J Inherit Metab Dis (2014) 37:587–598
DOI 10.1007/s10545-014-9718-3

ICIEM SYMPOSIUM 2013

Treatment of lysosomal storage disorders: successes and challenges

Carla E. M. Hollak · Frits A. Wijburg

Received: 28 January 2014 / Revised: 4 April 2014 / Accepted: 15 April 2014 / Published online: 13 May 2014

Abstract Treatment options for a number of lysosomal storage disorders have rapidly expanded and currently include enzyme replacement therapy, substrate reduction, chaperone treatment, hematopoietic stem cell transplantation, and gene-therapy. Combination treatments are also explored. Most therapies are not curative but change the phenotypic expression of the disease. The effectiveness of treatment varies considerably between the different diseases, but also between sub-groups of patients with a specific lysosomal storage disorder. The heterogeneity of the patient populations complicates the prediction of benefits of therapy, specifically in patients with milder disease manifestations. In addition, there is a lack of data on the natural history of diseases and disease phenotypes. Initial trial data show benefits on relevant short-term endpoints, but the real world situation may reveal different outcomes. Collaborative international studies are much needed to study the long-term clinical efficacy of treatments, and to detect new complications or associated conditions of the diseases. This review summarizes the available treatment modalities for lysosomal storage disorders and the challenges associated with long term clinical care for these patients.

Communicated by: Michael J. Bennett

Presented at the 12th International Congress of Inborn Errors of Metabolism, Barcelona, Spain, September 3-6, 2013.

C. E. M. Hollak (✉) · F. A. Wijburg
Department of Internal Medicine, Division of Endocrinology and Metabolism, SPHINX, Amsterdam Lysosome Center, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
e-mail: c.e.hollak@amc.nl

F. A. Wijburg
Department of Pediatric Metabolic Disorders, Academic Medical Center, Amsterdam, The Netherlands

Introduction

Lysosomal storage disorders (LSDs) comprise a group of rare inborn errors of metabolism, but collectively they have a birth prevalence of 1 in 5000–7700 (Meikle et al 1999; Sanderson et al 2006). These disorders are caused by a deficiency of one of the lysosomal enzymes or impairments in the lysosomal transport system. Impaired degradation of complex macromolecules leads to accumulation of substrates in tissues and subsequent cellular and organ dysfunction. There is considerable variability in clinical disease manifestations, with the central nervous system (CNS) being particularly vulnerable. Over the past two decades, several approaches have proven successful for the treatment of LSDs. Current available treatments have been specifically effective for the management of visceral manifestations, such as reductions in organomegaly by enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) for non-neuronopathic (type 1) Gaucher disease (Zimran 2011). Based on the highly successful introduction of ERT for the treatment of Gaucher disease more than 20 years ago, ERT has been studied and subsequently authorized in the EU for Fabry disease, mucopolysaccharidosis (MPS) types I, II, IV and VI, and Pompe disease. Several new approaches are currently investigated in pre-clinical and clinical trials. These strategies focus on improving convenience of use (oral versus intravenous therapy), or on reduction of toxicity (second generation SRTs). In addition, completely new approaches include improvement of enzyme stability, methods to diminish antibody responses to the infused proteins, small molecules approaches that act as pharmacological chaperones to enhance lysosomal enzyme activity and transport, gene therapy, and intrathecal enzyme delivery.

The number of innovative strategies to improve treatment of lysosomal storage disorders is very impressive, resulting in a long list of patents (for review see (Ortolano et al 2014)) that ultimately may or may not prove successful. The aim of this

review is to focus on the available treatment options, as well as on those treatments that are in an advanced stage of development in the EU. For this reason, we have limited ourselves to products that have already been authorized or have received an orphan drug designation by the EMA (Table 1).

In addition, we will discuss long term outcomes of available treatments and the clinical challenges that have emerged.

Treatment modalities

Supportive care

While over the last decades the focus of research and of most of the publications is on new treatments, supportive care for patients with LSDs, with a progressive and often debilitating symptoms, is key. Even for patients receiving highly effective therapies, such as Gaucher patients on ERT, individualized follow-up is needed to signal disease related long-term complications and provide adequate care. Guidelines or protocols for supportive care have for example been developed for several of the mucopolysaccharidoses, including general management guidelines (Muenzer et al 2009a, b), or for support of specific complications such as airway disease (Walker et al 2013), hip dysplasia (Langereis et al 2013) or spinal cord compression (Solanki et al 2013). Consensus on care and follow-up of Niemann-Pick type C (NPC) (Patterson et al 2012), neuronopathic Gaucher disease (Vellodi et al 2009), and physiotherapy management guidelines for patients with late onset Pompe disease have been reported (Favejee et al 2012). A multidisciplinary approach, with a dedicated team of specialists, is recommended for most disorders, although this may not be feasible in all hospitals taking care of these patients. The introduction of an online database with consensus guidelines for diagnosis, treatment and follow-up of all LSDs, including a list of specialized centers and options for referral may be the optimal way forward. This is becoming even more important after the recent transposition in all national laws of the EU Directive on Patients' rights in Cross-border Healthcare, adopted in 2011 (http://ir.amicustherapeutics.com/ReleaseDetail.cfm?ReleaseID=413437).

Enzyme replacement therapy (ERT)

ERT aims to restore the deficient enzyme through exogenous administration of purified enzyme. The first effective ERT was developed for type 1 Gaucher disease. Gaucher disease is one of the most prevalent LSDs, and is caused by deficient activity of glucocerebrosidase (GBA1). Hepatosplenomegaly with cytopenia, skeletal complications, and for the rare neuronopathic forms, central nervous system disease, are the most prominent symptoms (Hughes and Pastores 2013). ERT was developed in the 1980s, initially utilizing purified glucocerebrosidase from natural sources (human placental tissue), later followed by recombinant enzyme using a Chinese hamster ovary (CHO) cell system. ERT proved to be very effective in reducing the organomegaly and improving cytopenia and quality of life and preventing skeletal disease complications (Zimran 2011). Following its success, ERTs have been developed for several of the other LSDs and are nowadays approved for seven lysosomal storage diseases worldwide. For several of the other LSDs, ERT is under development (see Table 1). The efficacy and safety of ERT in Gaucher disease has raised high hopes for similar effectiveness in the other LSDs. However, there are several obstacles, including the generation of immune responses that may interfere with enzyme activity or induce mis-targeting of enzymes (Ohashi 2012). In Pompe disease, patients with the severe infantile form have less effect of therapy when antibodies toward the recombinant enzyme emerge (Banugaria et al 2011). Whether this is also true for Fabry disease and the mucopolysaccharidoses has not yet been fully resolved. However, in both diseases biochemical markers show recurrence of storage material in urine or plasma after emergence of antibodies against the infused enzyme, suggesting that effectiveness might indeed be impaired (Rombach et al 2012; Wraith et al 2007).

So far, only limited progress has been made in tackling these problems and new strategies are needed. For example, immune tolerance induction using a regimen of rituximab, methotrexate with or without intravenous immunoglobulin has been shown to be an effective strategy in infantile onset Pompe disease (Banugaria et al 2013). Alternative strategies could be the development of liposome encapsulated enzymes (Hsu et al 2012) or treatment by 'alternative enzymes'. Of particular interest in this respect is the development of modified alpha-N-acetylgalactosaminidase with alpha-galactosidase A substrate specificity, the enzyme deficient in Fabry disease, showing no cross-reactivity with antibodies toward the authorized enzyme (Tajima et al 2009).

