Molecular Genetics and Metabolism Reports 23 (2020) 100572

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Short Communication

Enzyme replacement therapy interruption in patients with Mucopolysaccharidoses: Recommendations for distinct scenarios in Latin America

MarthaL. Solano[a], Alejandro Fainboim[b], Juan Politei[c], Gloria L. Porras-Hurtado[d], Ana Maria Martins[e], Carolina F. Moura Souza[f], Felipe Mendez Koch[g], Hernan Amartino[h], Jose Maria Satizábal[i], Dafne D.G. Horovitz[j], Paula F.V. Medeiros[k], Rachel S. Honjo[l], Charles M. Lourenço[m,*]

[a] Fundacion Cardioinfantil de Bogota, Colombia
[b] Polivalent Day Hospital, Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina
[c] Laboratorio de Neuroquímica Dr. N. A. Chamoles, Fundación para el Estudio de Enfermedades Neurometabólicas (FESEN), Buenos Aires, Argentina
[d] Clinica Comfamiliar Risaralda, Colombia
[e] Reference Center of Metabolic Inborn Errors, Universidade Federal de São Paulo, São Paulo, Brazil
[f] Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
[g] Pediatric Neurology, Puerto Montt Hospital, Chile
[h] Servicio de Neurología Infantil y Clinica de Mucopolisacaridosis y transtornos relacionados, Hospital Universitario Austral, Buenos Aires, Argentina
[i] Department of Physiological Sciences, School of Basic Sciences, Faculty of Health, Universidad del Valle, Cali, Colombia
[j] Medical Genetics Department, National Institute of Women, Children and Adolescents Health Fernandes Figueira/Fiocruz, Rio de Janeiro, Brazil
[k] Unidade Acadêmica de Medicina, Hospital Universitário Alcides Carneiro, Universidade Federal de Campina Grande, Brazil
[l] Genetics Unit, Instituto da Criança do Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil
[m] Faculdade de Medicina, Centro Universitario Estácio de Ribeirão Preto, Ribeirão Preto, Brazil

ARTICLE INFO

Keywords:
Baseline data
ERT
Cessation
Interruption
Storage disease
Follow-up

ABSTRACT

Background: Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders, leading to the progressive accumulation of glycosaminoglycans (GAGs) and the subsequent compromising of tissues and organ malfunction. Although incurable, most types of MPS can be treated with enzyme replacement therapy (ERT), an approach that has had positive effects on the natural clinical evolution and which impact has been extensively investigated. Unfortunately, to date, there is relatively little data regarding the effects of ERT interruption, especially in Latin America, where such interruption may be frequent due to a variety of issues (for instance, difficulties involving logistics, reimbursement and/or payment withdrawal).

Method: A group of medical professionals from Latin America with experience in Genetics, Pediatrics and Neurology held an Advisory Board Meeting in the city of São Paulo, in October 2018, to discuss the issue of ERT interruptions in the region and recommendations health care professionals on how to deal with these interruptions and better assess the therapeutic effects of ERT.

Conclusion: Recommendations provided by the experts may support physicians in dealing with the most common reasons for ERT interruptions in Latin America. Most importantly, recommendations for data collection at specific timepoints (at baseline, throughout the treatment and during the interruption period of ERT and after its resumption) can significantly improve the collection of real world evidence on the effects of ERT and its interruptions, supporting health care professionals and policy makers in the decision making regarding the provision of these therapies for MPS patients.

1. Introduction

Mucopolysaccharidoses (MPS) are genetic disorders caused by specific lysosomal enzyme deficiencies, leading to the accumulation of glycosaminoglycans (GAGs) in the extracellular matrix and cells, and subsequently compromising tissues and leading to organ malfunction

* Corresponding author at: Centro Universitario Estácio de Ribeirão Preto, Rua Abrahão Issa Halach, 980 – Ribeirânia, Ribeirão Preto, SP 14096-160, Brazil.
E-mail address: charles.lourenfigco@estacio.br (C.M. Lourenço).

https://doi.org/10.1016/j.ymgmr.2020.100572
Received 17 November 2019; Received in revised form 27 January 2020; Accepted 28 January 2020

[1–3]. Currently, MPS are categorized in eleven subtypes in accordance with the specific lysosomal enzyme affected, leading to variable phenotype, severity and progression patterns among MPS types or even among patients with the same type of MPS due to the causative mutation and the level of residual enzymes [4–6].

The accumulation of GAGs affects various tissues, causing visual and auditory deficits, hepatosplenomegaly, spinal cord compression, and respiratory problems, with an increased frequency of upper airway infections, cardiac involvement, cognitive impairment leading to shortened life expectancy [7]. Treatment strategies have been developed to slow the disease progression induced by the accumulation of GAGs, including enzyme replacement therapy (ERT), gene therapy, small molecule therapies, and organ/cell transplantation. ERT is commercially available for MPS types I, II, IVA, VI and VII and requires weekly intravenous infusions of the recombinant enzyme, lasting three to four hours depending on the enzyme and its dosing regimen [8].

