Canadian Consensus Position Statement for the Diagnosis and Management of MPS II

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ABSTRACT

Mucopolysaccharidosis type II (MPS II), also known as Hunter Syndrome, is caused by a deficiency of the iduronate sulfatase (IDS), which leads to the widespread accumulation of glycosaminoglycans (GAGs), and to multisystem involvement. The availability of idursulfase for enzyme replacement therapy (ERT) improved the management of MPS II, and led to the development of treatment guidelines. However, since publication of the most recent guidelines, clinicians have gained much broader experience with ERT and the management of MPS. Therefore, the aim of this consensus statement is to provide updated Canadian guidelines for the management of patients with MPS II.

A consensus meeting was held in Toronto, Ontario, including a multidisciplinary group of experts in the management of patients with MPS II. The group reviewed available published guidelines and developed updated consensus guidelines, customized to the Canadian healthcare environment. Funding was provided by the Canadian MPS Society.

It is recommended that all patients with MPS II who do not have neurologic involvement be treated with ERT with idursulfase. Patients deemed to be severe phenotype, can be considered for ERT treatment on an individual case basis. Treatment should be initiated as early as possible in the course of the disease; in all patients less than 5 years of age and in those greater than 5 years on an individual basis depending on the stage of the disease. Progression of disease, and response to therapy should be thoroughly monitored and documented. Finally, the circumstances under which ERT would be stopped should be discussed and documented prior to starting therapy.

Importantly, clinicians should be encouraged to enrol patients in clinical trials, and all patients should be asked for informed consent to share outcome data with the Hunter Outcome Survey (HOS) registry.

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1. INTRODUCTION

Mucopolysaccharidosis type II (MPS II), also known as Hunter Syndrome, is a rare X-linked recessive disorder caused by a deficiency of iduronate sulfatase (IDS).[1] This deficiency leads to the widespread accumulation of the glycosaminoglycans (GAGs) dermatan and heparan sulfate, and to multisystem involvement including musculoskeletal, joint, cardiorespiratory, growth, hearing impairment, a coarsening of features, and organomegaly.[2] Up to two-thirds of patients with MPS II will also suffer a spectrum of neurocognitive involvement, leading to a progressive neurodegenerative course in severe cases.[2] Historically, cases were categorized as type A or B, depending on the presence (type A), or absence (type B), of primary neurocognitive disease. More recently, however, MPS II has been regarded as a spectrum of disease with both somatic and neurocognitive involvement, rather than a disease with a clear delineation between the previously defined two subtypes.[1]

Availability of the enzyme replacement therapy (ERT), Elaprase® (idursulfase), has enhanced the pre-existing management strategy of system-directed supportive care for MPS II. This in turn led to the development of treatment guidelines and recommendations both in Canada (Clarke JTR, personal communication, 2008) and Europe.[1,3]

In light of the broader experience clinicians now have with MPS II, as well as a better understanding of the role and response to ERT, the aim of this consensus statement is to provide updated Canadian guidelines. In addition, recent and upcoming therapeutic developments relating to MPS II management, including intrathecal ERT, the potential role of stem cell transplantation, and the impact of earlier diagnosis and treatment via strategies such as newborn screening will be discussed and recommendations provided. Finally, consideration of aspects specific to the various Canadian provincial healthcare systems and access to therapies for rare disorders such as MPS II will also be discussed.

2. METHODS

A consensus meeting was held in November 2015 in Toronto, Ontario, including a multidisciplinary group of experts in the management of patients with MPS II. The meeting reviewed available published guidelines from Europe,[1] as well as 2008 Canadian position statement (Clarke JTR, personal communication, 2008), in order to develop updated consensus guidelines, customized to the Canadian healthcare environment. Recommendations were made based on the available evidence, with consideration of improving Canadian reimbursement guidelines, to ensure patients have access to the best available care. The manuscript was developed and approved by the authors. Funding for the meeting and editorial support was provided by the Canadian MPS Society.

3. HOW IS MPS II DIAGNOSED?

Clinical indications for testing

A patient with features suggestive of MPS II must have the diagnosis confirmed by laboratory testing, since many of the clinical and radiological features of MPS II overlap with those seen in other mucopolysaccharidoses and related diseases.[4] Almost all patients with MPS II are male because *IDS* is on the X-chromosome, however, a small number of female patients have been described in the literature.[5,6]

The estimated incidence of MPS II was approximately 1 in 156,000 births in Germany (1980–1995 data),[7] 1 in 320,000 births in Western Australia (1969-1996),[8] and of any type of MPS was 1 in 51,791 births in British Columbia (1972-1996).[9]

Laboratory diagnostic criteria

The laboratory diagnosis of MPS II has three components: 1) the identification of elevated urine GAGs with the excreted GAG characterized as heparan sulfate and dermatan sulfate; 2) the absent or very reduced activity of IDS in the presence of a normal amount of activity of another sulfatase to rule out multiple sulfatase deficiency (MSD); and 3) the identification of a pathological mutation in *IDS*.[1]

Traditionally, a diagnostic algorithm to establish a laboratory diagnosis of MPS II is used. Urine GAGs are measured using quantitative dye binding 1,9-dimethyl-methylene blue (DMB) staining, with age appropriate reference ranges.[10] Specimens with elevated GAGs are subsequently analyzed by electrophoresis or thin layer chromatography in order to identify which GAGs (keratan sulfate, heparan sulfate, or dermatan sulfate) are elevated.

Patients with MPS II have increased excretion of dermatan sulfate and heparan sulfate. This distinguishes MPS II from most other MPS diseases, except the more common MPS I, as patients with both MPS I and MPS II excrete increased amounts of dermatan sulfate and heparan sulfate.[11] The quantitative DMB assay can provide both false-positive and false-negative results.[12,13]

Methodologies using quantitative ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) have been developed to rapidly and accurately quantify and characterize the excreted GAGs in a single analysis.[14] The UPLC-MS/MS methodology was unable to distinguish between MPS I and MPS II,[15] but may be able to

discriminate attenuated and severe subtypes of MPS II.[16]

IDS can be assayed in peripheral blood leukocytes, cultured skin fibroblasts, plasma, or dried blood spot specimens using artificial substrates. Patients with MPS II have absent or very reduced activity of IDS;[11] however, the level of IDS activity cannot be used to predict clinical phenotypes or to reliably identify heterozygous females.[4]

Two phenotypically similar diseases also have reduced tissue activities of IDS: MSD, which can be ruled out by a normal level of activity of another lysosomal sulfatase, and mucolipidosis type II /III, which can be ruled out by assaying increased plasma activity of IDS.[4]

Genetic testing to confirm the diagnosis

A biochemical diagnosis of MPS II should be confirmed by the identification of a pathogenic variant in the *IDS*. The Human Genome Mutation Database identifies 622 different mutations in *IDS*.[17] Although the majority of mutations are missense mutations, many patients have large intragenic deletions/duplications and complex rearrangements that involve a nearby pseudogene, *IDSP1*. Therefore, assessment of mutation status in patients with suspected MPS II should include sequencing analysis, as well as methods that detect deletions and rearrangements such as multiplex ligation-dependent probe amplification (MLPA) and microarray. Some genotype/phenotype correlations have been made,[16,18] but more work is needed before genotypic mutations can be routinely used to predict the phenotype.[4,19] The identification of the disease-causing mutation in the MPS II proband allows for assessment of the risk of recurrence for the mother, the risk of extended family members having an affected child, and enables prenatal diagnosis.[4]

Status of newborn screening for MPS II

The results of pilot studies using dried blood spot cards to assay IDS activity using either flurometric or mass spectrometric assays have indicated the feasibility of newborn screening for MPS II.[20,21] Currently, no Canadian province has included MPS II in newborn screening panels. In the United States, MPS II is not included in the recommended uniform screening panel (RUSP).[22]

> ### Recommendations
> - MPS II should be diagnosed in the presence of:
>   - o Elevated urine glycosaminoglycans (GAGs) with the excreted GAG characterized as

> heparan sulfate and dermatan sulphate
>   - o Absent or very reduced activity of iduronate 2-sulfatase (IDS) and exclusion of MSD and mucolipidosis II/III
>   - o Identification of a pathological mutation in *IDS*

4. WHAT ARE THE CURRENT TREATMENT OPTIONS?

Disease modifying treatment options include ERT and bone marrow transplant. There are currently two ERTs (Elaprase®, idursulfase[23] and Hunterase®, idursulfase beta[24]) in production; however, only Elaprase® is approved by Health Canada.