In addition, other factors contribute to the variability in clinical effectiveness of ERT. This may involve the degree of irreversible disease manifestations, or the variation in disease severity. For example, in Fabry disease, it is unclear to what extent the non-classically affected patients benefit from enzyme replacement therapy. Fabry disease is characterized in its classical form by a slowly progressive vasculopathy, in addition to painful acroparesthesias, angiokeratoma, and corneal abnormalities (Germain 2010). The degree of vasculopathy and involvement of kidney, heart, and brain is highly variable. Results of clinical trials have demonstrated clearance of substrate in endothelial cells, but to a lesser extent in organs (Eng et al 2001). In non-classical disease, storage is less clear in endothelial cells, but can be found for example in myocardial cells or podocytes in the kidney. ERT has less effect on clearance in these tissues (Tondel et al 2013) and so far no study has clearly distinguished responses in these patients as

Table 1 Overview of authorized products for the treatment of lysosomal storage disorders and products under development with an orphan drug designation in the EU

Disease	Treatment	Type of treatment	Company	Status
Gaucher disease	Imiglucerase	ERT	Genzyme Europe B.V.	Auth. 1995
	Velaglucerase	ERT	Shire HGT	Auth. 2010
	Taliglucerase	ERT	Protalix/Pfizer	Ref.EU/Auth.USA
	Miglustat	SRT	Actelion Ltd	Auth 2002
	eliglustat tartrate	SRT	Genzyme Europe B.V.	ODD 2007
	Isofagomine tartrate	Chaperone	Amicus Therapeutics	ODD 2007
Fabry disease	Agalsidase beta	ERT	Genzyme Europe B.V.	Auth. 2001
	Agalsidase alfa	ERT	Shire HGT	Auth. 2001
	1-deoxygalactonojirimycin hydrochloride	Chaperone	Glaxo Group Limited	ODD 2006
	N-Butyldeoxygalactonojirimycin	SRT	Actelion	ODD 2012
Mucopolysaccharidosis type I	Laronidase	ERT	Genzyme Europe B.V.	Auth. 2003
Mucopolysaccharidosis type II (Hunter syndrome)	Iduronate-2-sulfatase	ERT	Shire HGT	Auth. 2007
	Recombinant human insulin receptor monoclonal antibody-fused iduronate 2-sulfatase	ERT	Voisin Consulting S.A.R.L.	ODD 2013
Mucopolysaccharidosis type III (Sanfilippo syndrome)	Genistein sodium salt dihydrate	SRT	Axcentua Pharmaceuticals	ODD 2012
Mucopolysaccharidosis type IIIB (Sanfilippo B syndrome)	Adeno-associated viral vector serotype 9 containing the human N-acetylglucosaminidase alpha gene	Gene therapy	Laboratorios del Dr. Esteve, S.A.	ODD 2013
	Recombinant human alpha-N-acetylglucosaminidase	ERT	Synageva BioPharma	ODD 2013
Mucopolysaccharidosis type IIIA (Sanfilippo A syndrome)	Adeno-associated viral vector serotype 9 containing the human sulfamidase gene	Gene therapy	Laboratorios del Dr. Esteve, S.A.	ODD 2011
	Adenovirus-associated viral vector serotype 10 carrying the human N-sulfoglucosamine sulfohydrolase and sulfatase modifying factor 1 cDNAs	Gene therapy	LYSOGENE	ODD 2010
	Recombinant human heparan N-sulfatase	ERT	Shire HGT	ODD 2008
Mucopolysaccharidosis type IVA (Morquio A syndrome)	N-terminal hexaglutamine-tagged recombinant human N-acetylgalactosamine-6-sulfate sulfatase	ERT	Dr. Ulrich Granzer	ODD 2009
	Recombinant human N-acetylgalactosamine-6-sulfatase	ERT	BioMarin Europe	Auth. 2014
Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome)	N-acetylgalactosamine-4-sulfatase	ERT	BioMarin Europe	Auth 2006
	Adeno-associated viral vector containing the human *ARSB* gene	Gene therapy	Fondazione Telethon	ODD 2011
Mucopolysaccharidosis type VII (Sly syndrome)	Recombinant human beta-glucuronidase	ERT	NDA Regulatory Science	ODD 2012
Metachromatic leukodystrophy	Autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA	Gene therapy	Fondazione Telethon	ODD 2007
	Recombinant human arylsulfatase A[a]		Shire HGT	ODD 2010
Pompe disease	Alglucosidase alfa	ERT	Genzyme Europe	Auth.2006
	Glycosylation independent lysosomal targeting tagged recombinant human acid alpha glucosidase	ERT	BioMarin Europe	ODD 2011
	Recombinant adeno-associated viral vector containing human acid alfa-glucosidase-gene[b]	Gene therapy	TMC Pharma Services	ODD 2012
Niemann-Pick disease, type B	Recombinant human acid sphingomyelinase	ERT	Genzyme Europe	ODD 2001

Table 1 (continued)

Disease	Treatment	Type of treatment	Company	Status
Niemann-Pick disease, type C	Miglustat	SRT	Actelion	Auth 2006
	Hydroxy-propyl-beta-cyclodextrin	Other	Susan French	ODD 2011
	2-hydroxypropyl-beta-cyclodextrin		Int. Niemann-Pick Disease Alliance	ODD 2013
	Recombinant hum. heat shock protein 70	Other	Orphazyme ApS	ODD 2013
alpha-Mannosidosis	Recombinant human alpha-Mannosidase	ERT	Zymenex A/S	ODD 2013
Lysosomal acid lipase deficiency	Recombinant human lysosomal acid lipase	ERT	Synageva BioPharma Ltd.	ODD 2010
Neuronal ceroid lipofuscinosis type 2	Recombinant human tripeptidyl-peptidase 1	ERT	BioMarin Europe Ltd	ODD 2013
Globoid cell leukodystrophy (Krabbe disease)	Recombinant human galactocerebrosidase	ERT	ACE BioSciences A/S	ODD 2013
Farber disease	Recombinant human acid ceramidase	ERT	QOL Therapeutics UK Ltd	ODD 2014

ERT enzyme replacement therapy; *SRT* substrate redustion therapy. *Auth* authorized; *Ref* refused; *ODD* orphan drug designation

http://ec.europa.eu/health/documents/community-register/html/index_en.htm

[a] Earlier ODD for systemic treatment withdrawn; development of intrathecal ERT

[b] Earlier ODD for AAV vector based gene therapy withdrawn

compared to the classically affected patients. The degree of end-organ damage in Fabry disease, including fibrosis in kidney or heart, also determines clinical outcome and overall effectiveness is therefore difficult to assess (Weidemann et al 2013b). Clearly, for the entire group of patients, development of new complications cannot be fully prevented (Banikazemi et al 2007; Weidemann et al 2013a).

Another challenge is the targeting of the enzyme to less easily accessible tissues such as bone, cartilage or the brain. Over the last years, efforts have been made to target the brain for example by shifting from intravenous enzyme therapy to intra-thecal enzyme delivery (see Table 1). Effectiveness of this approach needs to be awaited.

Substrate reduction therapy

Substrate reduction therapy (SRT) has the potential to cross the blood brain barrier and thus treat CNS disease in LSDs. In addition, the small molecules used in SRT do not generate immune reactions. Another advantage is the route of administration, since these molecules can be given orally. This is of importance for at least a subset of patients in whom intravenous access is complicated. The concept of SRT is based on restoring a balance between synthesis and degradation of storage material. Small compounds, capable of partially inhibiting glucosylceramide synthase (GCS), have initially been developed for Gaucher disease. The first authorized product is miglustat, an iminosugar capable of partially inhibiting the production of glucosylceramide and other glycosphingolipids. This compound has shown to have modest effects on visceral manifestations in Gaucher disease (Cox et al 2000), and this oral treatment is preferred by some of the type 1 Gaucher patients. However, a decade after its authorization, miglustat use has remained limited in clinical practice due to its modest effectiveness and frequent side effects (Kuter et al 2013). Specifically the occurrence of abdominal complaints and tremor occurring in a substantial amount of patients has caused many patients to switch back to ERT (Kuter et al 2013). Although on a theoretical basis, patients with the neuronopathic form of Gaucher disease may benefit from this treatment, miglustat did not show convincing effectiveness in a clinical trial of type 3 Gaucher disease patients (Schiffmann et al 2008) and is currently not authorized for use in neuronopathic forms of Gaucher disease. However, early initiation of miglustat, before clinical onset of CNS disease, is suggested to be effective in some patients (Cox-Brinkman et al 2010).

