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Minireview

Critical review of current MPS guidelines and management

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ABSTRACT

Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders that impair degradation of glycosaminoglycans (GAG). The specific GAGs that accumulate depend on the type of MPS, leading to unique characteristic clinical features. Development of guidelines for treatment of MPS has traditionally been multifaceted and largely based on palliative care. In the last three decades, hematopoietic stem cell transplantation and enzyme replacement therapy have been developed based on experimental and clinical studies. Guidelines have been established with the accumulation of the clinical data from natural history of the disease and therapeutic consequences, mainly sponsored by pharmaceutical companies. In recent years, committees in three countries, Australia (2015), Japan (2017), and Brazil (2018) have adopted guidelines for the treatment of MPS II, sponsored and authorized by each government. As novel treatments for MPS including substrate reduction therapy, pharmacological chaperone therapy, and gene therapy become clinically available, it is increasingly necessary to establish the optimal guideline for each type of MPS, considering multiple factors including therapeutic efficacy, adverse effects, age, disease stage, prognosis, feasibility and availability of access to treatment, and cost- performance.

In this article, we discuss the historical guidelines for specific MPS types and the most recently adopted guidelines for MPS II and propose the development of future guidelines without conflict of interest and bias leading to mutual benefits to all parties including patients and families, professionals, tax payers, and governments.

Abbreviation list: 6MWT, six-minute walk test; AGREE II, appraisal of guidelines, research, and evaluation II; ANVISA, Brazilian National Agency of Health Surveilance; BBB, blood-brain barrier; BMT, bone marrow transplant; CNS, central nervous system; ERG, evidence review group; ERT, enzyme replacement therapy; FDA, Food and drug administration; GAG, glycosaminoglycan; GT, gene therapy; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; HSEEC, Hunter syndrome European expert council; IT, intrathecal; KS, keratan sulfate; LSD, lysosomal storage disorders; LSDP, Life saving drugs programme; MPS I, Mucopolysaccharidosis type I; MPS II, Mucopolysaccharidosis type II; MPS III, Mucopolysaccharidosis type III; MPS IV, Mucopolysaccharidosis type IV; MPS IX, Mucopolysaccharidosis type IX; MPS VI, Mucopolysaccharidosis type VI; MPS, Mucopolysaccharidosis; NBS, newborn screening; NICE, National Institute for Health Care and Excellence; NIH, National Institutes of Health; PCT, pharmacological chaperone therapy; QOL, quality of life; SRT, substrate reduction therapy; UCB, umbilical cord blood

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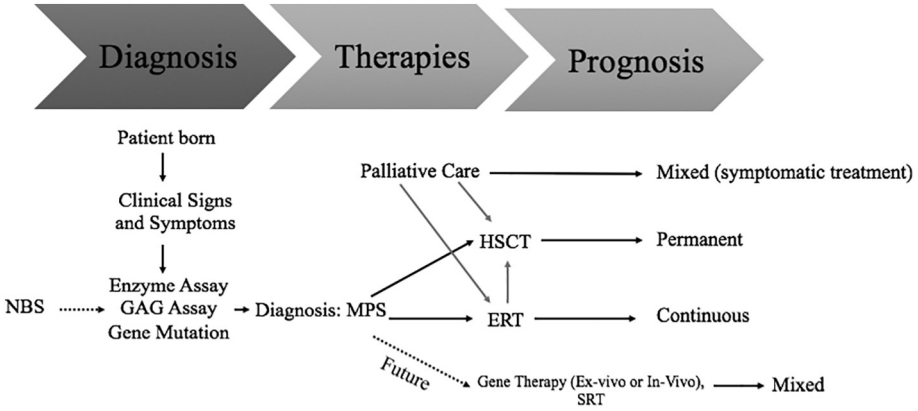

Fig. 1. Current and future management of MPS disorders.
Abbreviations: NBS: newborn screening; GAG: glycosaminoglycan; ERT: enzyme replacement therapy, HSCT: Hematopoietic stem cell therapy; SRT: substrate reduction therapy.

1. Introduction

Treatment guidelines for rare diseases are often scarce and difficult to find. Despite the lack of uniformity, general guidelines for orphan disease management are critical for fair and effective patient care, particularly when preemptive treatment leads to better patient outcomes, as is the case with mucopolysaccharidoses (MPS) (see Fig. 1 for MPS management strategy). Without guidelines that include treatment options appropriate for each patient with MPS, better care is delayed resulting in negative and, potentially fatal consequences. In the case of rare disorders, these guidelines should ideally be established based on the results from International patient registries. Such registries allow greater data comparison from patients with a wide range of clinical phenotypes and ethnic backgrounds [1]. Ideally these registries will include patient data obtained from randomized, double blind controlled trials. With the advent of increased International cooperation and standardized care, comprehensive, International databases have recently become a more realistic possibility. These databases can be created for and accessed by researchers, physicians, and patient community for information purposes. One example of such a collaboration is the Orphanet database, aimed at International data collection of patient information from those with rare diseases. Pavan et al… disseminated 277 clinical practice guidelines representing coverage of 1122 groups of diseases or subtypes between January 2012 and July 2015 into their database [2]. To determine the quality of the guidelines researchers used quality criteria derived from the AGREE II (Appraisal of Guidelines, Research, and Evaluation II) grading system, which was Internationally validated in 2002 [2]. This instrument contains 6 groups of criteria which are then subdivided into 23 separate quality domain items. Guidelines were further subjected to validation by third-party medical physicians before they were included in the Orphanet database. This process included guidelines originally written in 10 languages. Researchers found that many rare disease guidelines lacked specific AGREE II criteria. Common insufficiencies noted included rigor of development and editorial independence (see Table 1 for specific limitations of MPS guidelines) [2]. These common difficulties are not exclusive to this database and frequently cause potential bias in the development of comprehensive guidelines, as described in detail further on. With appropriate knowledge, specialized and unbiased editors and International collaboration, the development of such quality guidelines as assessed by criteria like AGREE-II is possible.

For MPS disorders, physicians and/or governments have proposed their own or collaborative guidelines for the care and treatment of patients based on MPS type, clinical phenotype, and age of the patients. We have reviewed these guidelines of each type of MPS and proposed how the unbiased guideline should be established.

