Mucopolysaccharidosis type II: Guidelines for Assessment, Monitoring and Enzyme Replacement Therapy (ERT)

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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 Birmingham, 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 AGNSS 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 (IDS), 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].
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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

Symptomatic treatment is available for specific complications. For example, surgery to reduce airway obstruction and continuous positive airway pressure (CPAP) have been used to treat sleep apnea.

Haematopoietic Stem Cell Transplantation (HSCT) has been performed in some patients. However, the long term results are unsatisfactory in symptomatic children. HSCT may be considered in a young infant where there is a family history of MPS II with progressive CNS involvement.

Currently, the specific treatment of choice in MPS II is enzyme replacement therapy (ERT).

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.

Pivotal Studies

**Phase I/II Trial [6].** 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[7]**. 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.

**Extension/other studies**

**Long term open-label extension study [8]**

All 94 patients who completed the pivotal study of idursulfase enrolled in this open-labeled extension study. They received idursulfase at a dose of 0.5 mg/kg weekly for 2 years, and clinical outcomes and safety were assessed. **Results-efficacy.** No change in percent predicted forced vital capacity was seen, but absolute forced vital capacity demonstrated sustained improvement and was increased by 25% at the end of the study. Statistically significant increases in 6-minute walking test distance were observed at most time points. The mean liver and spleen volumes remained reduced throughout the 2-year extension study. The mean joint range of motion improved for the shoulder and remained stable in other joints. Both the parent- and child-assessed Child Health Assessment Questionnaire Disability Index Score demonstrated significant improvement. **Results-safety.** Infusion-related adverse events occurred in 53% of patients. They peaked at Month 3 of treatment and declined thereafter. Neutralizing IgG antibodies were detected
in 23% of patients and seemed to attenuate the improvement in pulmonary function. Cognitive function was not reported in this study.

**Treatment of children younger than 6 years [9]**

The Hunter Outcome Survey (HOS) was used for this purpose. The study population included 124 patients enrolled in the HOS who started idursulfase infusions (0.5 mg/kg every other week) before 6 years of age and who had had at least one follow-up examination recorded. The mean age at start of ERT was 3.6 years. The mean duration of treatment was 22.9 months.

**Results - safety.** After at least 6 months of idursulfase, urine glycosaminoglycan levels decreased from 592 ± 188 to 218 ± 115 µg/mg creatinine (P < 0.0001, n = 34). Liver size, estimated by palpation, was also significantly decreased (P = 0.005, n = 23).

**Results - efficacy.** A total of 69 infusion-related reactions occurred in 33 (26.6%) patients, including three serious infusion-related reactions in a single patient. Similar safety and effectiveness results were seen in patients who were aged 6 years or older when initiating idursulfase. Intellectual function was not studied.

Unfortunately, several important questions remain unanswered.

1. In young patients, how can we identify those who are at risk of developing cognitive impairment?

2. Is there any evidence at all that cognitive function in such patients benefits from ERT?

3. Are the currently used outcome measures reliable?

1. Identification of early CNS disease in young patients

Holt et al [10] conducted a retrospective review of 49 patients, 37 of whom exhibited signs and symptoms of CNS disease. Of the 25 signs evaluated, 7 early clinical markers were strongly correlated with subsequent cognitive dysfunction: sleep disturbance, increased activity, behavior difficulties, seizure-like behavior, perseverative chewing behavior, and inability to achieve bowel training and bladder training. A new severity score index was developed, with a score ≥3 indicating a high likelihood of developing CNS disease.

2. Role of ERT in patients with CNS disease
ERT ameliorates many of the somatic manifestations of MPS II to some extent, eg upper airway obstruction, tiredness, reduced activity. However, there is no published data regarding its role in CNS disease.

A cross-sectional survey of UK patients showed that of 54 patients treated, 27 (50%) had CNS disease (this number is based on clinical impression only rather than formal assessment). However, treatment has been stopped in only 6 patients so far. Therefore a significant number of children with CNS disease are receiving ERT and are clearly felt to be stable. However, careful follow up of these children is required.

3. Currently available outcome measures.

An additional issue that has emerged recently is the usefulness of the currently available somatic outcome measures. Most centres use the outcome measures that were used in the clinical trials. However, a recent studies have questioned the validity of these outcome measures. A study by Wood et al [11] studied the 6MWT and concluded that it lacked sufficient sensitivity to be reliable. A further study by Glamuzina et al [12] concluded that none of the main outcome measures (FVC, 6 MWT or urine GAGs) were sufficiently reliable. Both these studies were retrospective. However, it does appear that newer and more reliable tools are needed.

It is also possible that a suboptimal response is related to antibody formation of neutralising antibodies. Currently a study is under way (Shire) to determine the role of such immunogenicity. At present it is unclear.

2.0 Confirmation of diagnosis

All patients must have a documented deficiency / absence of iduronate sulfatase enzyme activity measured in an appropriate tissue such as leukocytes or cultured skin fibroblasts and measurement of at least one other sulfatase enzyme to exclude multiple sulfatase deficiency.

3.0 Inclusion Criteria for Treatment

Since all most 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.

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). 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.

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. A second opinion from another centre should be sought at this stage.

4.0 Exclusion criteria

1) Pregnant or lactating patients. For obvious reasons this is a rare occurrence. However, a single patient who was on ERT had her treatment stopped for the first trimester and then recommenced for the remainder of her pregnancy. No adverse events were reported.

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

3) Lack of awareness

4) No useful social interaction

5) No communication

6) 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 height and weight, 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.
m) Assessment of neurological function
   a. Under 5
      i. Parental reporting (Vineland)
      ii. Standard neuropsychometric tool such as the BAS or whichever tool is used locally.
   b. Over 5
      i. Calculation of the Escolar severity score (Holt and colleagues)

5.2 Laboratory Tests

Urine quantitative glycosaminoglycans (GAG/Cr ratio) on morning specimen.

Genotyping to include full gene sequencing if required.

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 usually be infused over 3 hours.

In individual cases the dose of Elaprase may be increased to a maximum of 0.7 mg/kg. However, since this dose is not licensed, such an increase should be approved by the EAB.

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. Assessment of neurological status will be performed every year.

**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

c) Failure to attend for follow up at least once in a 12-month period, should lead to ERT being discontinued until regular attendance is re-established.

d) Significant and progressive decline in cognitive function.

Any decision to stop ERT should be supported by at least one other designated centre where there is a difference of opinion between the family and the primary clinical team. It should also take into account reports from other professionals caring for the child eg school, community team, palliative care etc.

The UK experience is as follows; so far, treatment has been stopped in six patients; four due to progression of CNS disease, one due to non-compliance and one due to unmanageable infusion-associated reactions. In the patients in whom treatment has been stopped due to CNS progression, there has been no discernible acceleration.

**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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Reference List