Second generation substrate inhibitors that target GCS are currently being developed. Eliglustat tartrate is a glucosylceramide analogue, that has demonstrated significant effects on visceral manifestations of Gaucher disease type 1. The compound is a P-glycoprotein substrate and therefore cannot cross the blood brain barrier (Shayman 2010). However, it is hoped that improved efficacy/toxicity ratio for eliglustat will offer patients with type 1 Gaucher disease an oral alternative to ERT. Whether its different mode of action will result in improved treatment of those sites of residual disease that are less accessible to ERT such as bone remains to be investigated.

As the class of drugs targeting GCS could potentially treat other LSDs, miglustat has also been tried in Fabry disease, Sandhoff disease, Tay Sachs disease and in NPC. The results in Fabry disease have never been published and in Sandhoff and Tay Sachs disease no convincing effects have been established (Shapiro et al 2009; Masciullo et al 2010). Interestingly, in

NPC, miglustat has been reported to have some beneficial effects. NPC is a devastating neurovisceral disorder characterized by progressive neurodegeneration, vertical supranuclear gaze palsy, ataxia, and a variable degree of visceral disease, caused by impaired cholesterol efflux from late endosomes and lysosomes and secondary accumulation of glycosphingolipids (Vanier 2013). Miglustat has shown an overall reduction in the progression of neurological manifestations (Patterson et al 2007; Pineda et al 2009). In a recent study, it is reported that even in late-infantile and juvenile-onset forms of the disease progression can be delayed (Heron et al 2012). The mode of action of miglustat in NPC is believed to be lowering of the levels of glycosphingolipids and gangliosides in the brain. However, in NPC mice, increased survival and reduced CNS inflammation following treatment with miglustat and other iminosugar-based GCS inhibitors does not coincide with clear reductions in brain gangliosides. In addition, an increase in brain glucosylceramide levels was observed, suggesting potential involvement of inhibition of the non-lysosomal glucosylceramidase (Nietupski et al 2012). Possibly, anti-inflammatory effects play a role. These results highlight the need for better understanding of mode of actions of these compounds as well as the pathophysiological concepts behind the neurodegeneration in NPC, but also in other conditions such as the mucopolysaccharidoses (MPSs).

MPSs comprise a heterogeneous group of disorders, resulting from a deficiency of one of the enzymes involved in the degradation of glycosaminoglycans. Symptoms are either primarily neurological, such as in Sanfilippo disease, with predominant storage of heparan sulfate, or visceral and musculoskeletal, with more extensive storage of keratan sulfate or dermatan sulfate (Wraith 2013). The complex constellation of skeletal dysplasia in MPSs, known as dysostosis multiplex, is the most striking feature of MPS IV and VI. MPS I and II show early onset forms with progressive CNS disease in addition to progressive musculoskeletal and visceral disease, as well as more attenuated forms without CNS disease. While ERT has been developed and introduced for MPS I and II, this will not treat the CNS symptoms. Genistein, a natural isoflavin occurring in soy, is a small molecule and is reported to inhibit GAG synthesis in vitro and in an MPS II and IIIB mouse model and is believed to act through inhibition of tyrosine kinase activity of the epidermal growth factor receptor, which controls GAG synthesis (Jakobkiewicz-Banecka et al 2009). This mode of action is also termed gene expression-targeted isoflavone therapy. In some cases improvements have been reported, but a placebo-controlled clinical trial in MPS III patients did not show any significant clinical benefit (de Ruijter et al 2012). This may have been due to relatively low dosages used or the relatively short duration of the trial and further studies are needed to establish if genistein may be of value in the treatment of MPSs.

Chaperone therapy

Pharmacological chaperones (PCs) are small molecules that bind and stabilize mutant lysosomal enzymes, thereby allowing proper cellular trafficking to the lysosome. These compounds are mutation specific, with some mutations being completely unresponsive, which may limit its application in clinical practice (Fan and Ishii 2007). Furthermore, since these compounds bind to the catalytic domains of enzymes, there may be a delicate balance between concentrations that enhance or inhibit the activity and thus the most significant challenge is the optimization of doses and administration regimens to maximize substrate turnover. Candidate molecules with capacity to stabilize lysosomal enzymes often show structural similarity to important regions of the substrate, capable of interacting with the enzyme's active site. Galactose has been reported to act as a PC in the treatment of Fabry disease, leading to increases in alfa-galactosidase A activity, and clinical effectiveness in a case of cardiac Fabry disease (Frustaci et al 2001).

Subsequently, 1-deoxygalactonojirimycin (DGJ), a substrate analogue, was shown to enhance alfa-galactosidase A activity in vitro (Fan et al 1999). Further studies indicated that modifications to the dosing regimen, with intermittent administration of the iminosugar, resulted in improved effects on enzyme activity and substrate reductions (Khanna et al 2010). Currently, this compound is in clinical studies for Fabry disease and has shown to reduce increased substrate levels in mice and plasma of patients (Young-Gqamana et al 2013). Clinical effectiveness has not yet been published. One of the potential hazards is that patients with responsive, missense, mutations often have non-classical disease. For evaluation of clinical effects, information on natural course of disease progression in this subgroup of patients is needed, but has so far been insufficiently studied. One compound that received orphan drug designation is isofagomine for the treatment of Gaucher disease. While this iminosugar showed enhancement of glucocerebrosidase activity (Chang et al 2006), preliminary studies in patients did not show any clinical effects (http://ir.amicustherapeutics.com/ReleaseDetail.cfm?ReleaseID=413437). Multiple small molecules have been investigated for their capacity to enhance lysosomal enzyme activities and several of these are investigated as single treatments or in combination with ERT (Boyd et al 2013).

Hematopoietic stem cell transplantation and gene therapy

Hematopoietic stem cell transplantation (HSCT) has been applied in several of the LSDs and serves as evidence that gene-transfer can ameliorate disease manifestations. The proposed mechanism is the cross-correction by normal enzyme producing donor cells, which migrate in recipient tissues. For the brain, the microglia cells are partially replaced by donor

cells and hence deliver enzyme to the neurons. However, this process may be slow and incomplete, which limits the success for rapidly progressive neurological disease manifestations. Currently, HSCT is considered for some of the LSDs based upon knowledge from earlier case series and individual disease characteristics (for review see (Boelens et al 2010)). HSCT has been most extensively studied for the severe Hurler phenotype of MPS I (MPS I-H), which is characterized by cognitive decline in addition to visceral and musculoskeletal symptoms, resulting in early death. Neurological outcome and survival of these patients has improved considerably compared to historical controls (Aldenhoven et al 2008). The efficacy of HSCT in MPS I depends on several factors, including timing of the intervention, donor cell source and engraftment (Boelens et al 2009). Currently, worldwide consensus exists that HSCT is the first line treatment in MPS I-H patients before the age of 2.5 years, without severe neurological damage (de Ru et al 2011). Less convincing results have been obtained for other mucopolysaccharidoses such as MPS II (Hunter disease) and MPS VI (Maroteaux-Lamy disease). While HSCT leads to rapid improvement of the visceral manifestations, neurological responses in MPS II are inconsistent and skeletal disease is relatively unresponsive (Boelens et al 2010). In Krabbe disease, HSCT has also produced variable success rates and it is clear that there is a need for early, preferably pre-symptomatic, intervention (Prasad et al 2008). As late onset, especially adult onset cases with Krabbe disease are rare, most of the HSCTs have been performed in patients with the classical infantile form. Timing of HSCT has shown that in these patients neonates had better neurologic outcome and developmental gains than babies with early symptomatic disease (Escolar et al 2005). However, despite early HSCT all children developed deficits in gross motor function.