ERT (IV idursulfase)

Definition and mechanism of action

ERT is a weekly intravenous (IV) infusion that takes advantage of the mannose-6-phosphate receptor on both the cell and lysosomal surface.[25] Elaprase® (idursulfase) is a recombinant enzyme that hydrolyzes the 2-sulfate esters of terminal iduronate sulphate residues from dermatan sulfate and heparan sulfate.[25]

Clinical efficacy of ERT

ERT has been shown to produce significant improvements in mobility and pulmonary function in patients with MPS II. The pivotal trial was a 53-week, randomized, double-blind, placebo-controlled study that included 96 patients between 5 and 31 years of age with MPS II.[23] However, it is important to note that the study population was not representative of the typical patient with MPS II, as it included only individuals with intermediate MPS II who either had minimal or no neurological involvement. Patients were randomized on a 1:1:1 basis to one of three groups: 0.5 mg/kg idursulfase qw, 0.5 mg/kg idursulfase q2w, or placebo qw. The primary efficacy outcome was change from baseline in the composite endpoint measuring both physical functional capacity via the six-minute walk test (6MWT) and pulmonary function via the percentage of predicted forced vital capacity (FVC).

The composite scores of patients who received active treatment were significantly higher than those who received placebo, with the mean difference from placebo being 18.96 ± 6.47 (p=0.0049) for the qw cohort and 12.86 ± 6.17 (p=0.0416) for the q2w cohort.[23] Separate analysis of physical and pulmonary functioning outcomes demonstrated that mean distance walked on the 6MWT was significantly farther among patients in the idursulfase qw group (44.3 ± 12.3 metres; p=0.0131) and those in idursulfase q2w

group (30.3 ± 10.3 metres; p=0.0732) compared to those in the placebo arm (7.3 ± 9.5 metres).[23] The mean change in % predicted FVC at study end was greater in the idursulfase qw group compared with placebo, however this difference was not statistically significant (3.45 ± 1.77 vs. 0.75 ± 1.71; p=0.0650).[23] Improvements in other secondary outcomes included significant reductions of both spleen and liver sizes, as well as improvement of absolute FVC with idursulfase qw.[23]

Based on data on a total of 108 patients from a phase I/II clinical trial, the pivotal phase II/III study, and three additional studies which examined the safety profile of idursulfase, Health Canada approved the agent in December 2007.[26] The decision was mainly based upon improvement in 6MWT, with biomarker results such as a reduction in GAG levels, as well as reductions in liver and spleen size also lending support. It was concluded that idursulfase demonstrated a favourable effect on the clinical manifestations of a life-threatening disease for which no other therapies are available.[26]

Limitations of ERT

Intravenously administered ERT with idursulfase does not cross the blood-brain barrier in sufficient amounts, therefore, it generally has little or no effect on the neurological deterioration associated with MPS II.[27,28] There have been vigorous debates on how to manage patients with CNS involvement including start and stop criteria (see criteria section below). Some argue that there is a benefit to continuing ERT in patients with severe phenotypes in order to treat peripheral manifestations (respiratory, joint mobility, sleep apnea, hepatomegaly).[29] However, some regions in Canada state that neurological progression is a contraindication for supplying funding for this medication. We propose that ERT be started as early as possible and for all symptomatic patients. If there is significant neurological involvement that develops (or if it is already present), a risk-benefit discussion should occur between the family, physician, hospital ethics board, and funding bodies.

Intrathecal idursulfase alpha was shown to be well tolerated in a phase I/II trial in 12 neurologically impaired patients with MPS II.[28] In December of 2017, Shire announced that a Phase II/III to determine if it can stabilize neurological progression failed to show differences in primary or secondary outcomes.[30] At this time, it is not clear whether this program will continue. Idursulfase beta has also been studied in phase I/II trials.[24]

Dosing and administration of ERT

The dosage of idursulfase used should be 0.5 mg/kg body weight, administered intravenously every week. Similar to other enzyme infusions, the product monograph proposes a gradual increase in the infusion rate.[25] Home infusion may be considered after a period of time with no serious infusion associated reactions. A 3 to 6-month period has been proposed in the literature;[31,32] however, some centers are moving toward home infusion in as few as 6 to 8 weeks if there are no infusion-related reactions.

Adverse events with ERT

The safety profile of idursulfase is acceptable, with the most common adverse events being infusion-related reactions such as urticaria, pyrexia, and headache.[25] Adverse reactions occur in approximately 30% of patients with the majority occurring in the first 3 months after starting infusions.[32] Most adverse reactions are mild to moderate and can be managed by decreasing the rate of, or stopping the infusion, and then treating with antipyretics, steroids, and antihistamines.[32] However, the idursulfase product monograph carries a black-box warning that life-threatening anaphylactic reactions have been observed in some patients during infusions, and appropriate medical support should be readily available during administration.[25]

Immune reaction to ERT

IgG anti-idursulfase antibodies have been detected in 45-55% of patients who received ERT with idursulfase. There was no relationship found between the presence of antibodies and adverse events.[23,33] There were no anti-idursulfase IgE antibodies detected in the pivotal study.[23]

Recommendations

1. All patients with MPS II who do not have neurologic involvement should be treated by ERT with idursulfase

2. Patients, who would by virtue of mutation analysis and/or history of previously affected relatives be deemed to be severe phenotype, can be considered for ERT treatment on an individual case basis. ERT in this group could be considered early in the course of disease prior to the onset of significant neurological disease. Clear discussion with the family must take place in relation to the lack of efficacy of ERT for CNS disease and the anticipation that ERT will be discontinued when significant CNS disease is detected

3. Treatment should be initiated as early as possible in the course of the disease

4. The dosage of idursulfase used should be 0.5 mg/kg body weight, administered intravenously every week

5. Treatment should be carried out at, or under the close supervision of, centres with experience and expertise in the management of MPS II and ERT. Home infusion may be considered after a period of 3-6 months if there have been no infusion-associated reactions

6. The initiation of treatment should be preceded by a thorough baseline assessment and the establishment of clear treatment outcome objectives in order to objectively evaluate the effect of the treatment. This should include the introduction of assessments in children less than 5 years of age, until reliably achievable

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5. WHEN SHOULD ERT (IV IDURSULFASE) BE STARTED?