2. Overview: historical aspect of guideline and management for treatment of MPS

2.1. Mucopolysaccharidosis type I (MPS I)

Currently, there are four guidelines and two review articles outlining treatment guidelines. In 2003, the International Consensus Panel on the Management and Treatment of MPS I met and established guidelines which were eventually updated and published in 2009. Since MPS requires a multidisciplinary approach, the team included specialists in pediatrics, cardiology, ophthalmology, anesthesiology, transplantation, orthopedics, and genetics [3]. The first guideline stated that all patients must receive a baseline evaluation for all systems that could be potentially affected. Comprehensive evaluations should be updated every 6–12 months. It is from initial evaluations that patients are grouped into one of two broad classes, Hurler syndrome (severe) and Hurler-Scheie or Scheie syndrome (attenuated). They suggest when deciding whether to treat patients with hematopoietic stem cell transplantation (HSCT) or enzyme replacement therapy (ERT) patient age, disease severity and the potential for growth should be considered. If a patient with MPS I is younger than 2 years and cognitively sufficient, HSCT is considered to be a better option as it provides a long-term impact and improvements on central nervous system (CNS) impairment. If a child is older than 2 years, already has experienced cognitive decline, or is believed to have an attenuated phenotype, ERT is considered more appropriate in addition to palliative care. It should be noted that these guidelines were sponsored by BioMarin/Genzyme, companies that currently market ERT.

Also in 2009, Martins et al. published “Guidelines for the Management of MPS I” in Brazil, again sponsored, in part, by Genzyme [4]. However, the guidelines were established exclusively by physicians and stressed a multifaceted and individualized approach for each patient. Nevertheless, the guidelines were similar to those proposed by the International Consensus Panel on the Management and Treatment. Treatment options included both ERT and HSCT. For ERT, patients must be evaluated for efficacy and response to treatment, but inclusion criteria included patients at any age. Patients whose symptoms imply imminent death as determined by at least two specialists, and patients who are pregnant or breastfeeding should be disqualified from ERT. For HSCT, inclusion criteria indicate that the patients must be under the age of 24-months and that preferably the transplant will be a human leukocyte antigen (HLA) identical sibling donor [4].

In 2010, Giugliani et al. published an updated “MPS I, II, and VI: Brief Review and Guidelines for Treatment” in Brazil in partnership with BioMarin and the Brazilian National Agency of Health Surveillance (ANVISA). Treatments again include HSCT, ERT, and palliative care.

Table 1
Guidelines and their limitations.

Guideline	Authors	Year	MPS disorder	Limitation
Mucopolysaccharidosis I: Management and treatment guidelines	Muenzer et al	2009	MPS I	Biomarin/Genzyme sponsorship; historical grouping of phenotype severity
Guidelines for the management of MPS I	Martins et al.	2009	MPS I	Genzyme sponsorship
ERT and/or HSCT at diagnosis with MPS I: results of a European concensus procedure	de Ru et al.	2011	MPS I	Biomarin/Genzyme sponsorship
ERT with Laronidase for treating MPS I	Jameson et al.	2013	MPS I	Biomarin sponsorship; only consideration for patients older than 2.5. Did not consider HSCT as viable treatment option.
LSDP guidelines and application form for subsidized treatment of MPS I	Australian government sponsored	2015	MPS I	Did not consider HSCT as viable treatment option
Mucopolysaccharidosis Type II: European recommendations for the diagnosis and management of a rare disease	Scarpa et al.	2011	MPS II	Shire Human Genetic Therapies sponsorship. Lack of involvement from fields of genetics and biochemistry. Did not consider HSCT
LSDP guidelines and application form for subsidized treatment of MPS II	Australian government sponsored	2015	MPS II	Lack of consideration of palliative care options. Did not consider HSCT as viable treatment option.
Practical guidelines for the management of mucopolysaccharidosis (MPS) type II	Eto et al. Japanese government sponsored	2017	MPS II	Historical treatment of phenotype severity
Inclusions of hematopoietic stem cell transplanation of mucopolysaccharidosis type II	Brazilian government sponsored	2018	MPS II	ERT and palliative care are not mentioned.
The international guidelines for the management of treatment of Morquio A syndrome	Hendriksz et al.	2015	MPS IVA	Biomarin sponsorship. ERT only therapeutic option consdered for patients. Did not consider HSCT as viable treatment option.
LSDP guidelines and application form for subsidized treatment of MPS IVA	Australian government sponsored	2015	MPS IVA	Limited tests of efficacy and data utilized. No data reported from surgical intervention. Did not consider HSCT as viable treatment option.
Elosulfase alfa for treating Mucopolysaccharidosis type IVA	NICE	2015	MPS IVA	Guideline to be eligibility for ERT. Lack of data for palliative care. Did not consider HSCT as viable treatment option.
LSDP guidelines and application form for subsidized treatment of MPS VI	Australian government sponsored	2015	MPS VI	Lack of palliative care consideration. Did not consider HSCT as viable treatment option.
Enzyme replacement therapy with gasulfase for mucopolsaccharidosis	Brunelli et al.	2016	MPS VI	Lack of longitudinal data, ERT was the only therapy considered, lack of accurate measures of efficacy. Did not consider HSCT as viable treatment option.

Guidelines for MPS I in this review were similar to those described above. ERT with HSCT was not considered in this review [5].

In 2011, de Ru et al. published "ERT and/or HSCT at diagnosis in patients with MPS I: results of a European Consensus procedure," where they discussed ERT versus conventional ERT followed by HSCT. The panel members of this meeting included specialists in multiple fields, not limited to physicians and including specialists in bone marrow transplantation (BMT) and metabolic disorders. The members used a modified Delphi process to develop consensus-based statements specifically on MPS I treatment. The initial opinions by specialists on transplantation based on prior expertise were collected, and the panel then met and composed a draft of MPS treatment options. The draft was revised until a consensus was obtained and the panel determined an algorithm for determination of either ERT or ERT followed by HSCT. Important factors in determining this algorithm included the age of the patient, lag time in treatment, and CNS involvement. This guideline was also sponsored by BioMarin/Genzyme [6].

