General discussion and future perspectives
GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Over recent decades, improved understanding of the pathogenesis of mucopolysaccharidosis type I (MPS I) and its natural history in combination with the availability of disease-modifying treatments has significantly improved the outcome of MPS I patients. However, many important questions regarding this potentially devastating disease still remain unanswered. This thesis comprises several studies focusing on improved assessment of disease severity, therapeutic options and diagnostic methods in MPS I.

Treatment outcomes: what we know and what we need to know

Due to the progressive nature of the disease, early diagnosis and timely start of treatment, before irreversible organ damage occurs, is considered essential. Indeed, our results stress the importance of an early MPS I diagnosis (chapters 2 and 4). However, little is still known about the actual long-term outcomes of MPS I patients after (early) initiation of treatment, and much of what we know is based on cases histories and expert opinions.

Improved knowledge on the natural history of the disease is imperative, as this knowledge is indispensable for assessment of effectiveness of any kind of treatment. Although much has already been learned about the natural history of the severe Hurler phenotype and the relatively mild Scheie phenotype, there is, due to both its rarity and the lack of a clear definition of the phenotype, hardly any knowledge on the natural history of the patients with the intermediate, Hurler-Scheie, phenotype. More information on the manifestations of this intermediate phenotype, with special focus on the central nervous system, may lead to improved understanding of how the disease naturally progresses in the different patient subgroups. This information may help to identify best practice guidelines for treatment, hopefully further improving patient outcomes. Due to the rarity of the disease, this can only be done in an international, interdisciplinary and collaborative approach (chapter 2). The MPS I registry (www.MPSIRegistry.com) offers such an approach, but also has important flaws (see below).

As it is generally accepted that the defective catabolism of glycosaminoglycans (GAGs) leads to progressive perturbations of cellular, tissue and organ homeostasis through activation and inhibition of secondary pathways, initiation of treatment early in the disease course will likely prevent and/or minimize irreversible damage (chapter 2). However, the evidence that demonstrates improved outcome with early start of enzyme replacement therapy (ERT) in MPS I only comes from one case history on siblings started on ERT at different ages [1] and anecdotal (oral) communications. In addition, although ERT has been shown to ameliorate several somatic signs and symptoms of MPS I [2-6], recently published longer-term, more gradually occurring effects (e.g. range of motion), raise some questions about the long-term efficacy of ERT [7-10]. Moreover, much is still unknown about the impact of the immune responses against the infused recombinant enzyme on its clinical efficacy. The actual long-term clinical benefits in different patient groups (e.g.
phenotypic severity, antibody status, degree of organ involvement) therefore remain to be studied in more detail.

This same issue was recently subject of intense debate in the Netherlands when the Dutch Health Insurance Board (College voor Zorgverzekeringen, CVZ) initially intended to advise to stop reimbursement for ERT for two other lysosomal storage diseases (LSDs): Fabry disease and late-onset Pompe disease. A committee of the CVZ decided that ERT for these two conditions has an extreme unfavorable cost-effectiveness. This preliminary advice provoked an intense and emotional discussion between politicians, treating physicians and patient organizations, arguing that these decisions with potential severe consequences for patients should not be made on the basis of insufficient data. In November 2012, the CVZ finally decided to continue reimbursement of ERT for Fabry and late-onset Pompe diseases under specified conditions. Based on their opinion on the unfavorable cost-effectiveness, the CVZ report contained several recommendations to the minister of Health, Welfare and Sport, including the advice to consider reimbursement of orphan drugs outside the basic insurance package in the (near) future. It was therefore advised to explore new mechanisms to create sustainable funding of orphan drugs, and to open discussions about drug pricing with the pharmaceutical manufacturers and about dosing strategies with the treating physicians. Moreover, further (international) research, leading to better definition of long-term treatment efficacy and important topics such as start and stop criteria, should be initiated. Installation of a special committee of experts, with a goal to help the treating physicians decide on initiation of ERT in new cases, weighing individual pros and cons, could be considered.