Natural history of MPS II

There is wide variation in the presentation and progression of MPS II. In the most severe phenotype, signs and symptoms develop around 2-4 years of age, progressive neurological involvement leads to extensive cognitive impairment, and death usually occurs in the second decade of life.[34] In the attenuated phenotype, patients experience somatic signs and symptoms, but are spared cognitive involvement, and typically survive into adulthood. In the Hunter Outcomes Survey, neurological involvement was common, being reported in 84% of patients.[34] The most common symptoms of neurological involvement were behavioural and cognitive problems, which were seen as early as 3.2 years old. Unfortunately clinical trials with ERT only include children with mild-to-moderate MPS II (ie, minimal neurological involvement), and are not representative of most of the children with MPS II.[23]

In patients diagnosed in early childhood, the development and the degree of future CNS involvement is difficult to predict. Hearing loss is almost universal among patients with MPS II and is generally diagnosed during active speech and language development, affecting the acquisition of these skills. Likewise, the degree of motor impairment in patients with MPS II is also related to skeletal problems and carpal tunnel syndrome. Gross motor skills plateau around 3–4 years of age and deteriorate thereafter, followed by a deterioration of fine motor skills.[35]

The majority of *IDS* mutations are private (ie, unique to the patient), making the evaluation of genotype/phenotype association very difficult. However, the occurrence of the phenotype of severe MPS II with neuronopathic involvement seems to be related to a complete absence of functional enzyme due to total or partial gene deletion or *IDS/IDS2* rearrangement. Unfortunately enzymatic analysis does not enable further prediction, as results from routine diagnostic assays that measure either the amount or activity of IDS have shown no correlation with phenotypic severity in patients with MPS II.[36]

Issues with starting ERT early

IV ERT is generally not effective in the treatment of CNS manifestations because the current generation of recombinant enzymes do not cross the blood-brain barrier.[27,28] Because of the isolated action of ERT on visceral, bone, and connective tissue, lack of CNS improvements, high costs of treatment, and the invasive nature of the therapy (ERT is given in weekly intervals, most patients have a venous access device [VAD]), it is important to properly select patients for ERT, including determining which patients will benefit the most from treatment, at what age treatment should be initiated, and when treatment should be discontinued.

Evidence for efficacy of IV idursulfase in younger children

Not only did the pivotal trial for ERT in MPS II include patients with minimal neurological involvement, all participants were greater than 5 years of age (mean 15.4 y). To address this, a phase IV, open-label, multicentre, single-arm study was undertaken to examine the safety and efficacy of idursulfase in patients 5 years or less.[37] Out of a total of 28 patients,

4 patients greater than 5 years of age were granted an exemption and permitted to enrol, resulting in an overall mean age at entry of 4 y (range 1.4–7.5 y). Study duration was 52 weeks with standard dosing of 0.5 mg/kg qw IV. By week 18, liver size (assessed by ultrasound) and urinary GAG levels were decreased compared to baseline values and remained stable. Growth rates remained within normal age-related ranges. Developmental quotients were lower than normal, but remained stable. Sixteen patients had an infusion-related reaction and 13 patients experienced 1 or more severe adverse event (most commonly pyrexia, bronchopneumonia). Pharmacokinetic assessment indicated no age- or body weight-related effects. The authors concluded that idursulfase can be initiated in patients younger than 5 years of age to stabilize and/or improve certain somatic effects of MPS II.[37]

A subgroup analysis of the Hunter Outcome Survey (HOS) was performed in order to assess the safety and effectiveness of ERT with idursulfase in patients who started treatment prior to 6 years of age.[33] The study population included 124 patients less than 6 years who had 1 or more follow-up visits. The mean (±SD) age at idursulfase initiation was 3.6 (±1.6) years, and the mean duration of treatment was 22.9 (±14.6) months. After a minimum of 6 months of treatment, significant reductions in urinary GAG levels and liver size (estimated by palpation) were reported. No new safety concerns were identified in patients less than 6 years of age, compared with those reported for older patients.

A case-series of 8 patients where ERT was initiated at less than 1 year of age (range 10 days–6.5 months) and continued for a duration ranging between 6 weeks–5 years reported no new safety concerns and no infusion-related reactions.[38] All patients who received treatment for more than 6 weeks showed improvements and/or stabilization of some somatic manifestations while on treatment. In some cases, caregivers made comparisons with other affected family members and reported that the early-treated patients experienced a less severe clinical course. The findings of other case reports, where ERT was started in infancy, including comparisons to older treated siblings, suggest that pre-symptomatic initiation of ERT may prevent or attenuate progression of the somatic features of MPS II.[39,40]

In terms of specific clinical effects, several studies including younger children with MPS II have shown a positive benefit on linear growth as a result of starting ERT at a younger age,[41-44] including the comparison study by Schulze-Frenking et al. where the greatest benefit was seen in patients beginning ERT prior to age 10 years, supporting the recommendation that ERT be started as early as possible in patients with MPS II.[45]

A prospective cohort study of 24 patients, including 6 patients with MPS II, assessed cardiac abnormalities and the effect of ERT. The age range at diagnosis of the patients with MPS II was 2–6 years, and the age range at ERT initiation was 1–10.8 years.[46] Post-ERT, left-ventricular mass index (LVMI) z-scores (-0.26; p=0.032) and interventricular septum diameter in diastole (IVSd) (-0.36; p=0.05) both decreased significantly in patients with MPS II. Mitral valve thickness decreased in 2 of the 6 patients with MPS II (and increased in 2 of 6 patients), and aortic valve also decreased in 2 of 6 patients.

The PODCI (Pediatric Outcomes Data Collection Instrument), a validated measure of musculoskeletal health in children with disabilities, was used by White et al. in a retrospective chart review to assess the effect of ERT on musculoskeletal function in 7 patients with MPS II, 5 of whom had received ERT.[47] The average age at diagnosis was 3.2 years (range 2–7 years), and 4 of 5 patients had severe disease; the duration of ERT was 12–24 months, though the exact age at ERT initiation was not reported. Statistically significant gains were made in 3 domains on the PODCI and there was a positive trend toward improvement in 3 other domains.

The limitations in undertaking functional testing to assess changes in mobility and pulmonary function in the younger age group was recognised by the HOS substudy authors[33] and others, highlighting challenges in measuring real-world ERT efficacy outcomes against clinical trial results.[48] This challenge has also been identified in the other MPS disorders affecting this age group. The recent Managed Access Agreement developed in the UK for the use of Elosulfase alfa in Morquio syndrome (MPS IVa) attempts to address this by recommending that *"[c]linically relevant assessments should be attempted at least once every 12 months until the age of 5, at which point all assessments become compulsory."*[49]

Recommendations for starting ERT from published guidelines

European guidelines recommended initiation of ERT as early as possible following diagnosis, as well as a "trial" period of at least 12–18 months, for all patients regardless of phenotype.[1] International guidelines also recommend initiating ERT in all newly diagnosed patients.[29] In addition, ERT was recommended in all previously diagnosed, symptomatic patients, in whom there is an expectation that ERT will alter the course of the somatic involvement, even if cognitive impairment is already evident.

Summary of initiating ERT, based on the evidence

In clinical practice, 1) incident cases should be treated at the time of diagnosis (usually under age 5 years), and closely monitored for efficacy on non-CNS manifestation and for the development/progression of CNS symptoms; and 2) a similar strategy should be applied for prevalent cases in patients who are likely older and more severely afflicted. Criteria for initiating ERT are shown in table 1. Although there is little or no evidence, given the pervasive nature of MPS II, newborns diagnosed with Hunter disease should be treated unless there is an index sibling with a mild disease (late onset visceral involvement). Infants should be treated as soon as the diagnosis has been established.