In 2013, BioMarin supported "ERT with laronidase for Treating MPS I" published by Jameson et al. The study outlines the treatment of MPS I with a specific type of ERT laronidase (Aldurazyme®) [7]. The review acknowledges that the gold standard treatment for MPS I is HSCT for young patients treated before the age of 2.5 years. This study, therefore, examines ERT treatment for patients who were only treated older than the recommended age for HSCT treatment [7]. The study evaluates the effectiveness and safety of treating MPS I with laronidase as compared to a placebo in 45 patients. Efficacy was evaluated based on GAG levels in the urine, improved functional capacity, and GAG storage as determined by reduction in the volume of the liver [7]. This study shows an increase in age of effective treatment benefit from HSCT, from the age of 2 years to 2.5 years. While it is excepted that young children who have not experienced any cognitive decline should be considered for HSCT as opposed to ERT treatment there is discrepancy about what age children are too old for the greatest efficacy from HSCT and, in the event of probable neurological decline, whether children should be eligible to receive HSCT once some degree of cognitive impairment is present.

In 2015, the Australian Government Department of Health published "Life Saving Drugs Programme (LSDP) Guidelines and Application Form for Subsidized Treatment for Mucopolysaccharidosis Type I Disease (MPS I)" [8]. This review established a rare disease as one that affects no > 2000 individuals in Australia at a time. This renewed the subsidized government sponsored treatment of MPS I with ERT on the condition of efficacy monitoring on a patient by patient basis. This review also states that if HSCT becomes available at any age to the patient (mentions the possibility of preferential outcomes for patients with neurological symptoms but no specific criteria), ERT should be provided to patients pre-transplantation.

2.2. Mucopolysaccharidosis type II (MPS II)

There are currently five guidelines and one review article available for MPS II.

In 2010, the article "MPS I, II, and VI: brief review and guidelines for treatment," by Giugliani et al. described treatment for MPS II [5]. This review described unique inheritance of this disease as the only MPS disorder with an X-linked genetic inheritance pattern, the symptoms typically experienced, and the incidence of attenuated versus severe MPS II. The authors concluded that HSCT has not been performed in enough patients to determine the degree of therapeutic efficacy. The article recommends that patients with all phenotypes should receive ERT initially. Patients with significant CNS involvement should be assessed over 12 to 18 months. Since ERT does not allow the enzyme to cross the blood-brain barrier (BBB), cognitive function is not improved, and therefore, such patients must be monitored for therapeutic efficacy [5].

In 2011, the Hunter Syndrome European Expert Council (HSEEC)

sponsored the publication of "Mucopolysaccharidosis Type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease" [9]. This was a collaborative work with a group of European clinicians with substantial experience in diagnosing in treating patients with MPS disorders and lysosomal storage disorders (LSDs). This work recognizes the variance in treatment methods in MPS II patients between countries and gives overarching and comprehensive recommendations for treatment and diagnosis of MPS across national boundaries. The most common method of treatment is listed as ERT. The authors state that all patients with a confirmed diagnosis of MPS II should be eligible to receive a trial period of weekly ERT infusions, regardless of their phenotype. If there is no change in the quality of life after the trial period, if adverse effects develop, or if the patient has a very advanced MPS II phenotype that is unlikely to be affected by ERT, treatment should be stopped. If ERT shows a positive impact and the patient does not have severe respiratory symptoms, patients should be considered for continued ERT, using at home infusion if available. The authors list HSCT as not having been conducted on enough MPS II patients to allow for determination of long-term outcomes. This work was sponsored in part by Shire Human Genetic Therapies [9].

In 2011, da Silva et al. reviewed the efficacy of ERT for MPS II patients, compared to untreated and placebo patients in "Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (Hunter syndrome)." Results from the study showed the limited efficacy of treatment. ERT was effective at reducing liver and spleen volumes, functional capacity, and urinary GAGs levels. It was inconclusive on improvement in sleep apnea, growth, and cardiac function. This review was supported by the National Institute for Health Research in the United Kingdom [10].

In 2012 Muenzer et al., published "The role of enzyme replacement therapy in severe Hunter syndrome- an expert panel consensus." These guidelines particularly pertain to patients who have cognitive impairment due to MPS II. Panel experts included specialists in primary care, genetics and physician specialists. ERT was the only therapy that was discussed and it was concluded that while patients can experience some somatic improvements, no cognitive benefits from ERT have been seen. It was therefore determined that the risks of ERT in neurologically impaired patients should be weighed heavily against difficulties in administration and risks of treatment. Patients should be treated for a 6–12 month trial with ERT, and significant somatic symptom recovery must be seen in order to continue treatment [11].

In 2015, the Australian LSDP published their "Guidelines and application form for subsidized treatment for Mucopolysaccharidosis Type II disease (MPS II)." Treatments included ERT and determination of appropriate treatment is dependent on severity, age at diagnosis, initial treatment, and the presence of neurological symptoms on a case-by-case basis. The guideline was adopted by the Australian Government Department of Health [12].

In 2017, the "Practical guideline for the management of Mucopolysaccharidosis (MPS) type II," which outlined and evaluated the current treatment regimen for MPS II patients was adopted in Japan [13]. Committee Members appointed by Japanese Health, Labor and Welfare Ministry made this guideline. ERT can start immediately with weekly intravenous infusions. The enzyme infused is cleared rapidly from the body and cannot penetrate the BBB. Therefore, there is no effect on CNS impairment. Antibodies to the infused enzyme provide adverse effects. HSCT is considered as more effective on CNS impairment than ERT. HSCT is also a permanent one-time therapy reducing inconvenience to patients and their caregivers. There are still concerns about significant risks of HSCT, including graft-versus-host disease (GVHD), infection, and limited availability of matched donors [13].

To determine the acceptable treatment, evaluation of clinical symptoms must be taken into account. ERT is the first choice to treat visceral organ involvement, physical activity including walking, pulmonary function, and might improve bone symptoms including growth. However, there is no evidence that conventional ERT improves joint symptoms, cardiac function, valvular heart disease, or CNS symptoms. HSCT does not improve respiratory dysfunction, gait disturbance, or joint symptoms. The positive effect of HSCT on neurological decline should be considered when determining ideal patient treatment. While there is no strong evidence that HSCT improves CNS lesions already present in MPS II patients, it is likely that onset or progression of neurological symptoms will be reduced by HSCT in younger patients. Efficacy may also be dependent on the type of mutation and the age at HSCT, and therefore, evaluation of these parameters must be addressed [13].

In 2017, we summarized the current treatments available for MPS II including HSCT, conventional and intrathecal ERT, palliative care with symptomatic surgeries, and anti- inflammatory treatment. Treatment approaches differ based on age, clinical severity, prognosis, cost, health insurance, and country in which treatment is accessed [14].

