Journal of Pediatric Sciences

SPECIAL ISSUE

Current opinion in pediatric metabolic disease

Editor:

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Journal of Pediatric Sciences 2011;3(1):e72

How to cite this article:

Hoffmann B, Mayatepek E. Lysosomal storage diseases to date. Journal of Pediatric Sciences. 2011;3(1):e72

REVIEW ARTICLE

Lysosomal Storage Diseases To date

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Abstract:
New therapeutic options and progress of approved therapies have made Lysosomal Storage Diseases (LSDs) one of the most exciting group of diseases. This review aims to summarize current achievements in these particular disorders and to give an outlook towards possible future treatment options. Enzyme replacement therapy is the gold standard for Gaucher disease, Fabry disease, Mucopolysaccharidosis type I, II, and VI, and for Pompe disease. Besides this, substrate reduction has been approved for Gaucher disease and Niemann-Pick disease type C. However, clinical outcome in particular for neurologic affection in these disorders has been disappointing. In selected patients, bone marrow or stem cell transplantation may be beneficial. Whether or not, treatment with pharmaceutical chaperones may be able to improve in particular the neurologic outcome, remains open. Animal studies on gene therapy were promising, however, clinical application will need several years.

Keywords: *lysosome, Fabry disease, Gaucher disease, mucopolysaccharidosis, enzyme replacement therapy, substrate reduction therapy, chaperone*
Received: 13/07/2010; Accepted: 14/07/2010

Introduction

The availability of new therapeutic options and further development of treatment strategies have made Lysosomal Storage Diseases (LSDs) one of the most progressing group of diseases. As an example a decade ago patients with Fabry disease often had to be left without sufficient treatment after an already disappointing and frustrating odyssey until diagnosis. To date, the perspective for the majority of these patients has changed, and sufficient treatment for most aspects of Fabry disease has been reported. Similar reports are given for other LSDs.

The term "Lysosomal Storage Diseases" may be misleading, since it may imply 'storage' of substrates for future needs by a certain purpose. Indeed, this is not the case, and 'storage' takes place by accident or more precise as a consequence of an inherited genetic defect.

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Lysosomes and Lysosomal Storage

Lysosomes are cell organells containing some 50 (mainly acid) hydrolases. They assure cellular digestion of biological macromolecules that assault during regular cell turnover. Lacking one of these hydrolases stops the degradation process leading to accumulation of the intermediate before the block. As a consequence of this 'storage' the lysosomes bulge and the corresponding cells swell up. Most often, the accumulated substrates are toxic, the affected cells become unable to fulfil their designated function, and cease prematurely. Hence, the clinical symptomatology in most LSDs is fluid rather than solid.

The purpose of this review is to summarize the achievements that have been made in the treatment of LSDs and to open the view towards possible future aspects of these diseases, and in particular future therapeutic options.

Gaucher Disease

Though rare, Gaucher disease (OMIM 230800) is the most common (1:57,000 newborns (1)) and probably best understood lysosomal storage disease. Deficiency of glucocerebrosidase is inherited in an autosomal-recessive trade (gene locus 1q21 (2)). The enzyme is typically found in cells of the monocyte-macrophage system, such as osteoclasts, hepatic Kupffer cells, and white pulpa cells of the splen. Patients with enzyme deficiency in these cells and organs are affected by the visceral form of Gaucher disease. In addition, astrocytes belong to the monocyte-macrophage system, and patients with additional CNS-affection (approximately twice as rare as visceral affection only) may suffer either from acute or chronic neuronopathic Gaucher disease. The acute form shows a fatal course during the first year of life already. Patients with chronic neuronopathic Gaucher disease may develop all possible symptoms of the visceral form but may also present with horizontal supranuclear gaze palsy (3), abnormal auditory brain stem responses (4) and a markedly impaired mean intelligence quotient of 75 (5). Differentiation between these forms may be difficult, in particular in younger children that may not present with the full spectrum of the disease from beginning on.

Current treatment

Glucocerebrosidase was the first lysosomal enzyme that has been engineered for therapeutic use as enzyme replacement therapy (ERT). Initially, it was derived from human placental tissue (6), however, the need of high amounts of enzyme could only be met by production in biotechnical cell lines, such as Chinese hamster ovary (CHO-)cells (7). ERT with this enzyme preparation (Cerezyme®, Genzyme Corp., Cambridge, USA) has been documented to be safe and to reverse most symptoms of the visceral type of Gaucher disease (8). However, neuronopathic involvement may be less responsive and until to date the outcome is disappointing (9).