Table 1: Criteria for initiating ERT

Inclusion criteria

1. A documented biochemical diagnosis of MPS II
2. All patients under the age of five
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. ALL PATIENTS PRIOR TO INITIATING ERT, to undertake comprehensive baseline assessment as outlined above AND establish/document goals of care/response targets

Exclusion criteria

1. Patients deemed too sick or whose disease is so far advanced that there is little prospect of ERT having any benefit
2. The presence of another life-threatening disease where prognosis is unlikely to be influenced by enzyme replacement therapy
3. Pregnant/lactating women

Recommendations

- Initiate ERT in patients who:
  - Have a documented biochemical diagnosis of MPS II
  - All patients less than 5 years of age
  - Patients greater than 5 years on individual basis, at discretion of the clinician and parents depending on disease stage
- Do not initiate ERT in patients with:
  - Severe or advanced disease who are unlikely to benefit from ERT
  - Another life-threatening disease where prognosis is unlikely to be influenced by ERT
  - Pregnant/lactating women

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6. HOW SHOULD PROGRESSION AND RESPONSE TO THERAPY BE MONITORED?

Considering the lack of demonstrated benefits of currently available ERT on neurological involvement, the progression of disease, and response to therapy should be thoroughly monitored and documented. However, no gold-standard currently exists for determining clinical efficacy of treatment for MPS II. Monitoring response to therapy in MPS II is hindered by the low prevalence of this disorder, paucity of natural history data, and the variability in the phenotype. Proving clinical benefit is difficult, especially in patients under 6 years of age.[33] Endpoints should be relevant to the disease process, as well as reliable, accurate, and responsive to change in the disease process.[50] These criteria are not obvious in orphan diseases. We are often left with biomarkers such as GAG levels, which have an unclear relationship with disease severity; or clinical tests such as the 6MWT, which have their own inherent limitations. Furthermore, the primary evidence for ERT was derived from a randomized double-blind trial of a subset of the MPS II population and it is not clear if the clinical trial endpoints can, or should, be applied to real-world situations. This section will summarize the suggested follow-up of patients with MPS II, both those who are on therapy and those who are off therapy. In keeping with the limitations previously mentioned, there is often a need to individualize treatment goals and outcome measures for each patient.

Ideal biomarkers for monitoring success of therapy (GAG, HCIIT)

Biomarkers that reflect disease progression and treatment outcomes are clearly needed. It is likely that

multiple biomarkers will be needed, to reflect the multisystem involvement of MPS II. Urine GAGs have been used to follow patients with MPS II for many years. Qualitative measures are a composite analysis of heparan sulfate, dermatan sulfate, and keratan sulfate.[1] GAGs can be a useful marker of therapy but there is little evidence that this measurement represents the total body burden of disease. GAG levels are affected by height, body mass, and age,[48] therefore, longitudinal interpretation can be difficult. The utility of GAG measurement may be improved by specific measurement of individual GAGs via MS/MS, and utilization of the dermatan sulfate to chondroitin sulphate ratio may be useful in determining long-term treatment efficacy.[51] However, GAG levels are a relatively easy biomarker to measure, and short-term changes may be reflective of a reduction of disease load.

In the both the pivotal trial and subsequent extension trials, significant decreases in urine GAG levels of 40–60% have been reported in patients treated with idursulfase alpha.[23,52] Typically, baseline GAGs are approximately three-fold higher than normal, and reductions of approximately 50% after 4 months of treatment, and to levels within the normal range after 36 months, have been documented in clinical trials.[52] However, real-world studies have reported less striking results.[48] A case series, reported normalization in only two of 11 patients and this may better reflect the clinical reality in more severe phenotypes,[48] which were not included in the pivotal ERT trial.[23]

Heparin cofactor II thrombin complex (HCII-T) has also been shown to be a relevant biomarker to assess therapeutic intervention.[51,53] HCII-T levels declined but never normalized in a report of 11 patients with treated MPS II.[53] This biomarker was also found to increase in patients with antibodies to idursulfase. Although availability may limit its clinical utility, HCII-T may serve as a more valuable predictor of clinical efficacy than GAGs, especially in the short-term. Ongoing studies aim to identify more specific biomarkers for MPS II and allied diseases through novel techniques such as proteomic analysis.[54]

Important non-neurocognitive parameters

The need for serial clinical assessment of patients with MPS II is clearly needed to monitor disease progression. This includes routine physical examination as well as more detailed baseline and serial investigation of allied systems such as cardiac, auditory, ophthalmic, and orthopaedic, as well as neurosurgical assessment including neuroimaging. Key non-neurocognitive parameters to assess response in patients with MPS II who are receiving ERT, include: endurance tests, pulmonary function tests (PFTs), physical measurements (eg, growth velocity, liver size, joint mobility), and quality of life measures.

Endurance tests

Walk tests have been shown to be valid and reliable tools for assessing functional status at submaximal intensity levels and are the most appropriate tests for assessment of functional deficits involving multiple organ systems.[55] These tests are inexpensive, easily performed, and readily reproducible. The most frequently used test for this purpose is the 6MWT. This is a standardized, submaximal exercise test—one which reflects the integrated function of all systems utilized in day-to-day exercise—with known normative data for the non-MPS community. It can be used to measure progression of a disease or treatment efficacy.[52] In the idursulfase pivotal trial extension study, there was a positive change in the 6MWT at all time-points with the mean increases being 14 metres (6.4%) at 4 months and 42 metres (11.7%) at 20 months.[52] This increase was seen at all ages but was greatest in those over 18 years.

The 3-minute stair climb (3MSC) is another standardized measure used to reflect respiratory, cardiac, and musculoskeletal involvement.[55] Limitations to endurance testing include practice effect and difficulties in interpretation of data in a young population where growth may confound interpretation. Cooperation and cognitive ability may also affect performance.[29] Despite these limitations, the 6MWT and 3MSC provide standardized measures that are easy to administer for the assessment of disease progression or response to therapy, especially when conducted in a longitudinal fashion. While these tests have not been standardized for MPS diseases they have been used widely in ERT trials including MPS II patients. Unfortunately, there are no endurance tests that can be reliably performed in children under 5 years of age.

Pulmonary function tests (PFTs)

Respiratory involvement in patients with MPS II is often a cause of morbidity and mortality.[56] Testing of pulmonary function is essential, as results reflect the burden of respiratory disease and improvement in pulmonary function should be a target of therapy. However, PFTs can be difficult for patients with MPS II because of interpretation secondary to size, difficulty in performing tests, and cognitive abilities.[48] Indeed, in a real-world trial no reliable data could be collected in 7 of 11 patients.[48] With respect to other measurements of respiratory manifestations, sleep studies can be performed and use of continuous positive airway pressure (CPAP) can be measured, which are useful in

terms of documenting progression of disease and efficacy of therapy, including changes in the apnea hypopnea index [AHI].