This recent debate stresses the importance of collecting high quality data on the long-term effectiveness of orphan drugs. To be able to draw firm conclusions this can, however, only be done in a multi-center, international collaboration. Analysis of data should preferably be undertaken by independent (i.e. non-pharmaceutical) experts, to ensure that potential biases in the interpretation of data are minimized. If data will be centralized at the European level, it is therefore recommended that funding and governance of these registries remain independent [11]. Models combining European with national funding sources need to be explored.

A similar discussion on cost-effectiveness and long-term efficacy of ERT in different patients groups might well be initiated for MPS I in the near future. The MPS I post-marketing surveillance registry (www.MPSIRegistry.com) already serves as an international and observational database that tracks outcomes of MPS I patients. However, it has important limitations, mainly due to its voluntary and observational nature, leading to data of variable quality and lack of completeness of data. Moreover, the interpretation of data is hampered by the large phenotypic variability in MPS I and the variability of the degree of disease progression at initiation of treatment. Finally, the registry was launched and is sponsored by the pharmaceutical company manufacturing the ERT (Genzyme, a Sanofi Company).
As for ERT, hematopoietic stem cell transplantation (HSCT) has its limitations. Although HSCT has shown the ability to alter the disease course, some disease manifestations, such as musculoskeletal symptoms, persist or even continue to worsen after HSCT, even if performed early [12,13]. Further evaluation of the transplant procedures and long-term clinical outcomes, including long-term effects on neurocognition and quality of life, is essential and should also be undertaken in international and longitudinal studies, and in collaboration with existing registries such as the European Group for Blood and Marrow Transplantation (EBMT) Registry, the Eurocord Registry and the Center for International Blood and Marrow Transplant Research (CIBMTR).

Early diagnosis and treatment optimization: the role of biomarkers and genotyping

Biomarkers are indispensable for early diagnosis and disease prognostication, as clinical manifestations in MPS I are highly variable and often cannot accurately predict the phenotype (chapter 3), even when a patient’s genotype is known. In addition, biomarkers are necessary for the optimization of therapy and for monitoring therapeutic responsiveness. For Gaucher disease, probably the most common LSD, it has been shown that plasma levels of chitotriosidase provides a measure of disease activity (i.e. macrophage activation), which is also useful for assessing the effectiveness of therapy, including ERT [14]. For MPS I, such an ideal biomarker has not been found yet [15], although significant progress has been made during the last years. Measurement of disaccharides derived from the primary storage products in MPS I, heparan sulfate and dermatan sulfate, in dried blood spots (DBS) easily distinguishes MPS I patients from controls and heterozygotes, making these disaccharides (HS and DS, respectively) promising biomarkers for early MPS I diagnosis, e.g. in the context of newborn screening (NBS) (chapter 6). However, the levels of HS and DS in DBS do not reliably predict disease severity, and these markers seem therefore not useful for disease prognostication, at least within the scope of NBS (chapter 6). In contrast, plasma HS and DS levels in (older) MPS I patients prior to initiation of treatment seem to correlate well with disease severity, and may eventually prove to be useful for more specific diagnostic purposes. In this respect, our results show that the potential predictive value of levels of total urinary GAGs (uGAGs), historically the most commonly used surrogate marker in the MPSs for assessment of early treatment response, is actually quite good, as it shows better distinction of the different phenotypes than HS and DS (chapter 7). This is in contrast with our observations that long-term ERT led to (near) normalization of total uGAGs, whereas plasma DS and urinary HS and DS remained clearly elevated (chapter 5). This finding suggests that total uGAGs might be used as biomarker for disease prognostication, but is less useful for monitoring long-term response to therapy, whereas HS and DS seem promising biomarkers for both diagnosis and management. It seems likely that in the future a combination of (two or more) plasma
and/or urinary biomarkers will facilitate improved diagnosis and assessment of treatment response. Total uGAGs, disaccharides derived from heparan and dermatan sulfate, the heparin cofactor-II thrombin complex and the urinary dermatan:chondroitin sulfate ratio are currently the most valuable biomarkers available. Further biomarker studies are required for the validation of (combinations of) these markers. Internationally coordinated collection of plasma and urine samples of both treated patients and patients prior to initiation of treatment will be necessary to be able to obtain useful evidence. Collaboration with patient registries could prove useful, as the availability of (longitudinal) clinical data is critical for biomarker validation.