Besides substitution of the missing enzyme which allows correct metabolism of the accumulated intermediate, substrate reduction therapy (SRT) has been developed (10). Due to its oral availability and its ability to pass the blood brain barrier, Miglustat (Zavesca®, Actelion Pharmaceutical Ltd., Switzerland) was thought to improve in particular neuronopathic Gaucher disease. However, reports regarding the efficacy of substrate reduction on neurologic symptoms have been controversial (11;12), though combination with ERT may yield synergetic effects (13). To date, Miglustate is the only oral therapeutic option for patients with Gaucher disease, and it is approved in particular for those patients where ERT is inappropriate.

Outlook and open issues

Besides production of glucocerebrosidase in CHO-cells, a human cell line has been established. Results of a phase I/II open label, single centre study with ongoing extension were promising: haemoglobin, platelet counts, liver and spleen volume improved significantly, and there were no severe adverse events reported (14). Results of a phase-III-study are under analyses, and marketing approval is expected in the near future.

In addition, a plant derived variant of glucocerebrosidase has been investigated in clinical studies, too (15), and a phase-III-study is currently ongoing.

An alternative oral treatment may be Eliglustat tartrate (Genzyme Corp., MA, USA) which is functioning as an substrate reducer (16). A multinational, open-label, single-arm Phase 2 study included 26 adults over one year, and mean hemoglobin level, platelet count, spleen and liver volume as well as lumbar spine bone mineral density were improved. The overall drug safety was good, and further studies are ongoing.

A novel treatment approach not only for LSDs may be chaperone therapy. Chaperones are small molecules which bind selectively to the target protein and support the correct three-dimensional folding of the protein. Chaperones may pass the blood brain barrier. Hence, it is expected that they may improve enzyme activity in particular in the brain. Isofagomine is an iminosugar that may be a chaperone in Gaucher disease (17), and a phase II study has been completed in late 2009 including 18 patients. Results are currently under analyzes, and until to date it is open whether or not the use

isofagomine will improve neurological affection or prevent neurological deterioration.

Fabry Disease

Deficiency of alpha-galactosidase A is the cause of (Anderson-)Fabry disease which is characterized by the accumulation of globotriaosylceramid (Gb3). Albeit, Fabry disease is inherited in an X-linked trade, females may present with the whole panel of complaints like male patients (18;19). The reported incidence is between 1:3500 (20) and 1:40,000 (1). Symptoms include neuropathic pain, gastrointestinal symptoms with diarrhoea and/or constipation, cardiomyopathy and progressive kidney disease. In addition, angiokeratoma, corneal clouding and hearing impairment may be complaints (21).

Current treatment

Since 2001 the gold-standard for the treatment of Fabry disease is ERT, and the introduction of the two available enzyme preparations has changed the history of alpha-galactosidase A deficiency (22;23). Before that date, treatment was driven by the individual complaints, often insufficient, and some patients were regarded as psychosomatics because of their unresponsiveness to these measures which had no causal approach. The risen awareness for Fabry disease after the introduction of ERT and the improved knowledge of diagnostic procedures (residual enzyme activity for males, mutation analysis for females) has changed the course of the disease. Patients are now often diagnosed in childhood already, and standards for the diagnostic workup have been implemented.

Numerous publications have proven the efficacy of ERT for cardiac manifestation (24-26), renal function (27;28), gastrointestinal complaints (29) and pain (30). In addition, affection of the ear (31;32), autonomic function of the skin (33) and health-related quality of life (34) has been reported to be improved. These beneficial effects have also been demonstrated for female patients (35) and children (36;37).

Outlook and open issues

An ERT-preparation deriving from plant sources is currently under pre-clinical development (PRX-102, Protalix Biotherapeutics, Israel), and chaperone therapy for Fabry disease has passed phase II clinical studies. Preliminary results from these studies using migalastat hydrochloride (Amicus Therapeutics, NJ, USA) (38) suggest at least stabilisation of estimated glomerular filtration rate and a tendency towards improved proteinuria. However, complete analyzes of these trials as well as data from phase-III-studies are not yet available.

Mucopolysaccharidoses type I, II, and VI (MPS I, II, and VI)

Mucopolysaccharidoses (MPS) are a group of LSDs characterised by a common pattern of clinical symptoms. Children with MPS are usually normal at birth but in most cases develop symptoms before the age of 2 years. At the age of 10 years almost all patients with MPS-disorders exhibit symptoms (39;40), however, the definite course of the disease is unforeseeable.

Characteristic symptoms include a coarse face with thickened nostrils, lips and earlobes, and an enlarged tongue. A short, stocky built stature with short neck and trunk completes the characteristic outer appearance. Skeletal deformities are subsumed as 'dysostosis multiplex' and include hip dysplasia, prominent forehead, hook-shaped vertebrae, and shortened tubular bones. Cardiovascular, respiratory and gastrointestinal symptoms may be found as well as oral, dermatological, psychiatric and neurological complications are described. Life expectancy often is reduced, and the most common causes of death are airway obstruction and cardiac failure (40;41).