Physical measurements

In the event of difficulties in performing PFTs or standardized mobility tests in young or developmentally impaired patients, physical examination can provide easy-to-measure markers. Growth is measured at each visit and may reflect treatment effect.[57] Patients with MPS II may actually have an increased growth velocity in the first three years as compared to unaffected controls.[57] Subsequent growth is impaired, with more than 50% of patients being less than 2 standard deviations (SD) for height as adults.[58] The Hunter outcome study (HOS) reported an improved growth velocity in patients treated with ERT.[57] Studies have found ERT to have less effect on growth in patients with the more severe form of the disease, compared to those with the milder phenotype.[41,43,57] MPS II specific growth charts are available and can be used.[59]

Liver size is an easy parameter to measure. Abnormal liver spans were seen in 79% of patients at baseline and were significantly reduced after 4 months of ERT,[33] and benefits were sustained long-term.[52]

In studies of idursulfase, improvements in joint mobility were only significant for the shoulder[52] or upper limbs.[60] In an open-label, Japanese study using idursulfase beta, range of motion improved in several joints but did not reach statistical significance.[61]

Quality of life

The first indications of treatment efficacy are believed to be improvements in well-being, energy, and the ability to partake in activities of daily living.[3] There remains a question of how best to measure these subjective outcomes. Quality of life (QoL) questionnaires that probe a number of different spheres of life and are relatively brief may be useful for documenting the impact of disease burden on an individual patient over time. And although QoL questionnaires exist (eg, PODCI, EQ5D5L, CHAQ), these have not been specifically developed for MPS II. In the idursulfase extension study, patients showed statistically significant improvement in the CHAQ over 30 months.[52] The Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS) was developed specifically for MPS II, and has been validated in the pivotal trial population.[62]

Important neurocognitive parameters

Patients with MPS II often have significant neurological manifestations.[63] In one case series, over 75% of patients exhibited neurologic deterioration,

during an 8-year follow-up period.[64] Manifestations can include impaired cognitive abilities, difficulties in language and speech, behavioural abnormalities, sleep problems, and/or seizures, with can have a substantial impact on the quality of life.[63] Predicting which patient will develop neurological manifestations is difficult but will become increasingly important as CNS-directed therapies are developed. Both residual enzyme activity, and estimation of glycosaminoglycans (GAGs) have limited importance for prognosis.[18] Genotype-phenotype correlations are difficult,[19] but may be predictive in up to half of patients.[18] Holt et al (2011) have proposed 7 early clinical markers that may differentiate individuals who would benefit from CNS directed therapies.[64]

A number of scoring tools have been developed for more in-depth neurocognitive assessments. The choice of assessment should consider the age of the patient in addition to sensory, motor, and behavioural issues, that may interfere with testing.[63]

Some instruments to assess cognitive endpoints may include the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III); the Kaufman Assessment Battery for Children, Second Edition (KABC-II); and the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3).[65,66]

Measuring antibodies

Infusion-related reactions typically occur within the first three months of therapy.[32] In the HOS, a substantial proportion of individuals developed IgG antibodies, being detected in 54% of patients less than 6 y of age and in 43% of patients greater than 6 years of age.[33] No IgE antibodies developed during long-term follow-up.[32] In attenuated patients, one-third will develop persistent IgG antibodies and half will develop antibodies at some point during therapy; about 20% will develop neutralizing antibodies.[67] Patients with IgG antibodies may have less of a decrease in GAG over time and may be more likely to have an antibody response (AR).[67] Neutralizing antibodies may also be relevant in assessing outcomes as patients without neutralizing antibodies seemed to have better outcomes.

Recommendations

- Progression of disease, and response to therapy should be thoroughly monitored and documented
- Serial clinical assessment should include:
  - Endurance tests
  - Pulmonary function tests (PFTs)
  - Physical measurements
  - Quality of life
  - Neurocognitive parameters

7. HOW SHOULD SYMPTOMS BE MANAGED TO MAXIMIZE QUALITY OF LIFE?

Few organ systems are spared by MPS II. The multi-systemic sequelae of the disease require a multidisciplinary approach to both clinical evaluations and symptom management. It is recommended that these evaluations be completed in a tertiary care setting and ideally by health care practitioners who have experience with rare diseases. In childhood, assessment by a specialist in metabolic diseases should be performed every six months at a minimum, and upon development of any new clinical symptoms. In adulthood, the follow-up frequency can be decreased depending on overall disease burden. Many adult patients only require a yearly follow-up with their metabolic disease specialist.

Table 2 outlines clinical findings that can affect QoL in patients with MPS II, and provides assessment and management recommendations for each. The clinical findings may not all be present, or may vary in level of severity among individual patients. A patient with an attenuated form of MPS II can still demonstrate MPS II-related comorbidities that can adversely affect their quality of life, particularly as the patient ages.[68] It is therefore imperative that a treating physician be aware of all possible complications of the condition with the aim of screening all patients regardless of apparent disease severity. The involvement of palliative care specialists may be beneficial in providing support for patients and their families, and can help during discussions of therapeutic goals.

Considerations for surgical interventions and anesthetic risks

Most patients with MPS II will require some type of surgery during their lifetime to treat disease-related manifestations.[69] Patients with MPS II are at higher risk of morbidity and mortality due to general anesthesia.[70,71] This may be related to anatomical considerations such as: a shortened neck and macroglossia, neck and jaw rigidity; cervical spinal instability with acute neurological symptoms after excessive neck manipulation; upper airway obstruction; and possible cardiac involvement.[71] Risks of general anesthesia must be balanced with the risks of delaying surgical intervention; spinal or regional anesthesia should be considered when appropriate. Given the upper airway involvement in MPS II, oral sedation may still impart significant risk and should be employed with caution.[71,72] Surgery should be ideally completed in a tertiary centre experienced in dealing with patients who have complex medical needs. Pre-operative anaesthetic, ENT, respiratory, and cardiac evaluations are recommended and only skilled anesthesia personnel should be employed for airway management during surgery. Smaller endotracheal tubing and fiberoptic laryngotracheoscopy is often necessary for intubation, and in many centres pre-operative bronchoscopy with a fiberoptic bronchoscope is completed such that the anesthesiologist can adequately prepare for differences in the patient's upper airway anatomy.[71,73] Post-operatively, extubation should be completed with extreme caution. Post-operative laryngeal edema, superimposed with the baseline MPS-related airway issues, may dictate the need for urgent re-intubation or tracheostomy, particularly if extubation is completed too quickly following surgery.[71,74] Consent to any surgical procedure should include a discussion of these MPS II-related anesthetic complications and the possible need for urgent tracheostomy in the event of an acute airway obstruction.

Ultimately, prior to any surgical procedure and anaesthetic in a patient with MPS II, the risks and benefits should be considered carefully with the goal of preserving quality of life for the patient.