In 2018, the Brazilian Health Ministry reevaluated treatment inclusion for MPS II. This study found that published studies about HSCT for MPS II tend to be outdated, and improvements for transplantations have been positively modified and improved in the last several years [15]. In addition, studies typically include heterogeneous groups of LSD who have varying degrees of advanced age and neurological impairment at the time of treatment. Although limitations of HSCT were included as previously mentioned, improvements were seen in patients treated at early stages [16–19]. The improvements included reduced mortality due to the advent of new protocols of immunosuppressant's, and better donor/patient selection criteria. These developments led to the recommendation of adding HSCT to government-sponsored treatments of neuropathic forms of MPS II in patients younger than three years old. This recommendation was accepted in January 2018, and allogeneic HSCT is now included as a therapeutic option according to clinical protocol and therapeutic guidelines [15].

2.3. Mucopolysaccharidosis type III (MPS III)

Management and Guidelines have not been determined yet since no effective treatment is established yet.

2.4. Mucopolysaccharidosis type IV (MPS IV)

There are several guidelines and reviews for treatment of MPS IVA. In 2013, "Review of clinical presentation and diagnosis of Mucopolysaccharidosis IVA" was published by Hendriksz et al., sponsored by BioMarin and the International Morquio Organization. This review focuses on methods of diagnosis and recognition of the signs and symptoms of MPS IVA and does not discuss any course of appropriate treatment [20].

A second review, published in 2014 by Tomatsu et al. addresses both current and future therapies for Morquio A. Therapies discussed include ERT, HSCT and palliative care including substrate reduction therapy (SRT) and symptomatic surgeries. Gene therapy (GT) is listed as a potential future treatment, with its limitation as a bone targeting agent also discussed. This article was supported by the Austrian MPS Society, the American National MPS Society, and the International Morquio Organization [21].

In 2014, Leadley et al. published "A systematic review of the prevalence of Morquio A Syndrome." This review highlights the misunderstanding of the definitions of prevalence versus incidence of this disease. It also emphasizes the necessity of extensive studies and universal assessment tools necessary for quality data collection [22]. Guidelines should be established over International boundaries, particularly in the case of rare disorders. This study encompasses patient data from over 24 countries and extrapolates data from observational studies, funded by BioMarin.

In January 2015, Hendriksz et al. published "The international guidelines for the management of treatment of Morquio A Syndrome." These guidelines were developed during two meetings, by an expert

panel of specialists in multiple fields including; pediatrics, cardiology, genetics, pulmonology, cardiology, and anesthetics [23]. The initial guidelines address the diagnosis of MPS IVA, which is beyond the scope of this paper. The final section of the guidelines address the management of this disorder. ERT is recommended as soon as the diagnosis has been confirmed as this treatment has shown effective in improving endurance and respiratory function. Baseline and follow-up assessments should be performed, but there is no mention of how long treatment should be continued if it is not initially effective. All patients should also receive a comprehensive multisystem evaluation of physical manifestations of the disease, and the disease burden should be performed just after initial diagnosis. Symptom-based disease management should continue. Every patient with MPS IVA should also receive a regular assessment of fine motor skills. In addition, an assessment of gastrointestinal problems and ocular abnormalities should be part of a basic physical exam performed at every visit. Audiological assessments should be conducted on an annual basis. ERT was the only therapeutic option considered in these guidelines.

In December 2015, The National Institute for Health Care and Excellence (NICE) in the U.K. published "Elosulfase alfa for treating Mucopolysaccharidosis type IVA," that gave an economic assessment for the treatment of MPS IVA with ERT. The assessment recommended ERT for all patients of any age, by intravenous infusion over a 4-h period once a week. The recommended dosage was 2 mg/kg [24]. This assessment utilized data on efficacy generated by the company that manufactures the drug, BioMarin. The evidence review group (ERG) noted statistically significant improvement in the six-minute walk test (6MWT) despite a limited number of samples and short duration of the trial. The review group recommended this treatment even though placebo effects were not taken into full account, and the respiratory and cardiac complications, which are the key drivers of mortality in patients, did not appear to be reduced by the treatment. Orthopedic surgery was considered as part of holistic and palliative treatment; however, the clinical trials did not report sufficient evidence of surgical outcomes. The committee did conclude that benefits of elosulfase alfa treatment likely were not adequately captured in such clinical trials. Thus, long-term outcomes in MPS IVA patients remain elusive [24]. Patients were recommended to start this treatment if they had a confirmed minimal enzymatic test, and elevated keratan sulfate (KS) levels. If over the age of 5, patients should have a full set of baseline assessments. ERT should be stopped if the patient is noncompliant with continued assessments for efficacy and recommended therapy, is unable to tolerate the infusion as determined by severe adverse effects, or fails to show improvement in the first year of treatment as defined by the list of naïve responder criteria. In addition, patients who are currently under treatment must continue to fulfill 4 out of 5 of the measures of efficacy and improvement. These criteria include; 1, the 6MWT score remaining at least 5% above baseline value; 2, lung capacity remaining 2% or more above baseline; 3, urinary KS values remaining reduced by at least 20% of baseline value; 4, no adverse change in quality of life (QOL); 5, Beck depression score and adolescent pediatric pain score and a decline in the ejection fraction of < 10% from the initial baseline. Patients who are diagnosed with an additional progressive life-limiting condition such as a lung capacity of < 0.3 l, or patients who are unwilling to comply with monitoring and assessment criteria are not eligible to begin treatment [24].

In 2017, Kahn et al. published "Mucopolysaccharidosis IVA and glycosaminoglycans." Therapy management included ERT, HSCT, and symptomatic surgeries including the newly designed tracheal reconstructive surgery. ERT, approved since 2014, is considered the typical gold standard of treatment; however, there is little evidence to suggest that such treatment has any effect on bone growth and joint laxity. HSCT was approved and insured for most MPS disorders including MPS IVA in Japan in 1995, after it was shown to cause amelioration of advanced respiratory malfunction, increased ADL, and decreased GAG concentration; however, this treatment has risk of adverse effects and limited efficacy on existing skeletal dysplasia. HSCT should be performed in selected cases with young patients after careful pretransplantation counseling, and clinical evaluation has been conducted. The guidelines and management strategies discussed were written by an International panel of specialists and was supported by both the National Institutes of Health (NIH) and the International Morquio Organization [25].