Current treatment in MPS I

Deficiency of iduronidase alpha is the cause for mucopolysaccharidosis (MPS) type I (OMIM # 607014; frequency ~1:100,000). The severe form of MPS I (Hurler disease) has its onset early in life with developmental delay, frequent upper airway infections and the typical outer appearance of patients with MPS. In addition, psychomotor retardation and early death are consistently found, whereas in the less severe form (Scheie disease) patients may reach a normal height and may not suffer from cognitive impairment (40). Irregardless of the clinical course, ERT with recombinant α-L-iduronidase (Aldurazyme®, Genzyme Corp., MA, USA) has been regarded as the gold-standard for the treatment of MPS I since 2001. Its safety and efficacy on excretion of glykosaminoglycanes (GAGs), decrease of liver volume, predicted forced vital capacity, and walking distance during the 6-minute-walk-test have

been demonstrated (42). Moreover, improvements of sleep apnea, shoulder flexion and health-related quality of life have been reported (43). However, neurological symptoms and cognitive impairment seem to be less responsive to ERT (44;45).

Facing the fact that ERT does not cure from MPS I, different transplantation approaches were used to improve outcome. Allogeneic bone marrow-transplantation (46), hematopoetic stem cell transplantation (47), cord blood transplantation (48) and combinations of these measures with ERT (49) have shown beneficial effects.

Current treatment in MPS II

In 2007, ERT with idursulfase (Elaprase®, Shire Inc., USA) has been approved for the treatment of MPS II (Hunter disease, OMIM #309900; frequency ~ 1:100,000). Safety and efficacy has been demonstrated and both, patients with and without neurological affection showed improvement of visceral organ involvement (50). Nevertheless, published post-marketing experiences are rare, and more information in particular on the long-term effects of ERT on neurological manifestations is needed. It is expected, that early initiation of ERT may be crucial to prevent neurological deterioration.

Current treatment in MPS VI

In May 2005 the FDA and in January 2006 the EMEA, respectively, approved recombinant human arylsulfatase B (Naglazyme®, Biomaring Pharmaceuticals, CA, USA) as ERT for the treatment of MPS VI (Maroteaux-Lamy-disease, OMIM #253200; frequency ~ 0.2:100,000) (51). Its long-term benefits, in particular on endurance and pulmonary function, have been reported in the meanwhile (52;53). Moreover, ocular affection showed stabilisation in 6/7 patients with MPS VI during a mean follow-up period of 3.5 years ERT (54). Of note, institution of ERT with a few weeks of life already preserved joint mobility, cardiac valves as well as facial morphology in a boy compared to his more than 3 years older sibling (55).

Long-term follow-up over a period of 12 years after bone marrow transplantation was reported in a patient with Maroteaux-Lamy-Syndrome, who had improvements in motor function, infection rate, snoring, vertigo and quality of life (56).

Outlook and open issues in Mucopolysachharidosis type I, II, and VI

Albeit, most patients welcomed the introduction of ERT for these disorders, regular treatment in hospitals and outpatient clinical settings is invasive for the patients and their families lifes. Often, patients have to cross long distances to their specialised treatment sites. ERT is given over several hours and afterwards they have to return to their home.

Home treatment has been reported to be safe in patients with MPS II and MPS VI, respectively (57), and as much patients as possible should receive ERT at home, rather than in hospital. Hence, health care authorities are called on to support and finance this treatment option in all countries, and appropriate programs have to be established.

However, all therapeutic strategies tried so far were unable to reverse mental retardation, or at least to convincingly improve cognitive function. The clinical experience of intrathecal application of ERT is limited to a single case in MPS I and another case in MPS VI, respectively (58;59). A prospective study on intrathecal administration of idursulfase for patients with MPS II is currently under way. Hence, it is open whether or not this measure will improve neurological affection in MPS disorders.

In addition, skeletal changes in MPS-disorders seem to be unresponsive to any ERT as reported so far. However, lentiviral-mediated gene transfer was recently reported as effective in providing the deficient enzyme to joint tissues of patients with MPS VI (60). Moreover, animal studies evaluated the feasibility of gene therapy in MPS I mice (61), but these approaches need further investigation before clinical trials in human may be performed.

Since there is no cure from MPS disorders in sight, and since ERT does not seem to impact on bone deformities in these disorders, supportive therapies including physiotherapy and orthopaedic treatment is of major importance. Apart from this, otolaryngologists, ophtalmologists, cardiologists, and hand- as well as neuro-surgeons may be involved, too, in the management of patients with MPS-disorders. In cases of mental retardation, developmental regression or cognitive impairment

psychologists and social aid workers may also be needed.