HSCT has been performed for more than two decades in patients with metachromatic leukodystrophy (MLD). In MLD, the spectrum is more evenly distributed among age groups compared to Krabbe disease, with more patients presenting at juvenile or adult age. Patients with late-infantile onset seemed to have little benefit of HSCT, but with the current use of cord blood as stem cell source and improved conditioning regimens, there is accumulating evidence that in asymptomatic or minimally affected patients cognitive decline may be halted by HSCT, even in some early juvenile cases (Boelens et al 2010). HSCT has also been performed in several of the other LSDs including type 1 and type 3 Gaucher disease. However, the success and safety of ERT has led to almost complete disappearance of HSCT for Gaucher disease, despite its positive outcomes. Recently, a plea has been made to reconsider this procedure, because of the increased safety of the conditioning regimens as well as minimization of the risk for graft versus host disease (Ito and Barrett 2013). Nowadays, it is estimated that the risk would compare to those patients transplanted for beta-thalassemia, with an overall survival of 90 %. Specifically for chronic neuronopathic (type 3) disease, this procedure might still be an option, although late neurological complications have been reported (Machaczka 2013).

The success of HSCT approaches has focused attention on LSDs as attractive candidates for gene therapy. Initial optimism for gene therapy to treat monogenic disorders has been set back by technical difficulties as well as by the development of complications in the first gene therapy trials, including the development of leukemia due to insertional mutagenesis (Hacein-Bey-Abina et al 2008). Recently, important progress has been made with the use of adeno-associated viruses (AAV) and lentiviruses to deliver therapeutic genes to peripheral tissues as well as to the central nervous system. Both vectors have shown to lead to sustained production of enzyme in mouse models of several LSDs. Table 1 lists six gene therapeutic approaches that have received an orphan drug designation, mostly for the mucopolysaccharidoses. An interesting combined approach between HSCT and gene therapy consists of the transduction of ex-vivo autologous hematopoietic stem cells with the gene of interest (HSC-GT), which would allow cross-correction with diminished side effects because of the transplantation of autologous rather than allogeneic cells (Boelens et al 2010). Optimization of gene expression could lead to enhanced enzyme delivery to tissues. This could particularly improve outcomes for LSDs affecting the brain, as one of the factors causing failure of allogeneic HSCT includes insufficient enzyme delivery. A preliminary, but very promising clinical study has shown that in three presymptomatic patients with late infantile MLD, an optimized lentiviral-based HSC-GT protocol induced supraphysiological expression of the functional ARSA gene, leading to high enzyme expression throughout hematopoietic lineages and in cerebrospinal fluid (Biffi et al 2013). Importantly, over an observation period of 7 to 21 months, no disease progression was noted. Similar approaches are currently being developed for other diseases.

Combination therapies and other approaches

Clearly, as different therapeutic options are aimed at different targets, combining treatments might be an attractive option. For example, it has been suggested that pre-treatment with ERT can improve the outcome of HSCT in MPS I Hurler patients, particularly by reducing airway problems and improving pulmonary function and hepatomegaly (Cox-Brinkman et al 2006). Whether there is additional benefit after HSCT is a matter of debate. In a small study, cognitive outcome unexpectedly appeared to be better in ERT treated MPS IH patients after HSCT than in those not receiving ERT (Eisengart et al 2013). A major limitation of this latter study was the fact that the patients were serially recruited.

Enhancing the capacity of ERT by adding a stabilizing chaperone is currently also investigated. The first study demonstrating a synergy between an iminosugar and ERT has been the enhancement of human alpha-glucosidase activity in fibroblasts of patients with Pompe disease (Porto et al 2009). The iminosugar used was N-butyl-deoxynojirimycin also known as miglustat, developed as substrate reduction therapy for Gaucher disease. The same group reported a synergistic effect of combining rh-alpha-Gal A with 1-deoxynojirimycin in cultured Fabry disease fibroblasts, which also led to increased clearance of lyso-Gb3 (Porto et al 2012). The mechanism of action is intriguing. It is suggested that the infused enzyme is probably unstable, and is partially degraded in the bloodstream or during its trafficking to the lysosome. In addition, the reversible binding of a chaperone may also protect the enzyme against interaction with neutralizing antibodies and thus possibly ameliorate the immune response caused by ERTs. Currently, Amicus Therapeutics Inc, USA, is exploring combined effectiveness of isofagomine with ERT for Gaucher disease, migalastat with ERT for Fabry disease and 1-deoxynojirimycin (duvoglastat) with ERT for Pompe disease. Whether combination of substrate reduction therapy and ERT improves the clinical outcome of patients is currently unknown. In some patients with type 1 Gaucher disease and with a high burden of residual disease after many years of high dose ERT, combination with miglustat has been tried, but effects have not been reported. In type 3 Gaucher disease, it is suggested in some cases that this combination might have some beneficial effects on cognitive outcome, however, the paucity of clinical data seriously hampers a definitive conclusion (Cox-Brinkman et al 2006; Capablo et al 2007).

Existing drugs may have properties that render them likely candidates for treatment of LSDs. For example, histone deacylation inhibitors have shown to reduce storage in fibroblasts of patients with NPC (Pipalia et al 2011) and Gaucher disease (Yang et al 2013). In a recent review it was suggested that for NPC this effect can be attributed to an increase in NPC1 protein, presumably by increasing its stability in the ER (Helquist et al 2013). In fibroblasts of Gaucher disease patients, histone deacetylase inhibitors were shown to increase the quantity and activity of glucocerebrosidase by inhibiting the degradation of the mutant protein (Yang et al 2013).

The role of defective autophagy in neurodegenerative disease has recently received considerable attention and may offer new targets for treatment of LSDs. Autophagy is a process involved in removal of cellular components, requiring a strictly regulated interaction with lysosomes. In LSDs, impaired autophagy plays a role in many of the neuronopathic forms of LSDs, e.g., in NPC (for review see (Lieberman et al 2012)). Currently, the use of cyclodextrin, which mediates efflux of cholesterol from within the cell is explored as a treatment for NPC. In animal models of NPC, hydroxypropyl-β-cyclodextrin prolonged the life span in an NPC mouse model and could reduce not only cholesterol but also ganglioside storage (Davidson et al 2009; Liu et al 2009). The exact mode of action is poorly understood, as the compounds do not penetrate the blood–brain barrier. Nevertheless, two compounds have currently received an orphan drug designation in the EU and are further explored in clinical studies (see Table 1). Heat shock protein 70 (Hsp70), involved in chaperone medicated autophagy, has been shown to stabilize lysosomes by binding to bis(monoacylglycero)phosphate (BMP) (Kirkegaard et al 2010). While this mechanism is essential for activity of acid sphingomyelinase, recombinant Hsp70 should have beneficial effects on the cellular pathology seen in other sphinglipidoses, including NPC. For the latter indication, an orphan drug designation has been received.