Recommendations

- The multi-systemic sequelae of the disease requires a multidisciplinary approach to both clinical evaluations and system management
- Evaluations should be completed in a tertiary care setting, ideally by health care practitioners who have experience with MPS
- Assessment by a specialist in metabolic diseases should be performed every six months at a minimum
- Physicians should be aware of all possible complications of the condition, and screen all patients regardless of apparent disease severity
- Table 2 shows clinical findings, and consensus recommendations for clinical evaluation, and symptom management by system for MPS II

Table 2: Clinical findings, and consensus recommendations for clinical evaluation, and symptom management by system for MPS II

Systems	Features and/or symptoms	Recommended assessment and frequency	Recommended management
General	• Progressive coarsening of facial features • QoL can be adversely affected by condition	• Clinical evaluation at each visit • QoL assessment (eg, SF-36) at each visit	• Review facial differences and acknowledge the presence of familial characteristics • Address any adverse changes reflected in the QoL questionnaire
Growth	• Initially normal or above average growth followed by decrease in growth velocity and short stature • Macrocephaly	• Monitoring of growth parameters at each visit • MPS II specific growth charts are available and can be used*	• Counselling for any excessive weight gain
Nutrition	• Risk swallow/feeding difficulties	• Clinical assessment each visit (eg, choking, aspiration, weight velocity) • Swallow/videofluoroscopy study under SLT/OT supervision	• Conservative management (eg, feed thickening) • Gastrostomy insertion maybe required
ENT/respiratory	• Upper airway obstruction caused by enlarged tonsils/adenoids, macroglossia, and tracheal changes • Thickened nasal or respiratory secretions and saliva	• Assess number of respiratory tract infections at each visit • Ensure vaccinations (including flu vaccine) are up to date • Evaluate upper airway by otolaryngology if clinical symptoms present • Pulmonary function testing (including spirometry) yearly • Sleep study yearly • Assess secretion management	• Tonsillectomy and adenoidectomy • CPAP therapy • Tracheostomy reserved for severe and progressive upper respiratory failure • Yearly influenza vaccine • Secretion management with anticholinergics (eg, atropine drops, glycopyrollate, salivary gland botox)
	• Sensorineural hearing loss • Conductive hearing loss	• Assess number of episodes of otitis media at each visit • Audiological assessments yearly	• Tympanostomy tubes if recurrent otitis media reported • Hearing aids
Cardiovascular	• Left or right ventricular cardiomyopathy • Valvular dysfunction • Coronary artery narrowing/occlusion	• Echocardiography and ECG yearly	• Pharmacological intervention may be necessary for afterload reduction • Valvular replacement for advanced disease
Central nervous system	• Developmental delay • Cognitive decline • Behavioural disturbances	• Developmental assessment/neuropsychological evaluation yearly • New cognitive or behavioural changes warrant investigations for other MPS II comorbidities	• Enrolment in early intervention programs • IEP enrolment • Management of sleep disturbances • Behavioural therapy • Behavioural disturbances can be treated with low dose monotherapy if cannot be controlled by non-pharmacologic means
	• Seizures	• MRI of brain • EEG	• Antiepileptics

Central nervous system (cont.)	• Communicating hydrocephalus	• MRI/CT head/craniocervical junction baseline in childhood and with any suggestive clinical symptoms • LP with opening pressure (after MRI) if clinical symptoms present	• Ventricular-Peritoneal shunt
Spine and peripheral nervous system	• Atlantoaxial instability	• Evaluate for cervical myelopathic signs and symptoms with each visit • Cervical spine flexion/extension radiographs in childhood and then prior to any surgical procedure and/or if there are any clinical signs of instability	• Cervical spinal fusion • Recommend patient avoid high-risk activities such as contact sports
	• Spinal stenosis with or without spinal cord compression	• Evaluate for myelopathic signs and symptoms with each clinical visit • Spinal MRI in childhood and with any new symptoms	• Spinal decompression
	• Carpal tunnel syndrome	• Evaluate for signs of carpal tunnel syndrome and assess function of hand during each visit • NCV every 2-3 years starting at age 5 years or with any suggestive clinical symptoms	• Conservative management (eg, splints) can be trialed for a limited period of time • Surgical management (median nerve release) is often necessary if there are any changes on NCV to preserve hand function
Orthopedic	• Erosive hip dysplasia • Genu valgum	• Clinical assessments of joint ranges of motion, gait, and pain symptoms • Skeletal survey in childhood and radiographs as needed	• Physical therapy may help in preserving joint function • Hip reconstruction/replacements may be more successful in childhood as compared to adulthood • Genu valgum surgery when there is alteration in the tibial-femoral angle • Total knee replacements may be necessary due to progressive arthrosis in adulthood
Ophthalmologic	• Retinopathy • Optic nerve head swelling and optic atrophy	• ERG and ophthalmologic evaluation with slit lamp examination	• No specific management
Herniae	• Increased incidence inguinal/umbilical hernia and risk of incarceration	• Clinical assessment and surgical opinion	• Surgical repair

CPAP: continuous positive airway pressure; CT: computed tomography; ECG: electrocardiogram; EEG: electroencephalogram; ENT: ear, nose, throat; ERG: electroretinography; IEP: individualized assessment program; LP: lumbar puncture; MPS: mucopolysaccharidosis; MRI: magnetic resonance imaging; NCV: nerve conduction velocity; OT: occupational therapy; QoL: quality of life; SLT: speech language therapy

*Refer to reference [59].

8. WHEN SHOULD ERT (IV IDURSULFASE) BE STOPPED?

Specific circumstances under which ERT should be discontinued

Despite the understanding of potential benefits and limitations of intravenous ERT, the decision of when to stop therapy may be challenging, particularly when the patient is not achieving the therapeutic targets that have been mutually agreed upon between a medical team and patient/family or as defined by funding criteria.

IV ERT does not cross the blood-brain barrier, and it is recognized that it will not have a direct effect on the neurocognitive aspects of MPS II.[28] However the impact of ERT in certain target areas should be taken into consideration—for example, the effect on motor function through improved joint mobility and the benefit to overall wellbeing, such as a decreased frequency of chest infections, which both positively impact the QoL in patients with neurocognitive involvement.[23,28,29]

As outlined above in the section on initiation of ERT, it is recommended that where there is the potential of treatment benefit resulting in improved QoL, patients be offered a 12-18 month trial of ERT, following clearly understood goals of care, which should be defined prior to initiation of treatment. Having these goals in place and documented in the patient record will facilitate the discussions and decision process of when to stop ERT if these goals are not met after initiating therapy or if there is disease progression to the extent where there is no further discernible benefit from the continuation of ERT.

In addition to actual disease status, other factors that may lead to stopping ERT include: development of severe reactions to ERT, failure to adhere to the prescribed regimen, and loss of public healthcare eligibility (Table 3).[29]

> ### Recommendations
> - Consensus proposed criteria for stopping ERT are shown in table 3
> - The circumstances under which ERT would be stopped should be discussed and documented prior to starting therapy

Table 3: Consensus proposed criteria for stopping ERT

- Progression of either neurological or somatic disease to an extent that, following agreement of the treating physician and parents, it is deemed no longer amenable to ERT (Eg, patient becomes gastrostomy fed due to an inability to swallow and/or in a vegetative state)
- Development of life-threatening infusion reactions not amenable to standard therapy
- Existence of a concurrent severe diagnosis in which ERT would have no effect
- Failure to adhere to the weekly prescribed infusion schedule or to undertake the appropriate schedule of investigations to assess disease status and response to therapy
- Patient no longer maintains their citizenship/residency status

9. WHAT POST-MARKETING SURVEILLANCE DATA ARE AVAILABLE FOR IV IDURSULFASE?

Long-term data are available from the ongoing global, Hunter Outcome Survey (HOS).[75] The HOS is a patient registry that was initiated in 2005. Data are collected and published on the long-term on the safety and effectiveness of ERT, as well as the natural history of MPS II. Treated or untreated patients with MPS II can be enrolled in HOS.[75] During a 10-year period more than 1,000 patients have been included in the registry. As of January 2018, there are 5 sites open in Canada, with 4 of them having enrolled patients into HOS [Julian Raiman, personal communication]. All patients should be asked for informed consent to share outcome data with this database.

In Canada, the CIMDRN (Canadian Inherited Metabolic Disease Research Network) is a CIHR funded network initiative. The main objective of this registry is to provide the infrastructure for a database to collect practice informed outcomes of several inherited metabolic diseases (IEM) (primarily those included in newborn screening). The registry is currently being populated with patient data. MPS II is not currently integrated into the existing database.