In March 2018, Finnigan et al. evaluated the efficacy of ERT in the study "Home infusion with Elosulfase alpha in a UK pediatric setting." While this study did not investigate options other than ERT treatment, they did suggest a course of action which would combat the lengthy, invasive difficulties faced by patients receiving in-hospital weekly intravenous infusions, which typically last 4–5 h each. Finnigan and colleagues suggest that if guidelines are in place including; appropriately trained staff who can provide a weekly report, patients and homecare staff regular contact with the hospital, and appropriate venous access at home, significant benefits to the patients and caregivers can be provided. In addition to increased QOL for the patient and family, they found that home treatment also provides a significant cost reduction (although this is specific to treatment under UK tax laws) [26].

2.5. Mucopolysaccharidosis type VI (MPS VI)

The first management guidelines for MPS VI, "Management guidelines for mucopolysaccharidosis VI," were established in 2007 and were published by Giugliani et al. The purpose of this guideline was to provide an Internationally applicable overview for assessment, management, and treatment of MPS VI [27]. Unlike many guidelines, this guideline not only included physicians but also experts in biochemistry and genetics. The molecular correlations with disease severity are discussed as well as treatment plans including palliative care, ERT, and HSCT. Historically, HSCT was the only treatment available to patients. If patients are under two years of age with the severe form of the disorder, HSCT can be considered as an option; however, HSCT data showed worsening of several side effects over time particularly corneal clouding. In addition, given the dangers of this treatment, including lack of available donors and increased morbidity and mortality, ERT should generally be considered a more viable option. While long-term data for treatment with ERT was unavailable, it should only be considered as an alternative for HSCT for patients older than two years of age. Additional palliative care for symptoms including ENT complications, hearing loss and sleep apnea should be conducted. The article was sponsored by BioMarin.

In 2010, Valayannopoulos et al. published a review article "Mucopolysaccharidosis VI" and listed ERT as the only common treatment option outside of palliative care. BMT is mentioned as not recommended and occurring only in rare circumstances. The future of treatment and issues that have yet to be addressed with current management are discussed [28].

The guidelines published by Giugliani et al. in 2010 "Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment," as previously described, summarizes the treatment experience for Brazilian MPS VI patients [5]. HSCT is described as an outdated treatment for MPS VI, whereas ERT is presented as the more favorable and less risky option for patients. ERT is recommended for all MPS VI patients regardless of age, severity or symptoms. These guidelines also discuss very rare instances when ERT would not be an appropriate treatment for MPS VI patients including instances where the patient develops severe adverse effects using the enzyme.

In 2015, the Australian Government Department of Health renewed the LSDP guidelines and application form for subsidized treatment of MPS VI [29]. These guidelines cover the necessity for a governmental subsidy for lifesaving treatment for rare and life-threatening conditions. The entrance criteria for a patient with MPS VI to receive care are included in these guidelines.

The following year in 2016 Brunelli et al. published "Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI," updating the efficacy and safety of treating MPS VI patients with ERT as compared to no intervention or other interventions [30]. Conclusions were made based on a small 24-week randomized trial and effectiveness of ERT was measured by 12-min walk test and urinary GAG reduction. ERT was found to have no effect on cardiac, pulmonary, liver or spleen functions. Limitations of the study and the need for longer studies to evaluate longer-term efficacy were discussed.

2.6. Mucopolysaccharidosis type VII (MPS VII)

Universal management and Guidelines of MPS VII have not been established yet, although ERT and HSCT are clinically used or under pre-clinical investigation. ERT was approved by the U.S Food and Drug Administration (FDA) as treatment for MPS VII in November 2017 [31]. In a published phase 1/2 clinical trial, patients between the ages of 5 and 35 were found to have a significant reduction in urinary GAGs excretion after 24 weeks of treatment and clinical improvement in 6MWT, fatigue and visual acuity [32]. Clinical trials are currently being conducted to determine the difference in efficacy in a younger patient group at initial treatment (< 5 years of age) versus the older patient group [32]. In 1996 a female patient underwent a BMT at 11 years of age and was experiencing positive results two years after transplantation. In a recent retrospective study, five MPS VII patients were identified as having been treated with BMT. Two patients were deceased by the time of the survey, and the remaining three experienced some clinical benefit [33]. Unfortunately, the limitations of BMT including difficulty finding appropriate donors and the continued high morbidity and mortality have made further modifications necessary. Use of umbilical cord blood (UCB) as a source of stem cell is a possible and effective way of improving safety and efficacy [33].

2.7. Mucopolysaccharidosis type IX (MPS IX)

Management and Guidelines of MPS IX were not available since only two families are known to be affected by this very rare disorder.

3. Future guidelines and development of guidelines

3.1. Determination of membership and appropriate sponsorship of guidelines

Given the multisystem involvement that occurs in patients with MPS, the formation of a panel for the development of guidelines requires a similarly diverse group of specialists. Expert panel members should include at a minimum; general attending pediatricians, clinical geneticists, metabolic specialists, orthopedic surgeons, anesthesiologists, cardiologists, neurologists, basic or translational experts on the preclinical study, governmental officials, patient care organizations and experts on newborn screening. Members should be entirely independent and without a stake in pharmaceutical companies that market specific treatments for MPS. In addition, as the development of International guidelines is ideal in the case of orphan disease, panel members should include representatives from different nations and regions (see Fig. 1). In the International guideline, choice of therapy should consider feasibility and accessibility of therapy. In addition, risk of mortality versus potential benefit of treatment given available data must be considered. Fig. 2

As evidenced in this text, a collection of clinical data on a larger scale through patient registries has been undertaken under the sponsorship of pharmaceutical companies. Unfortunately, this creates known bias in the reported results on efficacy and recommendations of treatment. Therefore, non-profit organizations or governmental agencies should exclusively sponsor the development of such guidelines. These organizations can include National societies, expert societies, and