Pompe Disease (Glycogene Storage Disease Type II, GSD II)

In Pompe disease (OMIM #232300, frequency ~ 1:35,000) mutations of the *GAA*-gene lead to deficiency of acid alpha-glucosidase resulting in a chronic proximal myopathy. More than 200 different mutations have been described without any genotype-phenotype correlation. Depending on the age at manifestation, an infantile, a juvenile and a late-onset form of the disease are separated from each other. Untreated patients with the infantile form of the disease usually show a fatal course. Residual enzyme activity typically is less than 1% of normal impacting on cardiac function, respiratory, skeletal muscles and liver function (62). In addition, disturbed myelination of the CNS is observed in patients with infantile Pompe disease (63). Late-onset Pompe disease is characterized by a less progressive but clinically remarkable muscle weakness and may also include respiratory muscles.

Current treatment in Pompe disease

In the past, two different enzyme preparations have been developed for the treatment of Pompe disease, one of which was purified from rabbit milk, the other was produced in a Chinese hamster ovary (CHO) cell line (64). The latter enzyme (Myozyme®, Genzyme Corp., MA, USA) received marketing approval in 2006, the other formulation has never been approved. Before the institution of ERT survival in infantile Pompe disease at 12 months of age were 25.7% overall and 16.9% for ventilator-free survival (65). ERT has been reported to reverse cardiomyopathy and ECG-abnormalities (66). Moreover, compared with an untreated historical control group the risk of death for infantile patients under ERT was reduced by 95%, the risk of invasive ventilation or death by 91%, and the risk of any type of ventilation or death by 87%, respectively (67). Therefore, newborn screening may be crucial to allow early diagnosis and timely onset of ERT in these children (68). Of note, ERT was also able to reverse brain abnormalities detected by cranial MRI (69).

Apart from infantile patients, beneficial effects of ERT have also been reported for juvenile patients with GSD II (70). In contrast to this, effects in adults are impacting less on survival (71), a fact which may be also be attributed to the less severe natural history of the disease in adult patients.

Since not all patients respond in the same way to ERT, attempts with higher dosage of enzyme were undertaken, however, the findings were controversial (72;73).

Outlook and open issues in Pompe disease

To overcome unresponsiveness to ERT in Pompe disease due to total lack of residual activity of acid alfa-glucosidase, an immune tolerance against the enzyme was induced in fibroblasts from affected patients by the use of adeno-associated virus-mediated gene therapy (74). This therapeutic strategy may enhance the response to ERT in the future, but further clinical trials have to confirm safety and efficacy of this intervention N-butyldeoxynojirimycin was investigated *in vitro* together with ERT and this intervention was reported to be synergistic in Pompe disease fibroblasts (75). The pharmacological chaperone 1-deoxynojirimycin increased enzyme activity and protein levels in 16 different mutations of the *GAA*-gene (76). It is currently matter of clinical trials as a pharmacological chaperone for the treatment of Pompe disease. Results of this phase-I-study are expected in the near future. Studies on gene therapy are in pre-clinical stages either using murine stem cells (77) or applied in human fibroblasts (78).

Niemann-Pick disease Type C (NPC)

Impaired trafficing and abnormal enrichment of cholesterol are the biochemical findings in Niemann-Pick disease Type C (NPC; OMIM 257220; frequency ~0.5:100,000). Inherited in an autosomal-recessive trade, NPC is characterized by accumulation of cholesterol and glycosphingolipids resulting in progressive loss of nervous system function by affecting the membranes of nerve cells. Since the age of onset of the disease is variable, either infants, older children, or adults may be affected. There is no known cure for NPC.

Typically, first neurological symptoms occur in childhood and may include prolonged neonatal jaundice, splenomegaly, ataxia, dysmetria, dysarthria, vertical supranuclear gaze palsy and cognitive decline.

Potential pathological processes include toxic effects of cholesterol or glycosphingolipid accumulation,

peroxisomal or mitochondrial dysfunction, inflammation or increased oxidative stress.

Current treatment of Niemann-Pick disease type C

Besides the improvements in Gaucher disease, Miglustat (Zavesca®) was found to be also beneficial in patients with NPC (79), and has been approved for the treatment of progressive neurological manifestations in NPC. Recently, long-term data reported stabilized neurological disease in affected children and adults after 12 and 24 months of treatment with miglustat (80;81).

Outlook for the treatment of Niemann-Pick disease type C

Currently, a randomized placebo-controlled study is under way to validate the effect of N-acetylcysteine (NAC) on a group of putative biomarkers in a therapeutic trial. Once taken up, NAC is converted to cysteine which than is converted glutathione. Glutathione is important for the cell especially with regard to oxidative stress which is believed to be increased in NPC. The hypothesis is, that by increasing glutathione levels oxidative stress may be reduced and cellular function may be stabilized or improved (http:/ /clinicaltrials. gov/ct2 /show/ NCT 00975689).