Discussion

The availability of different forms of treatment for LSDs has not only stimulated interest in the effects of therapy but also led to new initiatives to study the disease course and the pathophysiology. Natural history studies have been launched to improve our understanding of the disease progression in untreated patients, which is needed to identify meaningful clinical endpoints for therapeutic trials. Related to this, the search for biomarkers, being either biochemical markers, imaging or functional disease markers that can serve as surrogate endpoints, has been intensified. For most of the LSDs important novel observations have been made, some of which challenge old concepts of disease pathophysiology. For example, in Fabry disease the old concept of endothelial Gb3 storage as the main culprit for clinical disease cannot stand with the discovery that many patients have little, if any storage in endothelium and clearance may not halt disease progression (Schiffmann 2009; Rombach et al 2010). In addition, combining larger cohorts of patients with rare diseases has resulted in the observation that some patients are susceptible to certain complications and associated conditions that had not been identified before. Whether these "new" complications or associated conditions are related to the disease or the treatment is not always clear. Some generalizations can, however, be made. First of all, none of the current interventions cure the disease. The treatments can alter the phenotype and ameliorate disease symptoms and improve survival. However, complications can still occur. This is best illustrated for diseases with a relatively long history of treatment. A few examples are discussed.

Gaucher disease

In Gaucher disease, more than 20 years of treatment has led to some important new insights into the pathophsyiology of the disorder, potential late complications as well as the presence of associated conditions. While it is beyond the scope of this

article to discuss all abnormalities that have been found in association with Gaucher disease, a few prominent findings deserve attention. First of all, bone disease has always been considered part of the clinical spectrum of Gaucher disease and it has become clear that only partial improvement of bone disease can be achieved with ERT. It appears that in patients with a longstanding history of Gaucher disease, aggregates of Gaucher cells cannot be cleared, even when high doses of enzyme are supplied for many years (de Fost et al 2008; Lebel et al 2013). Post-mortem studies have shown persistent Gaucher cells despite ERT in other tissues as well (Hulkova et al 2009). Perhaps these Gaucher cells are not accessible for ERT, because they developed characteristics that make them resistant to treatment. Indeed, it has been suggested that mature Gaucher cells are highly resistant to ERT (Elleder 2006) and different subsets of Gaucher cells have been identified (Boven et al 2004). Elleder further hypothesized a role for extralysosomal transport of glucosylceramide from non-macrophage cells with unknown biological effects, perhaps related to toxicity of glucosylsphingosine (Elleder 2006). In some advanced cases, liver disease with cirrhosis and increased risk of development of hepatocellular carcinomas is seen. One may speculate that a certain amount of residual disease burden or persistent high levels of certain substrates could cause a risk for development of complications, including fibrotic changes in liver and bone marrow or induce cancer. Indeed, several studies have identified a highly increased risk for development of multiple myeloma, other hematological cancers, hepatocellular carcinoma, and perhaps also renal cell carcinoma (Arends et al 2013) (Weinreb and Lee 2013). A role for glucosylsphingosine has also been suggested for the generation of hematological cancer (Pavlova et al 2013). Perhaps (epi)- genetic factors may contribute to risks of developing associated conditions. These conditions include not only bone disease and specific cancers but also Parkinson's disease, metabolic syndrome, changes in lipid profiles, and pulmonary hypertension. Vice versa, understanding of mechanisms may elucidate pathways involved in common disorders such as insulin resistance (Aerts et al 2011).

Future studies should focus on ways to identify risk factors and how to prevent them. Identification of a "profile" of clinical, biochemical, and genetic factors that predicts a risk of cancer or bone complications would be an important step forward. Such an approach will lead to further individualization of treatment. It seems that the younger, less affected population may carry a lower risk for some of these complications. However, the pathophysiological mechanisms are still insufficiently understood and this observation should not lead to "over-treatment" of patients with minimal disease (Zimran 2011). Observations in adult patients have shown minimal disease progression in mildly affected patients and immediate responses to therapy even after years of untreated follow-up (Boomsma et al 2010).

Fabry disease

In 2001 two enzymes were authorized for the treatment of Fabry disease: agalsidase beta (Fabrazyme, Genzyme Corp) and agalsidase beta (Replagal, Shire HGT). Renewed interest in the disorder was also stimulated by the need for both pharmaceutical companies to launch a registry, as part of their post-marketing obligations to the EMA. Unfortunately, this has led to unwanted fragmentation of data (Hollak et al 2011) and slowed the understanding of the pathophysiology of the disease. As already discussed, the treatment effects were not as robust as hoped: patients still developed complications related to the disease, mainly progressions of renal failure, new strokes and cardiac events such as arrthymias and fibrosis of the heart with heart failure. What became clear is that there is an extreme variability in clinical disease: other than for example in Gaucher disease, the symptoms can be very aspecific and may also be attributed to far more common disorders such as dislipidemia, hypertension, diabetes, and other disorders affecting the vascular system. Together with a drive to screen for patients and a wealth of different mutations of unknown significance in the GLA gene, this has currently resulted in a large proportion of patients to be designated as "non-classical" patients. In fact, when applying more strict diagnostic criteria, in five out of six of these patients the diagnosis should be considered unconfirmed (van der Tol et al 2014). However, a subset of patients obviously indeed will have Fabry disease but with limited manifestations, for example only cardiac hypertrophy. These patients can be distinguished biochemically, as they do not have an elevated level of (lyso) Gb3 as is seen in classically affected patients (Aerts et al 2008) and have residual enzyme activity. Clearly, the natural course of disease of classically affected patients and these non-classical individuals is very different and it is expected that responses to treatment will also be different. It is currently very challenging to predict the disease course based only on genotype in a patient with non-classical disease. Treating early to prevent irreversible complications is often expressed as a dogma. However, currently available data from the literature and personal experiences have not yet shown that starting "early" can prevent complications. Although the early treatment dogma might hold true for classically affected patients, special caution is needed when considering early treatment in those individuals with an unclear phenotype. In addition, the classically affected males are particularly prone for development of neutralizing antibodies, reflected by recurrence of storage material in plasma. It is currently unclear whether these patients benefit from ERT in the presence of these antibodies. Research thus should focus on improving diagnostic criteria, defining subgroups of patients, study their natural disease course, pathophysiology, and benefits of existing treatments. Only when these basic questions have been resolved, treatment can be further individualized and, hopefully, improved.

MPS I, Hurler phenotype

HSCT was first introduced for the treatment of patients with the MPS I-Hurler in 1981 (Hobbs, Lancet, 1981) and, performed before the age of 2.5 years, it is now the treatment of choice for this group of patients (de Ru et al 2011). Although HSCT has favorable effects on the progression of several important clinical symptoms, the skeletal disease is particularly unresponsive, with a variable progression of genu valgum, thoracolumbar kyphosis and hip dysplasia (Field et al 1994; Weisstein et al 2004; Aldenhoven et al 2009). The cause of the skeletal disease in MPS I is multi-factorial and based on intra- and extracellular deposition of GAGs leading to impaired cell-to-cell signaling, altered mechanical properties and upregulated inflammatory pathways. All of these mechanisms have the potential to affect the growth plate, and osteoclasts and osteoblasts, leading to the typical bone pathology (Pan et al 2005; Simonaro et al 2008). Apparently, there is insufficient enzyme delivery via the bloodstream to poorly vascularized tissues, such as the skeleton. In addition, early deleterious effects of accumulating GAGs to the growth plate may result in irreversible damage and consequently in abnormal growth despite therapeutic interventions. New approaches, including autologous HSCT augmented by gene therapy (Visigalli et al 2010), anti-inflammatory and pro-chondrogenic drugs (Schuchman et al 2013) and newborn screening for MPS I-H patients allowing early HSCT (Kingma et al 2013; Scott et al 2013) are currently explored.