> ### Recommendations
> - All patients should be asked for informed consent to share outcome data with the Hunter Outcome Survey (HOS) registry
> - Steps should be taken to have MPS II integrated into the Canadian CIMDRN database

10. WHAT TREATMENTS ARE UNDER INVESTIGATION FOR MPS II AND MPS IN GENERAL?

While ERT has been the primary treatment available for MPS II, other therapies are currently available or being studied. Although these alternatives do require further study to establish safety and efficacy, they may hold some promise for the treatment of CNS involvement of MPS II—a currently unmet need with ERT.

HSCT in MPS II

Hematopoietic stem cell transplant (HSCT) provides continuous enzyme replacement through engrafted cells.[76] HSCT has been used as an effective option to mitigate the adverse central neurological outcomes in other lysosomal storage disorders such as MPS I,[77,78] but has not demonstrated similar benefits in MPS II.[79,80] The reasons for poorer outcomes in MPS II compared MPS I are unclear.[79-81] Patients with attenuated disease may have a better outcome as compared to patients receiving ERT,[81,82] but there is significant morbidity and mortality associated with HSCT.[81] For patients with severe disease, the benefits on neuropsychological outcomes remain unclear. It remains to be shown whether transplant performed at a very early age (1 year or less) will change the course of cognitive involvement.[83]

The largest reported case series with HSCT in MPS II is from Japan, where the treatment was employed as standard therapy for MPS II prior to the approval of ERT in that country.[84] A retrospective analysis of HSCT in Japanese patients with MPS II reported improvements in neuroradiologic parameters, stabilization of brain atrophy, and improved valvular disease in several patients who were more likely to be less severely affected.[84] However, no prospective studies have been completed to date and the efficacy of this treatment is not yet established. That said, newer modified cellular delivery techniques for HSCT as in metachromatic leukodystrophy[85] and improved conditioning regimens[86] have decreased the traditionally high morbidity and mortality associated with stem cell transplantation and may warrant a re-examination of the potential therapeutic benefits of HSCT in MPS II.

Intrathecal ERT for MPS II

Intrathecal ERT has been studied in MPS II with the aim of stabilization or improvement of CNS involvement in MPS II. A randomized, open-label, phase I/II study of intrathecal idursulfase (idursulfase-IT) in children with severe MPS II has been published.[28] In this study, idursulfase-IT was administered once monthly for six months in varying dosing regimens (10 mg, 3 mg, 1 mg, and no-treatment) to patients (n=16) with MPS II who were also given concurrent IV idursulfase ERT 0.5 mg/kg. The study drug was delivered using an intrathecal drug delivery device (IDDD). Idursulfase-IT administered intrathecally was well-tolerated in all patients, regardless of specific dose, and no serious treatment-related adverse events were reported. The majority of adverse events were related to IDDD malfunction, with surgical revision and removal of the IDDD required in six out of 12 patients who received idursulfase-IT. Cerebrospinal fluid (CSF) GAG levels decreased to a minimum of 80% in all treatment dosing groups within the first few months of treatment, and were sustained throughout the study. In contrast, CSF GAG levels remained unchanged over a six month period in the four patients who received no treatment. There was low immunogenicity noted with idursulfase-IT. An extension trial to evaluate longer term outcomes for idursulfase-IT is currently ongoing (NCT01506141). Top-line results from a phase II/III (NCT02055118) to determine if idursulfase-IT can stabilize neurological progression failed to show differences in primary or secondary outcomes.[30]

IV ERT with fusion proteins

To address the poor availability of ERT to the CNS, a recombinant IDS enzyme has been engineered to include a monoclonal antibody against the human insulin receptor that is expressed at the blood-brain barrier, theoretically enabling ERT to cross into the brain.[87] A study of the insulin receptor antibody-iduronate sulfatase fusion protein in Rhesus monkeys demonstrated an adequate safety profile.[88] A phase 1, open-label, multi-dose clinical trial is currently underway to evaluate the safety and tolerability of this recombinant IDS enzyme (AGT-182) in 8 adults with MPS II (NCT02262338).[89] Another fusion protein consisting of a recombinant IDS enzyme which includes an anti-transferrin receptor antibody (JR-141) is currently being studied in a phase 1/2 trial in 12 patients with MPS II (NCT03128593).[89]

Pharmacologic chaperone therapy

Small molecule therapies such as pharmacologic chaperone therapies and substrate reduction therapies have also been considered for MPS II. Chaperones are specifically designed to bind to the active site of the inactive lysosomal protein and cause it to fold into the appropriate confirmation, thereby improving its stability, and potentially allowing partial improvement of the lysosomal enzyme activity. In general, lysosomal storage diseases (LSDs) are good candidates for pharmacologic chaperone therapies as many

lysosomal diseases are caused by gene mutations that specifically create a misfolded lysosomal protein.[90] Clinical studies are underway for chaperones developed for Fabry disease, Gaucher disease, Pompe disease, and GM2 gangliosidosis, and preclinical cell-based studies are currently underway for other types of LSDs.[91]

In a recent study investigating the candidate chaperone for MPS II, DS20 (a sulfated disaccharide derived from heparin), there was a dose-dependent attenuation of thermal degeneration of recombinant mutated IDS enzyme in cells incubated with D2S0, as well as an increase in residual activity of mutant IDS in patient fibroblasts.[92]

While molecular chaperone therapy has therapeutic promise in LSDs, there are currently limitations requiring further study. These include difficulties in achieving increases in residual enzyme activities that would allow for significant clinical benefit, and difficulties in applying pharmacologic chaperone therapies for the full range of mutation types that may affect particular LSDs.[91,93]

Substrate reduction therapy

Substrate reduction therapy serves to inhibit GAG synthesis, and has held some promise in addressing the CNS complications of LSDs as these therapeutic agents are expected to cross the blood-brain barrier.[94] Several compounds that reduce MPS synthesis, such as the flavonoid genistein, have been studied with some effect on GAG reduction and concomitant clinical improvements in patients with MPS IIIA.[95] Effects of genistein on GAG reduction in various organs, including the brain, in a mouse model of MPS II have been observed.[96] In a study conducted in seven patients with MPS II, genistein was well-tolerated and resulted in improved joint mobility after 26 weeks of treatment.[97] Additional long-term studies are needed to assess the efficacy of substrate reduction in the CNS manifestations of MPS II.

Gene therapy/gene-targeted therapy

Gene therapy has been identified as a potential option for MPS II. *In vivo* gene therapy has been studied in a variety of MPS disorders, and involves injection of a vector that carries a healthy copy of the *IDS* and allows for expression within cells within various tissues.[98] *Ex vivo* gene therapy involves harvesting of the patient's cells, insertion of the normal transgene, and injection of these altered cells back into the patient.[99] Both approaches have been studied in cell and animal models for MPS II with promising results,[99] but have not been studied to date in patients with MPS II.