Other Lysosomal Storage Diseases

ERT is matter of clinical trials (phase-II) for MPS IV A (Morquio disease). For MPS III A (Sanfilippo disease), Niemann-Pick disease type B, Krabbe disease and Metachromatic leukodystrophy pre-clinical trials are under way. However, approval of defined drugs will take several years for these disorders.

Overall aspects of new treatments in LSDs

ERT in all these rare disease is cost-intense, and reimbursement decisions vary geographically. Criteria against or for ERT often appear arbitrarily, rather than rational decisions on the basis of medical findings, biochemical or clinical parameters. Schlander and Beck suggested that decisions for inclusion or exclusion of patients for treatment with ERT should be based on careful individual assessment (82). Moreover, expected short- and long-term benefits should be defined in order to prevent patients and affected families from over-optimistic expectations.

REFERENCES

1 Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999; 281: 249-54.

2 Beutler E, Grabowski GA. Gaucher disease. In: Scriver C, Beaudet A, Sly W, Valle D, editors. The metabolic and Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill; 2001. p. 3635-69.

3 Campbell PE, Harris CM, Harris CM, Sirimanna T, Vellodi A. A model of neuronopathic Gaucher disease. J Inherit Metab Dis 2003; 26: 629-39.

4 Campbell PE, Harris CM, Vellodi A. Deterioration of the auditory brainstem response in children with type 3 Gaucher disease. Neurology 2004; 63: 385-7.

5 Goker-Alpan O, Wiggs EA, Eblan MJ, Benko W, Ziegler SG, Sidransky E et al. Cognitive outcome in treated patients with chronic neuronopathic Gaucher disease. J Pediatr 2008; 153: 89-94.

6 Brady RO, Pentchev PG, Gal AE, Hibbert SR, Dekaban AS. Replacement therapy for inherited enzyme deficiency. Use of purified glucocerebrosidase in Gaucher's disease. N Engl J Med 1974; 291: 989-93.

7 Barton NW, Brady RO, Dambrosia JM, Di Bisceglie AM, Doppelt SH, Hill SC et al. Replacement therapy for inherited enzyme deficiency--macrophage- targeted gluco-cerebrosidase for Gaucher's disease. N Engl J Med 1991; 324: 1464-70.

8 Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P et al. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med 2002; 113: 112-9.

9 Goker-Alpan O, Wiggs EA, Eblan MJ, Benko W, Ziegler SG, Sidransky E et al. Cognitive outcome in treated patients with chronic neuronopathic Gaucher disease. J Pediatr 2008; 153: 89-94.

10 Cox T, Lachmann R, Hollak C, Aerts J, van Weely S, Hrebicek M et al. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet 2000; 355: 1481-5.

11 Schiffmann R, Fitzgibbon EJ, Harris C, DeVile C, Davies EH, Abel L et al. Randomized, controlled trial of miglustat in Gaucher's disease type 3. Ann Neurol 2008; 64: 514-22.

12 Davies EH, Erikson A, Collin-Histed T, Mengel E, Tylki-Szymanska A, Vellodi A. Outcome of type III Gaucher disease on enzyme replacement therapy: review of 55 cases. J Inherit Metab Dis 2007; 30: 935-42.

13 Cox-Brinkman J, van Breemen MJ, van Maldegem BT, Bour L, Donker WE, Hollak CE et al. Potential efficacy of enzyme replacement and substrate reduction therapy in three siblings with Gaucher disease type III. J Inherit Metab Dis 2008; 31: 745-52.

14 Zimran A, Altarescu G, Phillips M, Attias D, Jmoudiak M, Deeb M et al. Phase I/II and extension study of velaglucerase alfa (Gene-ActivatedTM human glucocerebrosidase) replacement therapy in adults with type 1 Gaucher disease: 48-month experience. Blood 2010; 115: 4651-6.

15 Aviezer D, Brill-Almon E, Shaaltiel Y, Hashmueli S, Bartfeld D, Mizrachi S et al. A plant-derived recombinant human glucocerebrosidase enzyme--a preclinical and phase I investigation. PLoS One 2009; 4: e4792.

16 Lukina E, Watman N, Arreguin EA, Banikazemi M, Dragosky M, Iastrebner M et al. A Phase 2 study of eliglustat tartrate (Genz-112638), an oral substrate reduction therapy for Gaucher disease type 1. Blood 2010 May 3.

17 Khanna R, Benjamin ER, Pellegrino L, Schilling A, Rigat BA, Soska R et al. The pharmacological chaperone isofagomine increases the activity of the Gaucher disease L444P mutant form of beta-glucosidase. FEBS J 2010; 277: 1618-38.