Pompe disease

ERT with purified alfa glucosidase for Pompe disease has already been developed in 1999 for the treatment of infantile cases, showing improvements in motor development and survival (Van den Hout et al 2000). A recent study, with the aim to determine cognitive outcomes, reported clear long-term benefits, but several late complications were noted (Ebbink et al 2012). These included the presence of periventricular white matter abnormalities as well as speech- and hearing deficits. Of importance was that some patients deteriorated after initial improvement and lost all motor skills after some years, while others stabilized for a long period of time. In another study, including a subset of infantile patients who initiated ERT before the age of 6 months and were not ventilatory dependent, sustained improvements in motor function and cardiac parameters were observed over a median period of 8 years (Prater et al 2012). However, a range of residual disease manifestations was present, including persisting muscle weakness, hearing loss, arrhythmias, hypernasal speech, dysphagia with risk for aspiration, and osteopenia.

Follow-up in later onset cases is as yet still limited. The initial pivotal study revealed that during 18 months of treatment, ERT was associated with improved walking distance and stabilization of pulmonary function (van der Ploeg et al 2010). A longer-term study in six late-onset Pompe patients reported progressive diaphragm weakness in three patients, although the authors concluded that ERT could potentially delay the requirement for ventilation (Schneider et al 2013). Possibly, subsets of patients exist that benefit more or less from treatment. While it was reported that longer disease duration and reduced pulmonary function were identified as predictors of disease progression (van der Beek et al 2012), it is so far unclear which of the late onset patients benefit most from treatment and what the optimal timing is to initiate therapy.

Conclusions

In spite of all the advancements made over the last decades, many challenges still exist with regard to the clinical support of patients with LSDs, irrespective of the availability of a disease modifying treatment. Internationally accepted protocols that can assist clinicians in making a correct diagnosis, recognize disease related complications, and harmonize criteria for initiation and cessation of therapy are urgently needed. Several initiatives have already been launched, often in relation to development or introduction of a new treatment. This has led to a number of important studies resulting in new insights in the disease course and the pathophysiology of diseases, but also to a domination of research by the pharmaceutical industry. Indeed, most of the large scale clinical studies are based on the data retrieved from industry-sponsored disease and treatment specific registries. As part of post-marketing authorization requirements by EMA, pharmaceutical companies have launched drug-oriented registries. These registries have severe limitations, including fragmentation of data, incomplete datasets, and insufficient independence. In the future, involvement of patient organizations and clinical researchers before the start of clinical studies of a new orphan drug, including the early launch of a high quality disease database might improve the ability to evaluate the natural disease course and effectiveness of treatments. Currently, discussions are ongoing in the EU how to improve the process of collaborative, faster, and more independent evaluation of the added value of orphan drugs (http://www.eucerd.eu: EUCERD recommendation for a CAVOMP workflow). Beyond the study of effectiveness of a treatment, there is a need for a better understanding of the "altered phenotype" as a consequence of treatment, which requires a similar structured approach. Clinical researchers and patient organizations are now increasingly starting to produce guidelines for therapy. Potential hurdles are the previously mentioned post-marketing requirements and lack of funding, partially due to insufficient non-industry funding sources for research on orphan diseases. In this respect, EU initiatives for

the support of sustainable rare disease networks may prove to be an essential step forward.

Conflict of interest None.

References

Aerts JM, Boot RG, van Eijk M et al (2011) Glycosphingolipids and insulin resistance. Adv Exp Med Biol 721:99–119

Aerts JM, Groener JE, Kuiper S et al (2008) Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proc Natl Acad Sci U S A 105:2812–2817

Aldenhoven M, Boelens JJ, de Koning TJ (2008) The clinical outcome of Hurler syndrome after stem cell transplantation. Biol Blood Marrow Transplant 14:485–498

Aldenhoven M, Sakkers RJ, Boelens J, de Koning TJ, Wulffraat NM (2009) Musculoskeletal manifestations of lysosomal storage disorders. Ann Rheum Dis 68:1659–1665

Arends M, van Dussen L, Biegstraaten M, Hollak CE (2013) Malignancies and monoclonal gammopathy in Gaucher disease; a systematic review of the literature. Br J Haematol 161:832–842

Banikazemi M, Bultas J, Waldek S et al (2007) Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med 146:77–86

Banugaria SG, Prater SN, Ng YK et al (2011) The impact of antibodies on clinical outcomes in diseases treated with therapeutic protein: lessons learned from infantile Pompe disease. Genet Med 13:729–736

Banugaria SG, Prater SN, Patel TT et al (2013) Algorithm for the early diagnosis and treatment of patients with cross reactive immunologic material-negative classic infantile pompe disease: a step towards improving the efficacy of ERT. PLoS One 8:e67052

Biffi A, Montini E, Lorioli L et al (2013) Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. Science 341:1233158

Boelens JJ, Prasad VK, Tolar J, Wynn RF, Peters C (2010) Current international perspectives on hematopoietic stem cell transplantation for inherited metabolic disorders. Pediatr Clin North Am 57:123–145

Boelens JJ, Rocha V, Aldenhoven M et al (2009) Risk factor analysis of outcomes after unrelated cord blood transplantation in patients with hurler syndrome. Biol Blood Marrow Transplant 15:618–625

Boomsma JM, van Dussen L, Wiersma MG, Groener JE, Aerts JM, Maas M, Hollak CE (2010) Spontaneous regression of disease manifestations can occur in type 1 Gaucher disease; results of a retrospective cohort study. Blood Cells Mol Dis 44:181–187

Boven LA, van Meurs M, Boot RG, Mehta A, Boon L, Aerts JM, Laman JD (2004) Gaucher cells demonstrate a distinct macrophage phenotype and resemble alternatively activated macrophages. Am J Clin Pathol 122:359–369

Boyd RE, Lee G, Rybczynski P, Benjamin ER, Khanna R, Wustman BA, Valenzano KJ (2013) Pharmacological chaperones as therapeutics for lysosomal storage diseases. J Med Chem 56:2705–2725

Capablo JL, Franco R, de Cabezon AS, Alfonso P, Pocovi M, Giraldo P (2007) Neurologic improvement in a type 3 Gaucher disease patient treated with imiglucerase/miglustat combination. Epilepsia 48: 1406–1408

Chang HH, Asano N, Ishii S, Ichikawa Y, Fan JQ (2006) Hydrophilic iminosugar active-site-specific chaperones increase residual glucocerebrosidase activity in fibroblasts from Gaucher patients. FEBS J 273:4082–4092

Cox T, Lachmann R, Hollak C et al (2000) Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet 355:1481–1485

Cox-Brinkman J, Boelens JJ, Wraith JE et al (2006) Haematopoietic cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome. Bone Marrow Transplant 38:17–21

Cox-Brinkman J, van den Bergh Weerman MA, Wijburg FA, Aerts JM, Florquin S, van der Lee JH, Hollak CE (2010) Ultrastructural analysis of dermal fibroblasts in mucopolysaccharidosis type I: effects of enzyme replacement therapy and hematopoietic cell transplantation. Ultrastruct Pathol 34:126–132

Davidson CD, Ali NF, Micsenyi MC et al (2009) Chronic cyclodextrin treatment of murine Niemann-Pick C disease ameliorates neuronal cholesterol and glycosphingolipid storage and disease progression. PLoS One 4:e6951

de Fost M, van Noesel CJ, Aerts JM, Maas M, Poll RG, Hollak CE (2008) Persistent bone disease in adult type 1 Gaucher disease despite increasing doses of enzyme replacement therapy. Haematologica 93:1119–1120

de Ru MH, Boelens JJ, Das AM et al (2011) 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 6:55

de Ruijter J, Valstar MJ, Narajczyk M et al (2012) Genistein in Sanfilippo disease: a randomized controlled crossover trial. Ann Neurol 71: 110–120