Registries and follow-up studies have indicated that, in spite of the differences and similarities across the MPS types, ERT has generally led to a reduction of urinary GAGs and organomegaly, an improvement of joint mobility, a reduction of airway infections, improved respiratory and cardiac functions, an enhancement in endurance and resistance, an improvement in visual acuity and a better quality of life [8–11]. In addition, studies with affected siblings have demonstrated that the earlier ERT is started the greater the clinical benefits will be in morphology, clinical manifestations and quality of life [12,13].

Data on the effects of ERT interruption in MPS are scarce, but point out to worsening of visceromegaly, respiratory function and walking capacity [14–17]. Despite of the evidence of the overall therapeutic benefit of ERT in MPS, access to these medications is challenged in some regions such as Latin America due to changes in health policies or reimbursement issues, with many patients facing frequent discontinuations in their therapy. In this scenario, high quality documentation of the disease status before the initiation of ERT, during ERT and after its discontinuation is critical to better appreciate the potential therapeutic benefits of this health technology in the real world setting, as well as the potential medical and economic consequences of the frequent discontinuations of its delivery to patients. To address this need, the present work provides expert-based recommendations on the medical follow-up of MPS patients during ERT treatment and following its interruption.

2. Methods

A group of Latin America medical experts in Genetics, Pediatrics and Neurology held an Advisory Board Meeting in São Paulo, Brazil, in October 2018. The meeting was sponsored by BioMarin. At the meeting, the experts reviewed the results of a survey about the main effects of ERT interruption they had completed, presented the articles on the issue and shared their perspectives on ERT interruption in their countries: the common reasons of interruption, the influence of the burden of infusions, the pros and cons of the home-based infusions, the therapeutic benefit of ERT, disease progression following ERT discontinuation and their recommendations of patient follow up. The key takeaways are summarized in the present work.

3. Effects of ERT on cardinal manifestations of MPS

The majority of the studies have pointed to beneficial effects of ERT on the reduction of urinary GAGs concentration in 3 to 6 months after the initiation of ERT [18–25]. Also, ERT positively impacts liver and spleen volumes, facilitating respiratory movements and improving the respiratory capacity of the patients [8].

ERT is effective in improving endurance measured by the 6-min walk test (6MWT) [29] in all the treatable types of MPS after short-term treatment. Collectively, the studies have reported that this improvement is limited after long-term ERT treatment [18,26]. Overall, the effects of ERT on bone abnormalities are minimal [20,27,28] possibly due to the inadequate distribution of the ERT molecules in this tissue [11,29]. Regarding pain control, studies have highlighted that ERT has had successful achievements in patients with MPS types I, II, IVA and VI.

Cardiac problems (especially valve disease) are common in MPS. The effects of ERT on the cardiovascular system may be dependent on the age ERT initiated and duration of ERT but mainly on the MPS type. Overall, it seems that ERT does not ameliorate the valve compromise [30–32], while there might be improvements in cardiac hypertrophy and remodeling. As summarized by Safary and colleagues [33], ERT has a poor biodistribution in hard-to-reach tissues. In this sense, blood-ocular and blood-brain barriers are the main obstacles to the ideal concentration of ERT molecules in the eyes and central nervous system.

Regardless of medical benefits, severe adverse effects have also been described, with the rare occurrence of life-threatening anaphylaxis [29]. Thus, desensitization protocols, which can avoid ERT interruption, have successfully been proposed [34,35]. Importantly, another drawback in ERT for MPS is the inability of the ERT molecules to cross the blood brain barrier, being much less effective in treating the accumulation of GAGs in the central nervous system [10,11].

3.1. Effects of ERT on cardinal manifestations of MPS I

MPS I presented with a broad spectrum of phenotypes. The most severe form of the disease –so-called Hurler syndrome, is characterized by cardiac and respiratory problems, facial and skeletal dysmorphism, intellectual impairments and a shorter lifespan [36]. The intermediate form (Hurler-Scheie syndrome) has similar somatic manifestations with mild or no cognitive impairment; the attenuated form (Scheie syndrome) has a slower progression with normal intelligence and lifespan [37].

It has been reported that ERT for 25 weeks reduced the hepatosplenomegaly in 10 patients with MPS I [38]. The same authors have verified that this ERT regime also promoted increase in growth in six prepubertal patients, decrease in joint stiffness and reduction of the number of episodes of apnea and hypopnea during sleep. All of these outcomes were concurrently to a reduction in urinary glycosaminoglycan excretion decreased after 3 to 4 weeks of treatment.

In patients with MPS I (Hurler subtype), progressive involvement of the CNS and somatic complication contribute to shorten lifespan within the first decade of life [4]. ERT was able to increase the lifespan from 6.4 years (untreated control group) to 9 years. However, such effect was exclusively observed in patients who started ERT prior to age 3 years [39].

Still regarding CNS involvement, as the ERT does not cross the blood-brain-barrier, the effects of this treatment on the brain are limited. In fact, such limited effect of ERT is particularly important for severe forms of MPS I and II. Currently, the initiation of ERT is a subjective of debate. The healthcare professionals recommend that ERT must be started in all patients who do not have a more effective treatment [8].