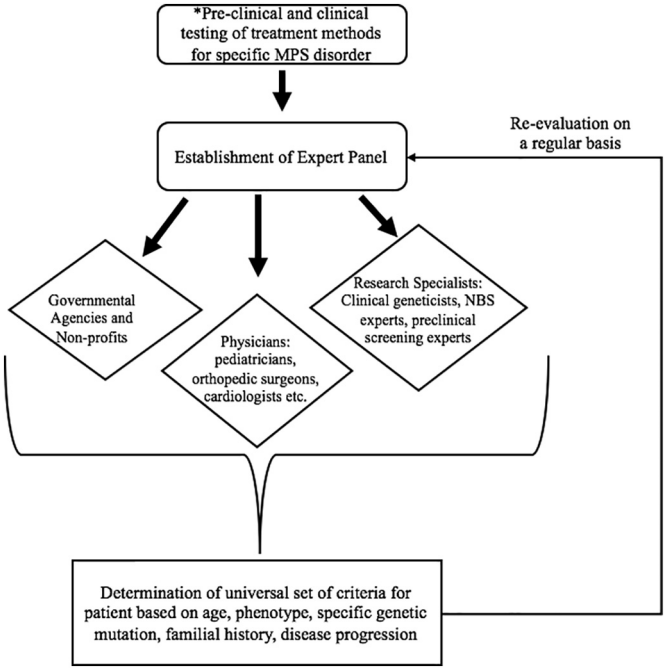

Fig. 2. Flow of organization for the development of expert guidelines for care in orphan diseases.

International organizations. Examples of such appropriate sponsors include the LSDP in Australia, the Brazilian Health Ministry, and the Health, Labor and Welfare Ministry in Japan [8–10,13,15,24].

3.2. Difficulties with current guidelines

MPS are a group of rare lysosomal storage diseases with the most common type of MPS occurring in approximately 0.31 to 0.71 per 100,000 live births [5,35,36,38]. Therefore, systematic reviews with MPS are limited in regards to the number of patients, resulting in insufficient and potentially inaccurate data [1,5]. It is an unmet challenge to collect systematic clinical data at both National and International levels. To resolve this issue, the establishment of an international registration system for each type of MPS is required. Currently, most registries are sponsored by pharmaceutical companies; however, access to the registry is restricted to the consultant doctors or panel members supported by the companies. In addition, different registries supported by different companies could be present, and it is very hard to exchange the data between registries. Thus, the registry data should also be established and exchanged independent of pharmaceutical companies.

3.3. Proposed future guidelines

The increased efficacy and reduced danger from certain treatments for MPS, including HSCT and ERT, allow for new opportunities for patients. Despite these advances, there is no curative treatment for any type of MPS disorder. Intravenous ERT shows poor efficacy in neural degeneration and avascular bone lesions. In addition, this treatment is very expensive ($250,000 to over $500,000 per year per patient) [39] and typically requires weekly or biweekly injections causing inconvenience for patients and their caregivers. To overcome these delivery limitations, intrathecal (IT) or intracerebral injection of the enzyme and modification of the enzyme to increase the affinity to bone and brain lesions has and continues to be investigated [32,40,41] although IT-ERTs for MPS I, II, IIIB, and IIIA have either not been approved or discontinued [40,41].

The major concern of HSCT is the risk of fatality of the procedure, which is highly dependent on the techniques used and skills of the

surgical team. However, being a single treatment, it is much more cost effective and easier to administer than ERT. New studies which provide evidence for the greater efficacy of this treatment have caused this to be a viable option for certain MPS disorders, most recently in the guidelines for treatment of MPS II in Brazil and Japan. In addition, many novel treatments including substrate reduction therapy (SRT), pharmacological chaperone therapy(PCT), gene therapy (GT)and genome editing [40,41] are under clinical trials or under pre-clinical development.

With the increase of new treatments, new evidence that suggests preemptive treatment can lead to greater efficacy rates and, new guidelines for MPS disorders need to be developed. These guidelines will allow clinicians to determine what treatment is optimal for each patient. Choice of treatment should be determined, based on a total assessment of the patient including age at diagnosis, age at initial treatment, clinical severity, prognosis, involvement or likely future involvement of the CNS and bone lesions, feasibility and availability to access of treatment, risk/benefit, and cost-performance. Guidelines should clearly identify benefits and pitfalls of each treatment option to enable physicians to choose the best option for individual patients.

In addition, the establishment of live newborn screening (NBS) should change the guidelines, as this will allow early identification and preemptive treatment. Accurate prognosis is critical before treatment starts, which requires the efforts of identification of specific genetic mutations. It is critical to collect longitudinal clinical data through an International registry of MPS patients the results of which can allow identification of biomarkers that can predict clinical phenotype. To generate unbiased guidelines, pharmaceutical companies should not be directly involved in developing guidelines. Panel members in various fields must be able to declare no conflict of interest and should be appointed independent of pharmaceutical companies. Ideally, governmental regulatory agents should also be involved throughout the process of development.

4. Conclusions

Historically, there were few treatment options for MPS, and patients were treated from an individual and system based approach. With the advent of new therapies, management and treatment of MPS disorders are more optimistic. An organized, early approach is critical for the most significant efficacy of treatment. Establishment of standard guidelines is necessary to choose optimal treatment for each patient. Many guidelines have been established with the support of profitable companies; however, future guidelines should be established independent of pharmaceutical companies. Guidelines should be based on longitudinal, clinical data, along with natural history and therapeutic efficacy. New guidelines established independently for the treatment of MPS II in both Japan and Brazil show movement in a positive direction with inclusion of treatment limitations and up to date therapies. From this point of view, an accessible registration system administered by a non-profit organization, government or society is critical. The collaboration of government, patients, and academic societies at an International level is required to establish such a registration system with unbiased guidelines.

Conflict of interest

All the authors contributed to this Article and had no conflict of interest with any other party. Molly Stapleton, Hiroo Hoshina, Kazuki Sawamoto, Francyne Kubaski, Robert W. Mason, William G. Mackenzie, Mary Theroux, Hironori Kobayashi, Seiji Yamaguchi, Yasuyuki Suzuki, Toshiyuki Fukao, Orii Tadao, Hiroyuki Ida, and Shunji Tomatsu declare that they have no conflict of interests.

Contributions to the project

Molly Stapleton has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described as the primary author.

Hiroo Hoshina has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described.

Kazuki Sawamoto has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described. Francyne Kubaski has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described.

Robert W. Mason has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described.

William Mackenzie has contributed to the concept and planning of the project, collection of data.

from the publications, the draft of the manuscript, and reporting of the work described.

Mary Theroux has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described.

Hironori Kobayashi has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described.