MPS I is characterized by a high degree of mutational heterogeneity. Many patients have at least one ‘private’ mutation [16,17]. This hampers accurate prediction of genotype-phenotype correlations. Future attempts should be made to obtain new insight into the consequences of novel mutations at the protein level, the effect of combinations of alleles and the modifying effect of non-pathogenic polymorphisms.

**Expanded newborn screening: are we ready?**

“The primary goal of NBS is to provide direct medical benefit to children affected by serious disease, and that mandatory NBS can be justified only when there is convincing evidence that the benefits for the infant of screening and treatment outweigh the risks and burden (US Council on Bioethics, 2008)”. Presymptomatic identification of MPS I patients is best accomplished by NBS. For MPS I-H patients, it is clear that early initiation of the treatment of choice, HSCT, can make a substantial difference in outcome. In addition, survival and engraftment rates of HSCT have improved in recent years. With respect to the attenuated patients, it is generally accepted that these patients will likely benefit from early start of ERT, and that the possible adverse events do not outweigh the benefits in the large majority of patients. The elimination of the often frustrating and stressful diagnostic odyssey and the ability of making reproductive choices are amongst other advantages of early diagnosis by NBS (chapter 4).

Population screening for MPS I by DBS has become technically feasible during the last decade, and several pilot studies have already started using multiplexed mass screening assays, analyzing IDUA enzyme activities [18-22]. MPS I was recently nominated to the US Advisory Committee on Heritable Disorders of Newborns and Children for inclusion in NBS programs, and was subsequently designated for an independent, evidence-based review to assess the appropriateness of adding MPS I to the recommended uniform screening panel in the US. A significant limitation of diagnosis in the first weeks of life is the fact that prediction of the clinical phenotype in a presymptomatic MPS I patient, and subsequent appropriate treatment decisions, can be very challenging due to the often poor correlations of residual enzyme activity and genotype with the phenotype. This limitation complicates the care for presymptomatic MPS I patients, especially as accepted biomarkers
for therapeutic decision making are still lacking. Although it has been shown that levels of HS and DS in DBS can be used as a diagnostic marker for MPS I, no clear associations with the clinical phenotype could be established (chapter 6). An advantage of the NBS method reported by our group is that it allows multiplex detection of several MPSs. Further studies into the role of these markers and other biomarkers within the scope of NBS are urgently warranted. A longitudinal follow-up program can only be performed as part of NBS programs, and will be necessary to capture these diagnostic as well as long-term follow-up data. In addition, attention should be paid to how to cope with important drawbacks of NBS for MPS I: the identification of novel and therefore difficult to predict variants and late-onset phenotypes [23-25].

The experience obtained by treatment and follow-up of MPS I patients with initially unclear phenotypes will guide treatment for future newborns diagnosed with MPS I by NBS. In the meantime, the guidelines proposed by Wang and co-workers for diagnosis and management of presymptomatic patients could be used as an example for follow-up [26], which should preferably take place in specialized medical centers and laboratories (chapter 2).

Novel treatment strategies

Historically, treatment of MPS I patients was supportive and symptom-based, and multi-disciplinary supportive care still plays an essential role in the clinical management of MPS I patients (chapter 2). Nowadays, the two disease-specific therapies, HSCT and ERT, are the standard of care [27]. However, both therapeutic options have their limitations (see above).

There is increasing evidence of an inverse correlation between an immune response in ERT-treated MPS I patients and metabolic and clinical outcome. However, the true incidence of functionally active, neutralizing antibodies, and subsequent risks of therapy failure in MPS I is unknown, and should be elucidated by further studies. For those patients who experience treatment failure due to their immune response, immunosuppressive medication might be used to overcome negative effects of antibodies [28]. However, HSCT may also serve as a treatment option [29]. The role of ERT in the peri-transplant period, with a goal to decrease the GAG burden and potentially transplant-related complications, has been studied, and showed that peri-transplantation ERT is well tolerated, and that overall survival is high [30-33]. The possible role of laronidase in MPS I patients after a successful HSCT is less clear. Experience with ERT in these patients is still very limited [34], however, a clinical trial to elucidate the role of laronidase in this group was recently started (clinical trials.gov, identifier NCT01173016).