18 Deegan P, Baehner AF, Barba-Romero MA, Hughes D, Kampmann C, Beck M. Natural history of Fabry disease in females in the Fabry Outcome Survey. J Med Genet 2006; 43: 347-52.

19 Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab 2008; 93: 112-28.

20 Spada M, Pagliardini S, Yasuda M, Tukel T, Thiagarajan G, Sakuraba H et al. High incidence of later-onset fabry disease revealed by newborn screening. Am J Hum Genet 2006; 79: 31-40.

21 Desnick RJ, Ioannou YA, Eng CM. alpha-Galactosidase A Deficiency: Fabry disease. In: Scriver C, Beaudet A, Sly W, Valle D, editors. The Meatbolic & Molecular Bases of Inherited Disease. 8th Edition ed. New York: McGraw-Hill; 2001. p. 3733-810.

22 Schiffmann R, Kopp JB, Austin HA, III, Sabnis S, Moore DF, Weibel T et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001; 285: 2743-9.

23 Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S et al. Safety and efficacy of recombinant human alpha-galactosidase A--replacement therapy in Fabry's disease. N Engl J Med 2001; 345: 9-16.

24 Hughes DA, Elliott PM, Shah J, Zuckerman J, Coghlan G, Brookes J et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart 2008; 94: 153-8.

25 Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A et al. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. Eur Heart J 2007; 28: 1228-35.

26 Spinelli L, Pisani A, Sabbatini M, Petretta M, Andreucci MV, Procaccini D et al. Enzyme replacement therapy with agalsidase beta improves cardiac involvement in Fabry's disease. Clin Genet 2004; 66: 158-65.

27 Feriozzi S, Schwarting A, Sunder-Plassmann G, West M, Cybulla M. Agalsidase Alfa Slows the Decline in Renal Function in Patients with Fabry Disease. Am J Nephrol 2008; 29: 353-61.

28 Germain DP, Waldek S, Banikazemi M, Bushinsky DA, Charrow J, Desnick RJ et al. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. J Am Soc Nephrol 2007; 18: 1547-57.

29 Hoffmann B, Schwarz M, Mehta A, Keshav S. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. Clin Gastroenterol Hepatol 2007; 5: 1447-53.

30 Hoffmann B, Beck M, Sunder-Plassmann G, Borsini W, Ricci R, Mehta A. Nature and prevalence of pain in Fabry disease and its

response to enzyme replacement therapy--a retrospective analysis from the Fabry Outcome Survey. Clin J Pain 2007; 23: 535-42.

31 Hegemann S, Hajioff D, Conti G, Beck M, Sunder-Plassmann G, Widmer U et al. Hearing loss in Fabry disease: data from the Fabry Outcome Survey. Eur J Clin Invest 2006; 36: 654-62.

32 Palla A, Hegemann S, Widmer U, Straumann D. Vestibular and auditory deficits in Fabry disease and their response to enzyme replacement therapy. J Neurol 2007; 254: 1433-42.

33 Schiffmann R, Floeter MK, Dambrosia JM, Gupta S, Moore DF, Sharabi Y et al. Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry disease. Muscle Nerve 2003; 28: 703-10.

34 Hoffmann B, Garcia DL, Mehta A, Beck M, Widmer U, Ricci R. Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey). J Med Genet 2005; 42: 247-52.

35 Baehner F, Kampmann C, Whybra C, Miebach E, Wiethoff CM, Beck M. Enzyme replacement therapy in heterozygous females with Fabry disease: results of a phase IIIB study. J Inherit Metab Dis 2003; 26: 617-27.

36 Ramaswami U, Wendt S, Pintos-Morell G, Parini R, Whybra C, Leon Leal JA et al. Enzyme replacement therapy with agalsidase alfa in children with Fabry disease. Acta Paediatr 2007; 96: 122-7.

37 Wraith JE, Tylki-Szymanska A, Guffon N, Lien YH, Tsimaratos M, Vellodi A et al. Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. J Pediatr 2008; 152: 563-70.

38 Benjamin ER, Flanagan JJ, Schilling A, Chang HH, Agarwal L, Katz E et al. The pharmacological chaperone 1-deoxygalactonojirimycin increases alpha-galactosidase A levels in Fabry patient cell lines. J Inherit Metab Dis 2009; 32: 424-40.

39 Schwartz IV, Ribeiro MG, Mota JG, Toralles MB, Correia P, Horovitz D et al. A clinical study of 77 patients with mucopolysaccharidosis type II. Acta Paediatr Suppl 2007; 96: 63-70.