Seiji Yamaguchi has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described. Yasuyuki Suzuki has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described. Toshiyuki Fukao has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described.

Orii Tadao has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described.

Hiroyuki Ida has contributed to the concept and planning of the project, collection of data from the publications, the draft of the manuscript, and reporting of the work described.

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References

[1] S. Pavan, K. Rommel, M.E.M. Marquina, S. Höhn, V. Lanneau, A. Rath, Clinical practice guidelines for rare diseases: the orphanet database, PLoS ONE 12 (1) (2017) e0170365.

[2] L. Terrace, Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project, Qual. Saf. Health Care 12 (2003) 18–23.

[3] J. Muenzer, J.E. Wraith, L. Clarke, Mucopolysaccharidosis I: management and

treatment guidelines, Pediatrics 123 (2009) 19–29.
[4] A.M. Martins, A.P. Dualibi, D. Norato, E.T. Takata, E.S. Santos, E.R. Valadares, G. Porta, G. de Luca, G. Moreira, H. Pimentel, J. Coelho, J.M. Brum, J. Seminoato Filho, M.S. Kerstenetzky, M.R. Guimares, M.V. Rojas, P.C. Aranda, R.F. Pires, R.G. Faria, R.M. Mota, U. Matte, Z.C. Guedes, Guidelines for the management of mucopolysaccharidosis type I, J. Pediatr. 155 (2009) S32–S46.
[5] R. Giugliani, A. Federhen, M.V.M. Rojas, T. Vieira, O. Artigalás, L.L. Pinto, A.C. Azevedo, A. Acosta, C. Bonfim, C.M. Lourenco, C.A. Kim, D. Horvitz, D. Bonfim, D. Norato, D. Marinho, D. Palhares, E.S. Santos, E. Ribeiro, E. Valadares, F. Guarny, D.R. da Lucca, H. Pimentel, I.N. de Souza, J.C. Neto, J.C. Fraga, J.E. Goes, J.M. Cabral, J. Siminoato, J. Llerena Jr., L. Jardim, L. Giuliani, L.C.S. da Silva, Mucopolysaccharidosis I, II, and VI: brief review and guidelines for treatment, Genet. Mol. Biol. 33 (2010) 589–604.
[6] M.H. de Ru, J.J. Boelens, A.M. Das, S.A. Jones, J.H. van der Lee, N. Mahlaoui, E. Mengel, M. Offringa, A. O'Meara, R. Parini, A. Rovelli, K.W. Sykora, V. Valayannopoulos, A. Vellodi, R.F. Wynn, F.A. Wijburg, Enzyme replacement therapy and/or hematopoietic stem cell transplantation at diagnosis in patients with Mucopolysaccharidosis type I: results of a European consensus procedure, Orphanet J. Rare Dis. 6 (2011) 55.
[7] E. Jameson, S. Jones, J.E. Wraith, Enzyme replacement with laronidase (Aldurazyme) for treating mucopolysaccharidosis type I, Cochrane Database Syst. Rev. 9 (2013) CD009354, https://doi.org/10.1002/14651858.CD009354.pub2/epdf/standard.
[8] Australian Government Department of Health, LSDP Guidelines and Application Form for Subsidized Treatment for Mucopolysaccharidosis Type I Disease (MPS I), http://www.health.gov.au/internet/main/publishing.nsf/content/FD13E541FA14735CCA257BF0001B0AC0/$File/MPSI-Guidelines.pdf, (2015).
[9] M. Scarpa, Z. Almassy, M. Beck, O. Bodamer, I.A. Bruce, L. De Meirleir, N. Guffon, E. Guillen- Navarro, O. Hensman, S. Jones, W. Kamin, C. Kampmann, C. Lampe, C. Lavery, E.L. Teles, D. Link, A.M. Lund, G. Malm, S. Pitz, M. Rothera, C. Stewart, A. Tylki- Szymanska, A. Ploeg, R. Walker, J. Zeman, J.E. Wraith, Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease, Orphanet J. Rare Dis. 6 (2011) 72.
[10] E.M.K. da Silva, M.W.L. Strufaldi, R.B. Andriolo, L.A. Silva, Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (hunter syndrome), Cochrane Database Syst. Rev. 9 (2011) CD008185.
[11] J. Muenzer, et al., The role of enzyme replacement therapy in severe hunter syndrome- an expert panel consensus, Eur. J. Pediatr. 171 (1) (2012) 181–188.
[12] Australian Government Department of Health, LSDP Guidelines and Application form for Subsidized Treatment for Mucopolysaccharidosis Type II Disease (MPS II), http://www.health.gov.au/internet/main/publishing.nsf/content/FD13E541FA14735CCA257BF0 001B0AC0/$File/MPSII-Guidelines.pdf, (2015).
[13] Y. Eto, T. Okuyama, T. Ohashi, K. Kato, T. Kato, M. Kosuga, H. Sakuraba, Y. Suzuki, M. Takayanagi, H. Yabe, J. Watanabe, Practical Guideline for the Management of Mucopolysaccharidosis (MPS) Type II, (2017) (Shindan to Chiryou (Japanese)).
[14] M. Stapleton, F. Kubaski, R.W. Mason, H. Yabe, Y. Su, K.E. Orii Zuki, T. Orii, S. Tomatsu, Presentation and treatments for Mucopolysaccharidosis type II (MPS II; hunter syndrome), Expert Opin. Orphan Drugs 5 (2017) 295–307.
[15] Brazilian Health Ministry, Inclusions of Hematopoietic Stem Cell Transplantation of Mucopolysaccharidosis Type II. Information of the Health Ministry Secretary of Science Technology and Strategy Inputs, http://conitec.gov.br/, (2018).
[16] F. Kubaski, Y. Suzuki, H. Yabe, R.W. Mason, L. Xie, T.G.H. Onsten, et al., Hematopoietic stem cell transplantation for patients with mucopolysaccharidosis type II, Mol. Genet. Metab. 120 (2017) S77.
[17] A.L. Barth, T.S.P.C. de Magalhães, A.B.R. Reis, M.L. de Oliveira, F.B. Scalco, N.C. Cavalcanti, et al., Early hematopoietic stem cell transplantation in a patient with severe mucopolysaccharidosis II: a 7 years follow-up, Mol. Genet. Metab. Rep. 12 (2017) 62–68.