3.2. Effects of ERT on cardinal manifestations of MPS II

Different from the other types o MPS, MPS II is a X-linked recessive disorder that leads to deficiency in iduronate sulfatase, thus promoting the accumulation of chondroitin sulfate B (dermatan sulfate) and heparitin sulfate (heparan sulfate) in tissues and organs [40]. As MPS I, MPS II is also multisystem disorder, affecting respiratory tract, skeletal deformities, cardiomyopathy and frequently cognitive impairment [40]. For MPS II, clinical phenotype was divided into two main subgroups, dependent on the presence (severe) or absence (mild, now termed attenuated) of neurological impairment [41].

The weekly administration of idursulfase in ten Japanese male patients reduced glycosaminoglycan urinary excretion and

hepatosplenomegaly. Patients also showed a better performance in the 6MWT and had improvement in the percent predicted forced vital capacity, left ventricular mass index and several joint range of motions [32]. These authors also verified an increase in the sleep study oxygen desaturation index.

The effects of idursulfase on visual disorders are limited because the enzyme does not cross the blood-brain barrier and may also not cross the blood-retinal barrier. However, Yamanishi and colleagues [43] have reported a case in which ERT improved visual acuity and visual fields of the patient. The author proposed that beneficial effects of ERT are related to a recovery of optic nerve function, which is outside blood-brain barrier.

3.3. Effects of ERT on cardinal manifestations of MPS IVA

MPS IVA is caused by a deficiency in *N*-acetyl-galactosamine-6-sulfatase enzyme, leading to the accumulation of keratan sulfate (KS) and chondroitin-6-sulfate (C6S) within lysosomes, as well as the extracellular matrix (ECM) of various tissues [44]. The disease is characterized by progressive multi-level airway obstruction, musculoskeletal abnormalities, coarse features, neurological compromise, ocular, dental, auditory and valvular cardiac corollaries [45].

Kenth and colleagues [46] verified a reduction in static spirometry values in all subjects, as well as cardiorespiratory function as assessed by the 6MWT, with the decline being delayed in the ERT group. Additionally, respiratory function was improved in oximetry measures and other procedures to improve respiratory function (such as non-invasive ventilation and adenotonsillectomy) were more effective in the ERT-treated patients, either improving pulmonary function or attenuating deterioration. In general, the performance of patients with MPS IVA is limited due to their hypermobile joints, differently from other forms of MPS.

ERT was effective in stabilizing cardiac hypertrophy in patients with MPS IVA Taiwanese patients who had cardiac hypertrophy, aortic dilatation, increased thickness of the interventricular septum, normal systolic function, and mildly valvular heart disease. Consistently with previous data, better outcomes were obtained when ERT started at a younger age [47].

Bone pathology is a main concern in patients with MPS IVA and the heterogeneity of phenotypes may hamper the evaluation of ERT effects. Again, the sooner ERT starts, the better outcomes are achieved [48]. ERT seemed to be effective in increasing the height of patients during the first year of the ERT, but no more height gain was observed after 18 months. Bone deformities are less affected by ERT and patients usually require decompression surgery for treating medullar cervical spine compression [49].

3.4. Effects of ERT on cardinal manifestations of MPS VI

MPS VI, or Maroteaux-Lamy syndrome, is caused by deficient lysosomal enzyme *N*-acetylgalactosamine-4-sulfatase or arylsulfatase B, resulting in coarse facial features, skeletal and joint abnormalities, short stature, cardiorespiratory disease, spinal cord compression, hepatosplenomegaly, impaired vision, and hearing loss [50].

ERT with galsulfase improved endurance (by increasing distance walked in both 6MWT and 12MWT and climbed steps in the 3MSCT), increased pulmonary function as both vital capacity and forced expiratory volume were improved [51].

Kampmann et al. [52] showed the impact of ERT on cardiac functioning in MPS VI patients with abnormal echocardiographic findings before and after the onset of ERT, suggesting an improvement of concentric left ventricle (LV) remodeling and LV hypertrophy, stabilization of LV overload, pulmonary hypertension and valvular structure and function. Despite the late onset (a mean age of 14.6 years) of treatment, ERT appeared to improve or arrest the progression of LV remodeling and LV hypertrophy and suspend the progression of cardiac valve disease.

Patients with MPS VI are commonly subjected to pain due to bone disease and spin compression. In fact, a phase II trial of ERT in ten MPS VI patients reported decreased VAS-scores (visual analogue scale) of pain on the CHAQ (childhood health assessment questionnaire) scale by the end of a 24-week window of treatment [51]. Recently, a long-term evaluation of ERT in MPS VI patients demonstrated that joint pain and stiffness questionnaire scores improved 21% [54].