Currently, several new therapeutic approaches are under investigation, focusing on strategies to deliver recombinant IDUA to the nervous system, such as intrathecal enzyme replacement therapy and modification of the enzyme protein so that it can cross the blood-brain barrier. Intrathecal delivery of ERT has been shown to reduce GAG storage in
the brains of MPS I dogs [35,36]. Whether these successful findings can be translated to humans will soon be studied in two clinical trials, currently recruiting participants. The first trial was designed to study the safety and efficacy of intrathecal laronidase to reduce or stabilize cognitive decline in MPS I patients with documented evidence of cognitive decline (clinical trials.gov, identifier NCT00852358). In addition, another study was designed to assess whether intrathecal ERT is a safe and effective approach to slow the neurologic degeneration seen in MPS I-H patients undergoing transplantation (clinical trials.gov, identifier NCT00638547).

In addition, small molecule therapy might be a therapeutic option for MPSs. The two main categories are substrate reduction therapy and chaperone therapy. The principle of substrate reduction therapy is to reduce the rate of substrate synthesis by inhibition of the synthetic enzyme, thereby preventing accumulation. There is extensive experience with this therapeutic approach in two other lysosomal disorder with miglustat (Zavesca®). Miglustat is licensed for the treatment of patients with mild to moderate type I Gaucher disease for whom ERT is not suitable [37], and for the treatment of neurologic disease in Niemann-Pick type C disease [38]. Genistein, a plant isoflavone, has been shown to reduce substrate synthesis in fibroblasts of various types of MPS patients [39], and was reported to cross the blood-brain barrier, at least in animal studies [40]. The clinical therapeutic effects were most extensively studied in MPS III, an MPS for which no effective disease-modifying treatment is available. Despite a reduction in GAG storage, no significant effects on clinical signs and symptoms of MPS III patients have been reported so far [41]. Substantially higher doses of genistein might be more effective [42], and should be studied in a longer-term follow-up study.

Protein misfolding is a major cause of enzyme deficiencies in a number of lysosomal disorders, including MPS I, in the presence of certain missense mutations. Chaperone therapy has the potential to correct the folding of misfolded proteins, allowing them to pass through the endoplasmatic reticulum and become correctly routed to the lysosomes, thus being still able to fulfill its function as a hydrolase. Experience with chaperone therapy in MPS is very limited, although several chaperones have been identified for MPS I-H/S and MPS III [43].

Finally, gene therapy, which involves transfer of a gene that encodes the deficient enzyme (IDUA) into the recipient’s cells is considered a very promising approach, because MPSs are monogenic diseases and it is expected that only a small increase in the activity of the deficient enzyme will lead to a therapeutic success. Several approaches have been studied or are under investigation, including the use of intravenous delivered viral vectors as a vehicle. Animal studies have shown that this approach was effective in controlling disease manifestations upon neonatal treatment [44-47], however, limited efficacy on CNS disease and musculoskeletal symptoms was reported after gene therapy in adult animals [48,49]. Another approach is transplantation of ex-vivo genetically modified cells derived from the patient (e.g. hematopoietic stem cells), thereby able to express the missing protein. This
approach has been used successfully in cerebral forms of X-linked adrenoleukodystrophy [50], and has been shown to be able to correct disease manifestations in MPS I mice, including neurologic and skeletal abnormalities [51]. Its safety and efficacy in human MPS I patients remains to be determined.

In summary, there is still much to learn about the potential biomarkers in MPS I and improved knowledge on genotype-phenotype correlations is needed, with a goal to improve (presymptomatic) phenotypic differentiation in newly diagnosed patients. With the prospects of NBS for MPS I, the benefits, such as elimination of the diagnostic odyssey, early start of treatment and the ability to make reproductive choices, and the potential drawbacks, such as the identification of novel disease variants, need to be well-documented. Moreover, guidelines for diagnosis and management after NBS should be established. To optimize treatment outcomes in MPS I, data on the long-term efficacy of laronidase should be gathered, including data on the role of neutralizing antibodies in ERT-treated patients and novel treatment strategies should be studied during the coming years. All these efforts should be made in an international and collaborative approach, the only way to reach useful evidence in an ultra-orphan disease like MPS I.
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