[18] A. Tanaka, T. Okuyama, Y. Suzuki, N. Sakai, H. Takakura, T. Sawada, et al., Long-term efficacy of hematopoietic stem cell transplantation on brain involvement in patients with mucopolysaccharidosis type II: a nationwide survey in Japan, Mol. Genet. Metab. 107 (2012) 513–520.
[19] M. Aldenhoven, S.A. Jones, D. Bonney, R.E. Borrill, M. Coussons, J. Mercer, et al., Hematopoietic cell transplantation for mucopolysaccharidosis patients is safe and effective: results after implementation of international guidelines, Biol. Blood Marrow Transplant. 21 (2015) 1106–1109.
[20] C.J. Hendriksz, P. Harmatz, M. Beck, S. Jones, T. Wood, R. Lachman, C.G. Gravance, T. Orii, S. Tomatsu, Review of clinical presentation and diagnosis of mucopolysaccharidosis IVA, Mol. Genet. Metab. 110 (2013) 54–64.
[21] S. Tomatsu, E. Yasuda, P. Patel, K. Ruhnke, T. Shimada, W.G. Mackenzie, R. Mason, M.M. Thacker, M. Theroux, A.M. Montano, C.J. Almeciga-Diaz, L.A. Barrera, Y. Chinen, W.S. Sly, D. Rowan, Y. Suzuki, T. Orii, Morquio asyndrome: diagnosis and current and future therapies the pathogenesis of systemic skeletal dysplasia in Morquio a syndrome remains an enigmatic, Pediatr. Endocrinol. Rev. 12 (2014) 141–151.
[22] R.M. Leadley, S. Lang, K. Misso, T. Bekkering, J. Ross, T. Akiyama, M. Fietz, R. Giugliani, C.J. Hendriksz, J. McGill, A. Olaye, M. Jain, J. Kleijnen, A systematic review of the prevalence of Morquio a syndrome: challenges for study reporting in rare diseases, Orphanet J. Rare Dis. 9 (173) (2014).
[23] C.J. Hendriksz, K.I. Berger, R. Giugliani, P. Harmatz, C. Kampmann, W.G. Mackenzie, J. Raiman, M.S. Villarreal, R. Savarirayan, International guidelines for the management and treatment of Morquio a syndrome, Am. J. Med. Genet. Part A 167 (2015) 11–25.
[24] National Institute for Health Care and Excellence, Elosulfase Alfa for Treating Mucopolysaccharidosis Type IVA, https://www.nice.org.uk/guidance/hst2, (2015).
[25] S. Khan, C. Almeciga-Diaz, K. Sawamoto, W.G. Mackenzie, M.C. Theroux, C. Pizarro, R.W. Mason, T. Orii, S. Tomatsu, Mucopolysaccharidosis IVA and glycosaminoglycans, HHS Public Access 120 (2017) 78–95.
[26] N. Finnigan, J. Roberts, J. Mercer, S.A. Jones, Home infusion with Elosulfase alpha (Vimizim R) in a UK Paediatric setting, Mol. Genet. Metab. Rep. (2018) 14–18.
[27] R. Giugliani, P. Harmatz, J.E. Wraith, Management guidelines for mucopolysaccharidosis VI, Pediatrics 120 (2007) 405–418.
[28] V. Valayannopoulos, H. Nicely, P. Harmatz, S. Turbeville, Mucopolysaccharidosis VI, Orphanet J. Rare Dis. 5 (2010) 5.
[29] Australian Government Department of Health, LSDP Guidelines and Application form for Subsidized Treatment for Mucopolysaccharidosis Type VI Disease (MPS VI), http://www.health.gov.au/internet/main/publishing.nsf/content/FD13E541FA14735CCA257BF0 001B0AC0/$File/MPSVI-Guidelines.pdf, (2015).
[30] M.J. Brunelli, A.N. Atallah, E.M.K. da Silva, Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI, Cochrane Database Syst. Rev. 3 (2016) CD009806.
[31] Food and Drug Administration, FDA Approves Treatment for Rare Genetic Enzyme Disorder MPS VII, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585308.htm, (2017).
[32] S.A. Jones, A. Ghosh, C. Breen, E.D. Kakkis, W.S. Sly, Enzyme replacement therapy (ERT) for mucopolysaccharidosis VII (MPS VII; Sly syndrome) reduces lysosomal storage in a 36-week phase 1/2 clinical study, Mol. Genet. Metab. 114 (2) (2015) S59.
[33] A.M. Montaño, N. Lock-Hock, R.D. Steiner, B.H. Graham, M. Szlago, R. Greenstein, ... M.S. Sands, Clinical course of sly syndrome (mucopolysaccharidosis type VII), J. Med. Genet. 53 (6) (2016) 401–418.
[35] J. Muenzer, Overview of the mucopolysaccharidoses, Rheumatology 50 (2011) 4–12.
[36] J. Nelson, J. Crowhurst, B. Carey, L. Greed, Incidence of the mucopolysaccharidoses in Western Australia, Am. J. Med. Genet. A 123A (2003) 310–313.
[38] F. Baehner, C. Schmiedeskamp, F. Krummenauer, E. Miebach, M. Bajbouj, C. Whybra, A. Kohlschütter, C. Kampmann, M. Beck, Cumulative incidence rates of the mucopolysaccharidoses in Germany, J. Inherit. Metab. Dis. Internet 228 (2005) 1011–1017. Available from: https://doi.org/10.1007/s10545-005-0112-z.
[39] F.H. de Bitencourt, T.A. Vieira, C.E. Steiner, J.C. Neto, R. Boy, I.V.D. Schwartz, Medical Costs Related to Enzyme Replacement Therapy for Mucopolysaccharidosis Types I, II, and VI in Brazil: A Multicenter Study. Value in Health Regional Issues, 8 (2015), pp. 99–106.
[40] I. Nestrasil, E. Shapiro, A. Svatkova, P. Dickson, A. Chen, A. Wakumoto, ... E. Maher, Intrathecal enzyme replacement therapy reverses cognitive decline in mucopolysaccharidosis type I, Am. J. Med. Genet. A 173 (3) (2017) 780–783.
[41] R. Giugliani, A. Federhen, A.A. Silva, C.M. Bittar, C.F. de Souza, C.B. Netto, ... U. Matte, Emerging treatment options for the mucopolysaccharidoses, Res. Rep. Endocr. Disord. 2 (2012) 53–64.