4. Effects of ERT interruption

Clear, specific medical criteria for ERT discontinuation are not available; however, there are a few reports of the effects of ERT interruption in clinical parameters and performance. The report from Anbu and colleagues [14] about a patient with MPS I who interrupted ERT due to pregnancy after deriving benefitfrom therapy on vital capacity and performance in the 6MWT as well as reversal of hepatomegaly and decrease in urinary GAGs describes clinical deterioration 24 months after discontinuation; however, the authors do not discard the potential role of pregnancy in the loss of beneficial effects of ERT. Wegrzyn et al. [15] described the effects of ERT interruption on a MPS I patient. Sixteen months of ERT had promoted normalization of urinary GAG levels, decreased sizes of the liver, spleen and tongue, and disappearance of diarrhea events within a few weeks. These effects were accompanied by an improvement of obstructive sleep apnea and enhanced distance covered in the 6MWT. The ERT was then discontinued over two months (reason not mentioned). The patient experienced a robust hepatomegaly (more pronounced than before the ERT), tongue enlargement, frequent diarrhea events and frequent respiratory events. Importantly, upon ERT resuming, some parameters did not improve (such as diarrhea and obstructive sleep apnea). Two series of five cases discussed not only the impact of ERT interruption on the cardinal signs of MPS but also the worsening of some signs [16,17]. Recurrent respiratory infections (such as severe pneumonia) with respiratory insufficiency were the most frequently found problems in these patients, followed by difficulty with walking/standing. The authors have made some remarks: first, ERT interruption can lead to the loss of the beneficial effects obtained by the patients and, in some circumstances, the abrupt withdrawal of ERT significantly worsened the clinical evolution of the patient, especially if the interruptions were for more than two months. Second, resuming the ERT did not seem to fully reverse the clinical decline caused by the discontinuation of the therapy. Within this context, patients and their caregivers must be aware of this before starting ERT [17].

So far, the mechanism for this rapid deterioration in some patients after the interruption of ERT has still yet to be fully understood. It has been proposed that the general GAG turnover in the organism in untreated MPS patients. More specifically, GAGs synthesis is inhibited due to the accumulation of these compounds as an autoregulation phenomenon developed with progression of the disease. When starting on ERT, there is a decrease in accumulated GAG compounds, which would then reverse the inhibition of GAG synthesis. Thus, sudden interruption of ERT would lead to a significantly delayed response of the regulatory systems responsible for impairment of GAG synthesis. As a consequence, a more rapid accumulation of GAGs would be seen in comparison with the natural state prior to implementation of ERT.

5. Recommendations following ERT interruption in real LIFE

The experts shared their experience with ERT interruptions in Latin America. In the region, most interruptions are prompted by non-medical circumstances, mainly financial or reimbursement issues. The experts are firm in defending that decisions regarding interruption or resumption of ERT should essentially rely on a strong doctor-patient relationship based on ethics and scientific evidence. The Table 1 lists the most common behind ERT interruption in Latin America, and the

Table 1
Most common scenarios leading to ERT interruption in Latin American MPS patients.

Scenario	Description	Recommendations
Request from patient or caregiver	Patients and/or caregivers question the advantages vs. disadvantages of receiving life-long weekly ERT.	Experts recommend that the decision to discontinue ERT must always be analyzed on a case-by-case basis, considering the severity of the patient's disease as well as the patient's preferences.
ERT is interrupted due to life-threatening side effects	ERT can lead to infusion-induced reactions.	Specialists can recommend additional prophylactic drugs prior infusions and consider desensitization protocols.
MPS patients with severe cognitive impairment or progressive cognitive decline	ERT has limited effectiveness in patients with severe cognitive impairment due to restricted access to the blood brain barrier.	Interruption of ERT may be recommended in agreement with the patient's caregivers.
Interruption of ERT due to logistics	Patients may have interrupted ERT due to hampered mobility.	In regions where home-based ERT is feasible and safe, experts recommend it in order to improve the quality of life of patients.
Interruption of ERT due to reimbursement issues and/or difficulty in obtaining high-cost treatment from the health system	This is the most frequent reason for the interruption of ERT in Latin America.	Physicians and health professionals should reinforce the rationale for ERT based on scientific evidence and enhance the quality of the medical records to generate reliable real-world evidence. The medical community should function as a trusted advisor of patients, caregivers and patient advocacy groups in their interactions with the regional policy makers in the area of MPS/rare diseases.

recommendations from the experts.

6. Proposed parameters for patient follow-up

Since data regarding the effects of the interruption of ERT among MPS patients is limited, the panel of experts considered that establishing a baseline evaluation of the patients is of critical importance. Initially, due to the nature of the disease, its varying severity and the patient's age at the time of diagnosis and initiation of the treatment, each patient responds differently to the ERT. Even though the international registers may provide information regarding the natural course of the disease and the long-term effects of ERT, the response to interruption of ERT is individual, thus requiring a personalized approach.

Another important issue is the length of time the ERT is interrupted for. As described by Jurecka et al. [16,17], when the interruption of ERT is longer than two months, some clinical deterioration may not be reverted after resumption of ERT. Then again, the patient's evaluation over the entire period of time, using the same parameters, can draw a picture of the tangible impact of the interruption of ERT.