40 Neufeld E, Muenzer J. The mucopolysaccharidoses. In: Scriver C, Beaudet A, Sly W, Valle D, editors. The metabolic and molecular bases of inherited disease. 8th ed. New York: McGraw-Hill; 2001. p. 3421-52.

41 Schwartz IV, Ribeiro MG, Mota JG, Toralles MB, Correia P, Horovitz D et al. A clinical study of 77 patients with mucopolysaccharidosis type II. Acta Paediatr Suppl 2007; 96: 63-70.

42 Clarke LA, Wraith JE, Beck M, Kolodny EH, Pastores GM, Muenzer J et al. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics 2009; 123: 229-40.

43 Clarke LA, Wraith JE, Beck M, Kolodny EH, Pastores GM, Muenzer J et al. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics 2009; 123: 229-40.

44 Thomas JA, Jacobs S, Kierstein J, Van Hove J. Outcome after three years of laronidase enzyme replacement therapy in a patient with Hurler syndrome. J Inherit Metab Dis 2006; 29: 762.

45 Mercimek-Mahmutoglu S, Reilly C, Human D, Waters PJ, Stoeckler-Ipsiroglu S. Progression of organ manifestations upon enzyme replacement therapy in a patient with mucopolysaccharidosis type I/Hurler. World J Pediatr 2009; 5: 319-21.

46 Remerand G, Merlin E, Froissart R, Brugnon F, Kanold J, Janny L et al. Four successful pregnancies in a patient with mucopolysaccharidosis type I treated by allogeneic bone marrow transplantation. J Inherit Metab Dis 2009 March 13.

47 Wynn RF, Wraith JE, Mercer J, O'Meara A, Tylee K, Thornley M et al. Improved metabolic correction in patients with lysosomal storage disease treated with hematopoietic stem cell transplant compared with enzyme replacement therapy. J Pediatr 2009; 154: 609-11.

48 Boelens JJ, Rocha V, Aldenhoven M, Wynn R, O'Meara A, Michel G et al. Risk factor analysis of outcomes after unrelated cord blood transplantation in patients with hurler syndrome. Biol Blood Marrow Transplant 2009; 15: 618-25.

49 Bijarnia S, Shaw P, Vimpani A, Smith R, Pacey V, O'Grady H et al. Combined enzyme replacement and haematopoietic stem cell transplantation in Hurler syndrome. J Paediatr Child Health 2009; 45: 469-72.

50 Muenzer J, Wraith JE, Beck M, Giugliani R, Harmatz P, Eng CM et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med 2006; 8: 465-73.

51 Harmatz P, Giugliani R, Schwartz I, Guffon N, Teles EL, Miranda MC et al. Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. J Pediatr 2006; 148: 533-9.

52 Harmatz P, Giugliani R, Schwartz IV, Guffon N, Teles EL, Miranda MC et al. Long-term follow-up of endurance and safety outcomes during enzyme replacement therapy for mucopolysaccharidosis VI: Final results of three clinical studies of recombinant human N-acetylgalactosamine 4-sulfatase. Mol Genet Metab 2008; 94: 469-75.

53 Harmatz P, Yu ZF, Giugliani R, Schwartz IV, Guffon N, Teles EL et al. Enzyme replacement therapy for mucopolysaccharidosis VI: evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. J Inherit Metab Dis 2010; 33: 51-60.

54 Pitz S, Ogun O, Arash L, Miebach E, Beck M. Does enzyme replacement therapy influence the ocular changes in type VI mucopolysaccharidosis? Graefes Arch Clin Exp Ophthalmol 2009; 247: 975-80.

55 McGill JJ, Inwood AC, Coman DJ, Lipke ML, de Lore D, Swiedler SJ et al. Enzyme replacement therapy for mucopolysaccharidosis VI from 8 weeks of age--a sibling control study. Clin Genet 2010; 77: 492-8.

56 Wang CC, Hwu WL, Lin KH. Long-term follow-up of a girl with Maroteaux-Lamy syndrome after bone marrow transplantation. World J Pediatr 2008; 4: 152-4.

57 Bagewadi S, Roberts J, Mercer J, Jones S, Stephenson J, Wraith JE. Home treatment with Elaprase and Naglazyme is safe in patients with mucopolysaccharidoses types II and VI, respectively. J Inherit Metab Dis 2008; 31: 733-7.

58 Munoz-Rojas MV, Vieira T, Costa R, Fagondes S, John A, Jardim LB et al. Intrathecal enzyme replacement therapy in a patient with mucopolysaccharidosis type I and symptomatic spinal cord compression. Am J Med Genet A 2008; 146A: 2538-44.

59 Munoz-Rojas MV, Horovitz DD, Jardim LB, Raymundo M, Llerena JC, Jr., de Magalhaes TS et al. Intrathecal administration of recombinant human N-acetylgalactosamine 4-sulfatase to a MPS VI patient with pachymeningitis cervicalis. Mol Genet Metab 2010; 99: 346-50.