Ebbink BJ, Aarsen FK, van Gelder CM et al (2012) Cognitive outcome of patients with classic infantile Pompe disease receiving enzyme therapy. Neurology 78:1512–1518

Eisengart JB, Rudser KD, Tolar J et al (2013) Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome. J Pediatr 162:375–80.e1

Elleder M (2006) Glucosylceramide transfer from lysosomes–the missing link in molecular pathology of glucosylceramidase deficiency: a hypothesis based on existing data. J Inherit Metab Dis 29:707–715

Eng CM, Guffon N, Wilcox WR et al (2001) Safety and efficacy of recombinant human alpha-galactosidase A–replacement therapy in Fabry's disease. N Engl J Med 345:9–16

Escolar ML, Poe MD, Provenzale JM et al (2005) Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med 352:2069–2081

Fan JQ, Ishii S (2007) Active-site-specific chaperone therapy for Fabry disease. Yin and Yang of enzyme inhibitors. FEBS J 274:4962–4971

Fan JQ, Ishii S, Asano N, Suzuki Y (1999) Accelerated transport and maturation of lysosomal alpha-galactosidase A in Fabry lymphoblasts by an enzyme inhibitor. Nat Med 1:112–5

Favejee MM, Huisstede BM, Bussmann JB, Kruijshaar ME, van der Ploeg AT (2012) Physiotherapy management in late-onset Pompe disease: clinical practice in 88 patients. Mol Genet Metab 107:111–115

Field RE, Buchanan JA, Copplemans MG, Aichroth PM (1994) Bone-marrow transplantation in Hurler's syndrome. Effect on skeletal development. J Bone Joint Surg (Br) 76:975–981

Frustaci A, Chimenti C, Ricci R et al (2001) Improvement in cardiac function in the cardiac variant of Fabry's disease with galactose-infusion therapy. N Engl J Med 345:25–32

Germain DP (2010) Fabry disease. Orphanet J Rare Dis 5:30

Hacein-Bey-Abina S, Garrigue A, Wang GP et al (2008) Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. J Clin Invest 118:3132–3142

Helquist P, Maxfield FR, Wiech NL, Wiest O (2013) Treatment of Niemann–pick type C disease by histone deacetylase inhibitors. Neurotherapeutics 10:688–697

Heron B, Valayannopoulos V, Baruteau J et al (2012) Miglustat therapy in the French cohort of paediatric patients with Niemann-Pick disease type C. Orphanet J Rare Dis 7:36

Hollak CE, Aerts JM, Ayme S, Manuel J (2011) Limitations of drug registries to evaluate orphan medicinal products for the treatment of lysosomal storage disorders. Orphanet J Rare Dis 6:16

Hsu J, Northrup L, Bhowmick T, Muro S (2012) Enhanced delivery of alpha-glucosidase for Pompe disease by ICAM-1-targeted nanocarriers: comparative performance of a strategy for three distinct lysosomal storage disorders. Nanomedicine 8:731–739

Hughes DA, Pastores GM (2013) Haematological manifestations and complications of Gaucher disease. Curr Opin Hematol 20:41–47

Hulkova H, Ledvinova J, Poupetova H, Kohout A, Malinova V, Elleder M (2009) Autopsy case of Gaucher disease type I in a patient on enzyme replacement therapy. Comments on the dynamics of persistent storage process. J Inherit Metab Dis 32:551–559

Ito S, Barrett AJ (2013) Gauchers disease–a reappraisal of hematopoietic stem cell transplantation. Pediatr Hematol Oncol 30:61–70

Jakobkiewicz-Banecka J, Piotrowska E, Narajczyk M, Baranska S, Wegrzyn G (2009) Genistein-mediated inhibition of glycosaminoglycan synthesis, which corrects storage in cells of patients suffering from mucopolysaccharidoses, acts by influencing an epidermal growth factor-dependent pathway. J Biomed Sci 16:26

Khanna R, Soska R, Lun Y et al (2010) The pharmacological chaperone 1-deoxygalactonojirimycin reduces tissue globotriaosylceramide levels in a mouse model of Fabry disease. Mol Ther 18:23–33

Kingma SD, Langereis EJ, De Klerk CM et al (2013) An algorithm to predict phenotypic severity in mucopolysaccharidosis type I in the first month of life. Orphanet J Rare Dis 8:99

Kirkegaard T, Roth AG, Petersen NH et al (2010) Hsp70 stabilizes lysosomes and reverts Niemann-Pick disease-associated lysosomal pathology. Nature 463:549–553

Kuter DJ, Mehta A, Hollak CE et al (2013) Miglustat therapy in type 1 Gaucher disease: clinical and safety outcomes in a multicenter retrospective cohort study. Blood Cells Mol Dis 51:116–124

Langereis EJ, Borgo A, Crushell E et al (2013) Treatment of hip dysplasia in patients with mucopolysaccharidosis type I after hematopoietic stem cell transplantation: results of an international consensus procedure. Orphanet J Rare Dis 8:155

Lebel E, Elstein D, Peleg A, Reinus C, Zimran A, Amir G (2013) Histologic findings of femoral heads from patients with Gaucher disease treated with enzyme replacement. Am J Clin Pathol 140:91–96

Lieberman AP, Puertollano R, Raben N, Slaugenhaupt S, Walkley SU, Ballabio A (2012) Autophagy in lysosomal storage disorders. Autophagy 8:719–730

Liu B, Turley SD, Burns DK, Miller AM, Repa JJ, Dietschy JM (2009) Reversal of defective lysosomal transport in NPC disease ameliorates liver dysfunction and neurodegeneration in the npc1−/− mouse. Proc Natl Acad Sci U S A 106:2377–2382

Machaczka M (2013) Allogeneic hematopoietic stem cell transplantation for treatment of Gaucher disease. Pediatr Hematol Oncol 30:459–461

Masciullo M, Santoro M, Modoni A, Ricci E, Guitton J, Tonali P, Silvestri G (2010) Substrate reduction therapy with miglustat in chronic GM2 gangliosidosis type Sandhoff: results of a 3-year follow-up. J Inherit Metab Dis 33(Suppl 3):S355–S361

Meikle PJ, Hopwood JJ, Clague AE, Carey WF (1999) Prevalence of lysosomal storage disorders. JAMA 281:249–254

Muenzer J, Beck M, Eng CM et al (2009a) Multidisciplinary management of Hunter syndrome. Pediatrics 124:e1228–e1239

Muenzer J, Wraith JE, Clarke LA (2009b) Mucopolysaccharidosis I: management and treatment guidelines. Pediatrics 123:19–29

Nietupski JB, Pacheco JJ, Chuang WL et al (2012) Iminosugar-based inhibitors of glucosylceramide synthase prolong survival but paradoxically increase brain glucosylceramide levels in Niemann-Pick C mice. Mol Genet Metab 105:621–628

Ohashi T (2012) Enzyme replacement therapy for lysosomal storage diseases. Pediatr Endocrinol Rev 10(Suppl 1):26–34

Ortolano S, Vieitez I, Navarro C, Spuch C (2014) Treatment of lysosomal storage diseases: recent patents and future strategies. Recent Pat Endocrinol Metab Immune Drug Discov 8:9–25

Pan C, Nelson MS, Reyes M et al (2005) Functional abnormalities of heparan sulfate in mucopolysaccharidosis-I are associated with defective biologic activity of FGF-2 on human multipotent progenitor cells. Blood 106:1956–1964

Patterson MC, Hendriksz CJ, Walterfang M, Sedel F, Vanier MT, Wijburg F (2012) Recommendations for the diagnosis and management of Niemann-Pick disease type C: an update. Mol Genet Metab 106: 330–344

Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE (2007) Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. Lancet Neurol 6:765–772

Pavlova EV, Wang SZ, Archer J, Dekker N, Aerts JM, Karlsson S, Cox TM (2013) B cell lymphoma and myeloma in murine Gaucher's disease. J Pathol 231:88–97

Pineda M, Wraith JE, Mengel E et al (2009) Miglustat in patients with Niemann-Pick disease type C (NP-C): a multicenter observational retrospective cohort study. Mol Genet Metab 98:243–249

Pipalia NH, Cosner CC, Huang A et al (2011) Histone deacetylase inhibitor treatment dramatically reduces cholesterol accumulation in Niemann-Pick type C1 mutant human fibroblasts. Proc Natl Acad Sci U S A 108:5620–5625

Porto C, Cardone M, Fontana F et al (2009) The pharmacological chaperone N-butyldeoxynojirimycin enhances enzyme replacement therapy in Pompe disease fibroblasts. Mol Ther 17:964–971

Porto C, Pisani A, Rosa M et al (2012) Synergy between the pharmacological chaperone 1-deoxygalactonojirimycin and the human recombinant alpha-galactosidase A in cultured fibroblasts from patients with Fabry disease. J Inherit Metab Dis 35:513–520

Prasad VK, Mendizabal A, Parikh SH et al (2008) Unrelated donor umbilical cord blood transplantation for inherited metabolic disorders in 159 pediatric patients from a single center: influence of cellular composition of the graft on transplantation outcomes. Blood 112:2979–2989

Prater SN, Banugaria SG, DeArmey SM et al (2012) (2012) The emerging phenotype of long-term survivors with infantile Pompe disease. Genet Med 14:800–810

Rombach SM, Aerts JM, Poorthuis BJ et al (2012) Long-term effect of antibodies against infused alpha-galactosidase A in Fabry disease on plasma and urinary (lyso)Gb3 reduction and treatment outcome. PLoS One 7:e47805

Rombach SM, Twickler TB, Aerts JM, Linthorst GE, Wijburg FA, Hollak CE (2010) Vasculopathy in patients with Fabry disease: current controversies and research directions. Mol Genet Metab 99:99–108

Sanderson S, Green A, Preece MA, Burton H (2006) The incidence of inherited metabolic disorders in the West Midlands, UK. Arch Dis Child 91:896–899

Schiffmann R (2009) Fabry disease. Pharmacol Ther 122:65–77

Schiffmann R, Fitzgibbon EJ, Harris C et al (2008) Randomized, controlled trial of miglustat in Gaucher's disease type 3. Ann Neurol 64:514–522

Schneider I, Hanisch F, Müller T, Schmidt B, Zierz S (2013) Respiratory function in late-onset Pompe disease patients receiving long-term enzyme replacement therapy for more than 48 months. Wien Med Wochenschr 163:40–44

Schuchman EH, Ge Y, Lai A et al (2013) Pentosan polysulfate: a novel therapy for the mucopolysaccharidoses. PLoS One 8:e54459

Scott CR, Elliott S, Buroker N et al (2013) Identification of infants at risk for developing Fabry, Pompe, or mucopolysaccharidosis-I from newborn blood spots by tandem mass spectrometry. J Pediatr 163: 498–503

Shapiro BE, Pastores GM, Gianutsos J, Luzy C, Kolodny EH (2009) Miglustat in late-onset Tay-Sachs disease: a 12-month, randomized, controlled clinical study with 24 months of extended treatment. Genet Med 11:425–433

Shayman JA (2010) ELIGLUSTAT TARTRATE: glucosylceramide synthase inhibitor treatment of type 1 Gaucher disease. Drugs Future 35:613–620

Simonaro CM, D'Angelo M, He X, Eliyahu E, Shtraizent N, Haskins ME, Schuchman EH (2008) Mechanism of glycosaminoglycan-mediated bone and joint disease: implications for the mucopolysaccharidoses and other connective tissue diseases. Am J Pathol 172:112–122

Solanki GA, Martin KW, Theroux MC et al (2013) Spinal involvement in mucopolysaccharidosis IVA (Morquio-Brailsford or Morquio A syndrome): presentation, diagnosis and management. J Inherit Metab Dis 36:339–355

Tajima Y, Kawashima I, Tsukimura T et al (2009) Use of a modified alpha-N-acetylgalactosaminidase in the development of enzyme replacement therapy for Fabry disease. Am J Hum Genet 85:569–580

Tondel C, Bostad L, Larsen KK, Hirth A, Vikse BE, Houge G, Svarstad E (2013) Agalsidase benefits renal histology in young patients with Fabry disease. J Am Soc Nephrol 24:137–148

Van den Hout H, Reuser AJ, Vulto AG, Loonen MC, Cromme-Dijkhuis A, Van der Ploeg AT (2000) Recombinant human alpha-glucosidase from rabbit milk in Pompe patients. Lancet 356:397–398

van der Beek NA, de Vries JM, Hagemans ML (2012) Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. Orphanet J Rare Dis 7:88

van der Ploeg AT, Clemens PR, Corzo D et al (2010) A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med 362:1396–1406

van der Tol L, Smid BE, Poorthuis BJ, Biegstraaten M, Deprez RH, Linthorst GE, Hollak CE (2014) A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. J Med Genet 51:1–9

Vanier MT (2013) Niemann-Pick diseases. Handb Clin Neurol 113: 1717–1721

Vellodi A, Tylki-Szymanska A, Davies EH et al (2009) Management of neuronopathic Gaucher disease: revised recommendations. J Inherit Metab Dis 32:660–664

Visigalli I, Delai S, Politi LS et al (2010) Gene therapy augments the efficacy of hematopoietic cell transplantation and fully corrects mucopolysaccharidosis type I phenotype in the mouse model. Blood 116:5130–5139

Walker R, Belani KG, Braunlin EA et al (2013) Anaesthesia and airway management in mucopolysaccharidosis. J Inherit Metab Dis 36: 211–219

Weidemann F, Niemann M, Stork S et al (2013a) Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications. J Intern Med 274:331–341

Weidemann F, Sanchez-Nino MD, Politei J, Oliveira JP, Wanner C, Warnock DG, Ortiz A (2013b) Fibrosis: a key feature of Fabry disease with potential therapeutic implications. Orphanet J Rare Dis 8:116

Weinreb NJ, Lee RE (2013) Causes of death due to hematological and non-hematological cancers in 57 US patients with type 1 Gaucher Disease who were never treated with enzyme replacement therapy. Crit Rev Oncog 18:177–195

Weisstein JS, Delgado E, Steinbach LS, Hart K, Packman S (2004) Musculoskeletal manifestations of Hurler syndrome: long-term follow-up after bone marrow transplantation. J Pediatr Orthop 24: 97–101

Wraith JE (2013) Mucopolysaccharidoses and mucolipidoses. Handb Clin Neurol 113:1723–1729

Wraith JE, Beck M, Lane R et al (2007) Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: results of a multinational study of recombinant human alpha-L-iduronidase (laronidase). Pediatrics 120:e37–e46

Yang C, Rahimpour S, Lu J, Pacak K, Ikejiri B, Brady RO, Zhuang Z (2013) Histone deacetylase inhibitors increase glucocerebrosidase activity in Gaucher disease by modulation of molecular chaperones. Proc Natl Acad Sci U S A 110:966–971

Young-Gqamana B, Brignol N, Chang HH et al (2013) Migalastat HCl reduces globotriaosylsphingosine (lyso-Gb3) in Fabry transgenic mice and in the plasma of Fabry patients. PLoS One 8:e57631

Zimran A (2011) How I treat Gaucher disease. Blood 118:1463–1471