The panel of experts endorsed a recommendation for a minimal schedule able to reveal the initial status of the patient before the ERT, the evolution throughout the treatment and the impact of interrupting and resuming ERT, as summarized in Table 2. Ideally, the evaluation should be performed annually or semiannually. If ERT is interrupted, the evaluation should be performed before resumption of the ERT and repeated six or twelve months after the interruption. The experts recommended a minimal set of assessments, which can facilitate the collection of data and the possibility of analyzing data as a whole, thereby improving the reliability of the information obtained.

Table 2
Minimal parameters recommended for assessment at baseline (immediately prior to initiating ERT), throughout ERT and after its interruption or resumption in patients with MPS.

Clinical evaluation
Medical history for monitoring infection frequency during the follow-up consultation
Urinary glycosaminoglycans (GAGs)
Organomegaly (abdominal echography)
Echocardiogram
Spinal cord compression evaluation
6-MWT and forced vital capacity
Joint mobility evaluation
Audiometry
Visual evaluation
Evaluation of pain with suitable questionnaires
Evaluation of quality of life with suitable questionnaires

7. Conclusion

The expert panel was convened with the aim of studying the impact of an interruption in ERT on patients with MPS and providing recommendations for healthcare professionals on how to deal with this issue in Latin America, which is usually prompted by access and reimbursement barriers. Within this context, the period of ERT interruption and its impact on patient evolution should be systematically approached. Thus, structured follow-up and data collection from these patients are vital to advocate for better access to ERT and to improve patient management and individual treatment decisions on maintenance or discontinuation. Further discussions should be held among experts, and studies in this area should be encouraged, especially with real world data, for a better understanding of the value of ERT for MPS patients in the region.

Author contribution

All authors were responsible for the conceptualization; formal analysis and review of the manuscript.

Details of ethics approval, the patient consent statement or Documentation of approval from the Institutional Committee for Care and Use of Laboratory Animals (or comparable committee)

Not applicable.

Availability of data and materials section

Not applicable.

Details of funding

BioMarin Brasil Farmacêutica LTDA. sponsored the preparation of this article.

Declaration of Competing Interest

Martha L. Solano has received honoraria for presentations from Shire and BioMarin and received advisory board honoraria from BioMarin.

Alejandro Fainboim has received honoraria for presentations and board meetings, and has received unrestricted educational grants and research grants from Genzyme and Shire. He has received advisory board honoraria from BioMarin.

Juan Politei has received advisory board honoraria from BioMarin.

Gloria L Porras-Hurtado has received advisory board honoraria from

BioMarin.

Ana Maria Martins has received honoraria for presentations from Sanofi-Genzyme and BioMarin and received advisory board honoraria from BioMarin.

Carolina F. Moura de Souza has received honoraria for presentations from Shire and BioMarin and received advisory board honoraria from BioMarin.

Felipe Mendez has received advisory board honoraria from BioMarin.

Hernan Amartino has received educational travel grants and/or speaker honoraria from BioMarin, Takeda/Shire and Sanofi Genzyme, and received board honoraria from BioMarin.

Jose Maria Satizábal has received advisory board honoraria from BioMarin.

Dafne Horovitz has received educational travel grants and/or speaker honoraria from BioMarin, Shire, Sanofi Genzyme and Ultragenyx.

Paula FV de Medeiros has received advisory board honoraria from BioMarin.

Rachel S Honjo has received advisory board honoraria and/or speaker honoraria from BioMarin, Shire/Takeda and Sanofi-Genzyme.

Charles M. Lourenço has received speakers' honoraria from Actelion, Genzyme, BioMarin, PTC and Shire HGT.

Acknowledgments

The authors would like to thank Tatiana Magalhães, MD, Daniela Giovannetti, MD, Guillhermo Seratti, MD, Felipe Navarrera, MD and Debora Mesojedovas, PharmD for contributions, as well as BioMarin Brasil Farmacêutica LTDA. which sponsored the preparation of this manuscript and reviewed the manuscript for medical and scientific accuracy. A special thanks to Stream Medical Affairs and Camilla Patti Hissamura for providing medical writer services for the elaboration of this manuscript.

