental discussion.

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.

Reference List

- (1) Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly W, Valle D, editors. *The Metabolic and Molecular Basis of Inherited Disease*. New York: McGraw-Hill, 2001: 3421-3452.
- (2) Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA* 1999; 281(3):249-254.
- (3) Tuschl K, Gal A, Paschke E, Kircher S, Bodamer OA. Mucopolysaccharidosis type II in females: case report and review of literature. *Pediatr Neurol* 2005; 32(4):270-272.
- (4) Archer IM, Young ID, Rees DW, Oladimeji A, Wusteman FS, Harper PS. Carrier detection in Hunter syndrome. *Am J Med Genet* 1983; 16(1):61-69.
- (5) Young ID, Harper PS. The natural history of the severe form of Hunter's syndrome: a study based on 52 cases. *Dev Med Child Neurol* 1983; 25(4):481-489.
- (6) Ginzburg AS, Onal E, Aronson RM, Schild JA, Mafee MF, Lopata M. Successful use of nasal-CPAP for obstructive sleep apnea in Hunter syndrome with diffuse airway involvement. *Chest* 1990; 97(6):1496-1498.
- (7) Orliaguet O, Pepin JL, Veale D, Kelkel E, Pinel N, Levy P. Hunter's syndrome and associated sleep apnoea cured by CPAP and surgery. *Eur Respir J* 1999; 13(5):1195-1197.
- (8) Vellodi A, Young E, Cooper A, Lidchi V, Winchester B, Wraith JE. Long-term follow-up following bone marrow transplantation for Hunter disease. *J Inherit Metab Dis* 1999; 22(5):638-648.