A study of MPS II mice administered with adeno-associated virus vectors encoding IDS (AAV9-*Ids)* into the cerebrospinal fluid showed a significant increase in IDS activity throughout the brain, resolution of storage lesions, reversal of lysosomal dysfunction, and reversal of neuroinflammation, with normalization of behaviour, and prolonged survival.[100] Another group also demonstrated the efficacy of AAV9-*Ids* delivered intracerebroventricularly with sustained IDS expression in circulation and peripheral organs, normalization of GAG levels, and concomitant prevention of neurocognitive deficits in mice treated at 2 months of age.[101] This group also demonstrated that a zinc-finger nuclease (ZFN) approach could be used to insert the human IDS coding sequence into the AAV2/8 vectors, which resulted in stable, high-level IDS enzyme expression and metabolic correction in MPS II mouse models.[102]

The recent discovery of genome editing systems such as CRISPR-CAS-9 provides a promising approach for gene therapy.[103] Genome editing technologies will likely change the future landscape of therapy for all genetic disorders, including MPS II.

Recommendations
- HSCT, intrathecal ERT, and ERT with fusion proteins show promise for MPS II
- Other therapies are under investigation, but have not yet been adequately studied
- Clinicians should closely follow clinical trials and be encouraged to enrol patients when appropriate

11. WHAT STRATEGIES CAN HELP ENSURE ACCESS TO TREATMENT?

Challenges to timely diagnosis (need for newborn screening programs)

Newborn with MPS II have a normal appearance and can be diagnosed only on the basis of family history. Newborn screening has the potential to enable pre-symptomatic diagnosis; however, it is not currently available for MPS II. Consequently, most patients with MPS II are diagnosed based on clinical signs and symptoms. The median age of diagnosis of 847 MPS II patients in the Hunter Outcome Survey was 3.3 years.[75]

There are no randomized-controlled trial data available to demonstrate improvements in disease-related symptoms or long-term clinical outcomes of MPS II patients treated between 16 months and 5 years of age with idursulfase.[104] However, Muenzer

reviewed the limited available evidence of benefits of early treatment in pairs of older and younger siblings and advocated for pre-symptomatic ERT in infants with MPS II.[105] Early diagnosis of MPS II is important in initiating timely treatment.

Without a family history or newborn screening, the clinical suspicion of MPS II requires the primary care physician or pediatrician to recognize a cluster of signs and symptoms many of which are non-specific, such as recurrent otitis media, umbilical and inguinal hernias, recurrent respiratory infections, upper airway obstruction with noisy breathing and snoring. More specific indications include coarse facial features, joint stiffness and dysotosis multiplex that are shared with other lysosomal storage diseases including the more common MPS I. Often the referral to a medical geneticist will result in the recognition of a lysosomal storage disease phenotype and enable the diagnosis of MPS II. The physical characteristics of MPS II generally appear around 2-4 years of age for the early onset progressive form, however about one-third of MPS II patients have attenuated disease in which the features may appear later and be more subtle. A study of 15 patients with attenuated MPS II found that 3.7-4 years elapsed between the time of the initial observations of chronic ear infections and hearing loss and the diagnosis of MPS II.[106] *The early diagnosis of MPS II remains a challenge in the absence of family history and newborn screening.*

ERT reimbursement policies across Canada

It has been estimated that 3 million Canadians will suffer from a rare disease within their lifetime.[107] In recent years, academic researchers and pharmaceutical companies have paid increasing attention to developing treatments for rare diseases.[108] Health Canada approved the use of idursulfase for enzyme replacement therapy for MPS II on December 17, 2007. However, at the same time the Canadian Expert Drug Advisory Committee recommended that idursulfase not be listed for funding on provincial formularies for the following reasons:[109]

"1. While idursulfase has been shown to have a biologic effect and improve some outcomes in patients with Hunter syndrome, the clinical significance of its effects is not established. For example, idursulfase improves distance walked in six minutes but the average improvement is less than 10% above baseline values. Idursulfase has not been shown to improve clinically relevant outcomes such as quality of life, pain, rates of hospitalization or the resources required for home care support.

2. It is unlikely that idursulfase enters the central nervous system and therefore, it is not

expected to improve the neurological complications of Hunter syndrome.

3. Idursulfase costs $4215 for a 6 mg vial and the cost for treatment of a 35 kg patient (the average weight of patients in the clinical trial reviewed by the Committee) was $657,000 per year."

"The Committee did not feel that the high cost was justified given the lack of evidence or improvement in clinically important outcomes."[109]

Similar concerns about the lack of improvements in clinically important outcomes (eg, growth, sleep apnoea, cardiac function, quality of life, and mortality) were expressed in a Cochrane review of clinical trials of idursulfase.[110]. However, a more recent analysis of clinical outcomes in 639 patients in the Hunter Outcome Survey database who had received up to 3 years of idursulfase reported positive effects on urine glycosaminoglycan levels, 6MWT, left ventricular mass index, FVC, FEV_1 and hepatosplenomegaly.[111]

A particular concern was the lack of cognitive benefits as idursulfase does not cross the blood brain barrier. Muenzer et al established an expert panel consensus on the role of idursulfase in severe MPS II.[29] The expert panel recommended that all patients be offered a treatment trial to improve or stabilize somatic signs and symptoms and improve quality of life, with the exception of patients who are severely neurologically impaired. They suggested that the idursulfase trial be initiated with consideration of termination if there is no evidence of benefit.

In Canada, provincial health plans have taken a variety of approaches to requests for funding idursulfase. In June 2011, Ontario developed a funding framework for Drugs for Rare Diseases (DRDs). Idursulfase for MPS II ERT can be reimbursed through the Exceptional Access Program within the Ontario Public Drug Program (OPDP) on an individual case basis. The patient must meet disease severity criteria and evidence of continued efficacy. New Brunswick has established a Rare Diseases Program and follows the same process as Ontario. There are similar rare disease drug coverage programs that provide reimbursement for idursulfase on a case-by-case basis in Alberta, British Columbia, Quebec, and Manitoba. Idursulfase is listed in the Nova Scotia formulary but a reimbursement program is not identified. The Saskatchewan formulary, Prince Edward Island formulary, and the Newfoundland and Labrador list of Special Authorization Drugs do not list idursulfase.

Patient advocacy societies

Canadian Agency for Drugs and Therapeutics in Health (CADTH)

The Canadian Agency for Drugs and Therapeutics in Health (CADTH) is an independent, not-for-profit organization created by Canada's federal, provincial, and territorial governments. It is responsible for providing healthcare decision makers with objective evidence in order to help them make informed decisions about the optimal use of medications.[112] CADTH is undertaking an environmental scan called the "Recommendations Framework for Drugs for Rare Diseases: A Review of Health Technology Assessment Agencies."[113] The environmental scan will aim to assess how Health Technology Assessment agencies review and make reimbursement decisions for drugs for rare diseases, and whether any of Canada's publicly-funded drug plans use a "drug for rare diseases-specific evaluation framework" to evaluate funding.

Patient advocacy groups

Patient advocacy groups should encourage research to improve the therapeutic potential of idursulfase in order to meet the efficacy concerns of agencies that advise on reimbursement. For example research on the:
   a) Development of a newborn screening test to enable pre-symptomatic diagnosis
   b) Efficacy of pre-symptomatic idursulfase treatment
   c) Development of an effective therapy to prevent the CNS disease

These groups should also advocate to health technology assessment organizations to identify new and lower cost models for conducting clinical trials for rare diseases, including more relevant assessments.[108,114]

Recommendations

- A newborn screening program will help overcome the challenges to a timely diagnosis

- Evidence for the efficacy of idursulfase on pre-symptomatic MPS-II, and effective therapy to prevent CNS symptoms will address concerns of funding bodies

- Patient advocacy groups can help encourage ongoing research and advocate to health plans to ensure that all appropriate patients have access to a treatment trial to improve or stabilize symptoms and quality of life

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