References

[1] S. Lakhotia, A. Sharma, G.P. Shrivastava, S.K. Jain, Maroteaux-Lamy syndrome, Indian J. Pediatr. 71 (10) (2004) 933–935.
[2] J. Muenzer, The mucopolysaccharidoses: a heterogeneous group of disorders with variable pediatric presentations, J. Pediatr. 144 (2004) S27–S34, https://doi.org/10.1016/j.jpeds.2004.01.052.
[3] S.A. Khan, H. Peracha, D. Ballhausen, A. Wiesbauer, M. Rohrbach, M. Gautschi, et al., Epidemiology of mucopolysaccharidoses, Mol. Genet. Metab. 121 (3) (2017) 227–240 (10.1016/j.ymgme.2017.05.016).
[4] E.F. Neufeld, J. Muenzer, The mucopolysaccharidosis, in: C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle (Eds.), The Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill, New York, 2001, pp. 3421–3452.
[5] C. Lavery, C. Hendriksz, Mortality in patients with Morquio syndrome A, JIMD Rep. 15 (2015) 59e66, https://doi.org/10.1007/8904_2014_298.
[6] S. Khan, C.J. Alméciga-Díaz, K. Sawamoto, W.G. Mackenzie, M.C. Theroux, C. Pizarro, et al., Mucopolysaccharidosis IVA and glycosaminoglycans, Mol. Genet. Metab. 120 (1–2) (2017) 78–95, https://doi.org/10.1016/j.ymgme.2016.11.007.
[7] H. Kobayashi, Recent trends in mucopolysaccharidosis research, J. Hum. Genet. 64 (2018) 127–137, https://doi.org/10.1038/s10038-018-0534-8.
[8] D. Concolino, F. Deodato, R. Parini, Enzyme replacement therapy: efficacy and limitations, Ital. J. Pediatr. 44 (2018) 120, , https://doi.org/10.1186/s13052-018-0562-1.
[9] P.S. Kishnani, P.I. Dickson, L. Muldowney, J.J. Lee, A. Rosenberg, R. Abichandani, et al., Immune response to enzyme replacement therapies in lysosomal storage diseases and the role of immune tolerance induction, Mol. Genet. Metab. 117 (2) (2016) 66–83.
[10] D.S. Anson, C. McIntyre, S. Byers, Therapies for neurological disease in the mucopolysaccharidoses, Curr. Gene Ther. 11 (2011) 132–143, https://doi.org/10.1016/j.ymgme.2015.11.001.
[11] W.S. Sly, Enzyme replacement therapy: from concept to clinical practice, Acta Paediatr. 439 (2002) 71–78.
[12] O. Gabrielli, L.A. Clarke, A. Ficcadenti, et al., 12 year follow up of enzyme-replacement therapy in two siblings with attenuated mucopolysaccharidosis I: the important role of early treatment, BMC Med. Genet. 17 (2016) 19, , https://doi.org/10.1186/s12881-016-0284-4.
[13] J.F. Franco, D.C. Soares, L.C. Torres, G.N. Leal, M.T. Cunha, R.S. Honjo, et al., Short communication impact of early enzyme-replacement therapy for mucopolysaccharidosis VI: results of a long-term follow-up of Brazilian siblings, Genet. Mol. Res. 15 (1) (2016), https://doi.org/10.4238/gmr.15017850.
[14] A.T. Anbu, J. Mercer, J.E. Wraith, Effect of discontinuing of laronidase in a patient with mucopolysaccharidosis type I, J. Inherit. Metab. Dis. 29 (2006) 230–231, https://doi.org/10.1007/s10545-006-0237-8.
[15] G. Wegrzyn, A. Tylki-Szymańska, A. Liberek, E. Piotrowska, J. Jakóbkiewicz-Banecka, J. Marucha, et al., Rapid deterioration of a patient with mucopolysaccharidosis type I during interruption of enzyme replacement therapy, Am. J. Med. Genet. A 143A (16) (2007) 1925–1927, https://doi.org/10.1002/ajmg.a.31831.
[16] A. Jurecka, V. Malinova, A. Tylki-Szymańska, Effect of rapid cessation of enzyme replacement therapy: a report of 5 more cases, Mol. Genet. Metab. 111 (2) (2014) 212–213, https://doi.org/10.1016/j.ymgme.2013.08.019.
[17] A. Jurecka, Z. Żuberuber, V. Opoka-Winiarska, Effect of rapid cessation of enzyme replacement therapy: a report of 5 cases and a review of the literature, Mol. Genet. Metab. 107 (2012) 508–512, https://doi.org/10.1016/j.ymgme.2013.08.019.
[18] R. Giugliani, C. Lampe, N. Guffon, D. Ketteridge, E. Leão-Teles, J.E. Wraith, et al., Natural history and galsulfase treatment in mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome):10-year follow-up of patients who previously participated in an MPS VI Survey Study, Am. J. Med. Genet. A 164A (8) (2014) 1953–1964, https://doi.org/10.1002/ajmg.a.36584.
[19] C.J. Hendriksz, B. Burton, T.R. Fleming, P. Harmatz, D. Hughes, S.A. Jones, et al., Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study, J. Inherit. Metab. Dis. 37 (6) (2014) 979–990, https://doi.org/10.1007/s10545-014-9715-6.
[20] M. Kılıç, A. Dursun, T. Coşkun, Genotypic-phenotypic features and enzyme replacement therapy outcome in patients with mucopolysaccharidosis VI from Turkey, Am. J. Med. Genet. A 173 (2017) 2954–2967, https://doi.org/10.1002/ajmg.a.38459.
[21] C. Lampe, A.K. Bosserhoff, B.K. Burton, R. Giugliani, C.F. de Souza, C. Bittar, et al., Long-term experience with enzyme replacement therapy (ERT) in MPS II patients with a severe phenotype: an international case series, J. Inherit. Metab. Dis. 37 (5) (2014) 823–829, https://doi.org/10.1007/s10545-014-9686-7.
[22] J. Muenzer, M. Beck, C.M. Eng, R. Giugliani, P. Harmatz, R. Martin, U. Ramaswami, et al., Long-term, open-labeled extension study of idursulfase in the treatment of hunter syndrome, Genet. Med. 13 (2) (2011) 95–101, https://doi.org/10.1097/GIM.0b013e3181fea459.
[23] M.U. Akyol, T.D. Alden, H. Amartino, J. Ashworth, K. Belani, K.I. Berger, MPS Consensus Programme Steering Committee, MPS Consensus Programme Co-Chairs, et al., Recommendations for the management of MPS IVA: systematic evidence- and consensus-based guidance, Orphanet. J. Rare Dis. 14 (1) (2019) 137, https://doi.org/10.1186/s13023-019-1074-9.
[24] M.U. Akyol, T.D. Alden, H. Amartino, J. Ashworth, K. Belani, K.I. Berger, MPS Consensus Programme Steering Committee, MPS Consensus Programme Co-Chairs, et al., Recommendations for the management of MPS VI: systematic evidence- and consensus-based guidance, Orphanet. J. Rare Dis. 14 (1) (2019) 118, https://doi.org/10.1186/s13023-019-1080-y.
[25] M. Sifuentes, R. Doroshow, R. Hoft, G. Mason, I. Walot, M. Diament, et al., A follow-up study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years, Mol. Genet. Metab. 90 (2) (2007) 171–180, https://doi.org/10.1016/j.ymgme.2006.08.007.
[26] D.D.G. Horovitz, A.X. Acosta, L. de Rosso Giuliani, E.M. Ribeiro, Mucopolysaccharidosis type VI on enzyme replacement therapy since infancy: six years follow-up of four children, Mol. Genet. Metab. Rep. 5 (2015 Sep) 19–25, https://doi.org/10.1016/j.ymgmr.2015.09.002.
[27] J.E. Wraith, L.A. Clarke, M. Beck, E.H. Kolodny, G.M. Pastores, J. Muenzer, et al., Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase), J. Pediatr. 144 (5) (2004) 581–588, https://doi.org/10.1016/j.jpeds.2004.01.046.
[28] J. Muenzer, J.E. Wraith, L.A. Clarke, International consensus panel on management and treatment of mucopolysaccharidosis I. Mucopolysaccharidosis I: management and treatment guidelines, Pediatrics. 123 (2009) 19–29, https://doi.org/10.1542/peds.2008-0416.
[29] L.A. Clarke, J.E. Wraith, M. Beck, E.H. Kolodny, G.M. Pastores, J. Muenzer, et al., Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I, Pediatrics. 123 (1) (2009) 229–240, https://doi.org/10.1542/peds.2007-3847.
[30] L. Boffi, P. Russo, G. Limongelli, Early diagnosis and management of cardiac manifestations in mucopolysaccharidoses: a practical guide for paediatric and adult cardiologists, Ital. J. Pediatr. 44 (2018) 122, , https://doi.org/10.1186/s13052-018-0560-3.
[31] M.M. Brands, E. Oussoren, G.J. Ruijter, A.A. Vollebregt, H.M. van den Hout, K.F. Joosten, et al., Up to five years experience with 11 mucopolysaccharidosis type VI patients, Mol. Genet. Metab. 109 (1) (2013) 70–76, https://doi.org/10.1016/j.ymgme.2013.02.013.
[32] T. Okuyama, A. Tanaka, Y. Suzuki, H. Ida, T. Tanaka, G.F. Cox, et al., Japan elaprase treatment (JET) study: idursulfase enzyme replacement therapy in adult patients with attenuated hunter syndrome (Mucopolysaccharidosis II, MPS II), Mol. Genet. Metab. 99 (1) (2010) 18–25, https://doi.org/10.1016/j.ymgme.2009.08.006.
[33] A. Safary, M. Akbarzadeh Khiavi, R. Mousavi, J. Barar, M.A. Rafi, Enzyme replacement therapies: what is the best option? Bioimpacts. 8 (3) (2018) 153–157, https://doi.org/10.15171/bi.2018.17.
[34] C.S. Aranda, L.F. Ensina, I.C. Nunes, M.C. Mallozi, C. Mendes, A.M. Martins, et al., Diagnosis and management of infusion-related hypersensitivity reactions to enzyme

replacement therapy for lysosomal diseases: the role of desensitization, J Allergy Clin Immunol Pract 4 (2) (2016) 354–356, https://doi.org/10.1016/j.jaip.2015.11.012.
[35] L.F. Ensina, C.S. Aranda, A.E. de Lacerda, I. Camelo-Nunes, D. Sole, A.M. Martins, et al., Laronidase hypersensitivity and desensitization in type I mucopolysaccharidosis: a case report, Pediatr. Allergy Immunol. 25 (5) (2014) 498–499, https://doi.org/10.1111/pai.12209.
[36] J.L. Ashworth, S. Biswas, E. Wraith, I.C. Lloyd, Mucopolysaccharidoses and the eye, Surv. Ophthalmol. 51 (1) (2006) 1–17, https://doi.org/10.1016/j.survophthal.2005.11.007.
[37] F.A. Abraham, S. Yatziv, A. Russell, E. Auerbach, Electrophysiological and psychophysical findings in hunter syndrome, Arch. Ophthalmol. 91 (1974) 181–186.
[38] E.D. Kakkis, J. Muenzer, G.E. Tiller, L. Waber, J. Belmont, M. Passage, et al., Enzyme-replacement therapy in mucopolysaccharidosis I, New Eng. J. Med. 344 (2001) 182–188.
[39] J.B. Eisengart, K.D. Rudser, Y. Xue, P. Orchard, W. Miller, T. Lund, et al., Long-term outcomes of systemic therapies for hurler syndrome: an international multicenter comparison, Genet. Med. 20 (11) (2018) 1423–1429, https://doi.org/10.1038/gim.2018.29.
[40] J.E. Wraith, M. Scarpa, M. Beck, O.A. Bodamer, L. De Meirleir, N. Guffon, et al., Mucopolysaccharidosis type II (hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy, Eur. J. Pediatr. 167 (2008) 267–277.
[41] I.D. Young, P.S. Harper, R.G. Newcombe, I.M. Archer, A clinical and genetic study of Hunter's syndrome. 2. Differences between the mild and severe forms, J. Med. Genet. 19 (1982) 408–411.
[43] R. Yamanishi, N. Nakamura, K. Tsunoda, Recovery of vision following enzyme replacement therapy in a patient with mucopolysaccharidosis type II, hunter syndrome, Case Rep. Ophthalmol. 10 (2019) 186–194, https://doi.org/10.1159/000500804.
[44] S. Jones, F. Wijburg, Mucopolysaccharidoses, oligosaccharidoses and sialic acid disorders, in: J.M. Saudubray, M.R. Baumgarter, J. Walter (Eds.), Inborn Metabolic Diseases: Diagnosis and Treatment, 577 Springer, Berlin, 2016.
[45] S. Tomatsu, A.M. Montaño, H. Oikawa, M. Smith, L. Barrera, Y. Chinen, et al., Mucopolysaccharidosis type IVA (Morquio A disease): clinical review and current treatment, Curr. Pharm. Biotechnol. 12 (6) (2011) 931–945 (doi:1389-2010/11 $58.00+.00).
[46] J.J. Kenth, G. Thompson, C. Fullwood, S. Wilkinson, S. Jones, I.A. Bruce, The characterisation of pulmonary function in patients with mucopolysaccharidoses IVA: a longitudinal analysis, Mol. Genet. Metab. Rep. 20 (2019) 100487, , https://doi.org/10.1016/j.ymgmr.2019.100487.
[47] H.Y. Lin, M.R. Chen, S.M. Lin, C.L. Hung, D.M. Niu, C.K. Chuang, et al., Cardiac features and effects of enzyme replacement therapy in Taiwanese patients with Mucopolysaccharidosis IVA, Orphanet. J. Rare Dis. 13 (1) (2018) 148, , https://doi.org/10.1186/s13023-018-0883-6.
[48] S. Tomatsu, C.J. Alméciga-Díaz, A.M. Montaño, H. Yabe, A. Tanaka, V.C. Dung, et al., Therapies for the bone in mucopolysaccharidoses, Mol. Genet. Metab. 114 (2015) 94–109, https://doi.org/10.1016/j.ymgme.2014.12.001.
[49] J. Do Cao, A. Wiedemann, T. Quinaux, S.F. Battaglia-Hsu, L. Mainard, R. Froissart, et al., 30 months follow-up of an early enzyme replacement therapy in a severe Morquio A patient: about one case, Mol. Genet. Metab. Rep. 9 (2016) 42–45, https://doi.org/10.1016/j.ymgmr.2016.10.001.
[50] P. Harmatz, R. Shediac, Mucopolysaccharidosis VI: pathophysiology, diagnosis and treatment, Front. Biosci. (Landmark Ed). 22 (2017) 385–406.
[51] P. Harmatz, D. Ketteridge, R. Giugliani, N. Guffon, E.L. Teles, M.C. Miranda, MPS VI Study Group, et al., Direct comparison of measures of endurance, mobility, and joint function during enzyme-replacement therapy of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): results after 48 weeks in a phase 2 open-label clinical study of recombinant human N-acetylgalactosamine 4-sulfatase, Pediatrics. 115 (6) (2005) e681–e689.
[52] C. Kampmann, C. Lampe, C. Whybra-Trümpler, C.M. Wiethoff, E. Mengel, L. Arash, et al., Mucopolysaccharidosis VI: cardiac involvement and the impact of enzyme replacement therapy, J. Inherit. Metab. Dis. 37 (2) (2014) 269–276, https://doi.org/10.1007/s10545-013-9649-4.
[54] H.Y. Lin, C.K. Chuang, C.H. Wang, Y.H. Chien, Y.M. Wang, F.J. Tsai, et al., Long-term galsulfase enzyme replacement therapy in Taiwanese mucopolysaccharidosis VI patients: a case series, Mol. Genet. Metab. Rep. 7 (2016) 63–69, https://doi.org/10.1016/j.ymgmr.2016.04.003.