60 Byers S, Rothe M, Lalic J, Koldej R, Anson DS. Lentiviral-mediated correction of MPS VI cells and gene transfer to joint tissues. Mol Genet Metab 2009; 97: 102-8.

61 Metcalf JA, Ma X, Linders B, Wu S, Schambach A, Ohlemiller KK et al. A self-inactivating gamma-retroviral vector reduces manifestations of mucopolysaccharidosis I in mice. Mol Ther 2010; 18: 334-42.

62 Dixon CA, Anderson JB, Ruddy RM, Cripe LH. Infantile-onset Pompe disease: a diagnosis not to miss. Pediatr Emerg Care 2010; 26: 293-5.

63 Chien YH, Lee NC, Peng SF, Hwu WL. Brain development in infantile-onset Pompe disease treated by enzyme replacement therapy. Pediatr Res 2006; 60: 349-52.

64 McVie-Wylie AJ, Lee KL, Qiu H, Jin X, Do H, Gotschall R et al. Biochemical and pharmacological characterization of different recombinant acid alpha-glucosidase preparations evaluated for the treatment of Pompe disease. Mol Genet Metab 2008; 94: 448-55.

65 Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, Corzo D. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. J Pediatr 2006; 148: 671-6.

66 Chen LR, Chen CA, Chiu SN, Chien YH, Lee NC, Lin MT et al. Reversal of cardiac dysfunction after enzyme replacement in patients with infantile-onset Pompe disease. J Pediatr 2009; 155: 271-5.

67 Kishnani PS, Corzo D, Leslie ND, Gruskin D, van der PA, Clancy JP et al. Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease. Pediatr Res 2009; 66: 329-35.

68 Chien YH, Lee NC, Thurberg BL, Chiang SC, Zhang XK, Keutzer J et al. Pompe disease in infants: improving the prognosis by newborn

screening and early treatment. Pediatrics 2009; 124: e1116-e1125.

69 Chien YH, Lee NC, Peng SF, Hwu WL. Brain development in infantile-onset Pompe disease treated by enzyme replacement therapy. Pediatr Res 2006; 60: 349-52.

70 Nicolino M, Byrne B, Wraith JE, Leslie N, Mandel H, Freyer DR et al. Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease. Genet Med 2009; 11: 210-9.

71 Strothotte S, Strigl-Pill N, Grunert B, Kornblum C, Eger K, Wessig C et al. Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial. J Neurol 2010; 257: 91-7.

72 Yanovitch TL, Casey R, Banugaria SG, Kishnani PS. Improvement of Bilateral Ptosis on Higher Dose Enzyme Replacement Therapy in Pompe Disease. J Neuroophthalmol 2010 April 16.

73 Kishnani PS, Corzo D, Leslie ND, Gruskin D, van der PA, Clancy JP et al. Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease. Pediatr Res 2009; 66: 329-35.

74 Sun B, Young SP, Li P, Di C, Brown T, Salva MZ et al. Correction of multiple striated muscles in murine Pompe disease through adeno-associated virus-mediated gene therapy. Mol Ther 2008; 16: 1366-71.

75 Porto C, Cardone M, Fontana F, Rossi B, Tuzzi MR, Tarallo A et al. The pharmacological chaperone N-butyldeoxynojirimycin enhances enzyme replacement therapy in Pompe disease fibroblasts. Mol Ther 2009; 17: 964-71.

76 Flanagan JJ, Rossi B, Tang K, Wu X, Mascioli K, Donaudy F et al. The pharmacological chaperone 1-deoxynojirimycin increases the activity and lysosomal trafficking of multiple mutant forms of acid alpha-glucosidase. Hum Mutat 2009; 30: 1683-92.

77 van Til NP, Stok M, Aerts Kaya FS, de Waard MC, Farahbakhshian E, Visser TP et al. Lentiviral gene therapy of murine hematopoietic stem cells ameliorates the Pompe disease phenotype. Blood 2010 April 12.

78 Richard E, Douillard-Guilloux G, Batista L, Caillaud C. Correction of glycogenosis type 2 by muscle-specific lentiviral vector. In Vitro Cell Dev Biol Anim 2008; 44: 397-406.

79 Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. Lancet Neurol 2007; 6: 765-72.

80 Patterson MC, Vecchio D, Jacklin E, Abel L, Chadha-Boreham H, Luzy C et al. Long-term miglustat therapy in children with Niemann-Pick disease type C. J Child Neurol 2010; 25: 300-5.

81 Wraith JE, Vecchio D, Jacklin E, Abel L, Chadha-Boreham H, Luzy C et al. Miglustat in adult and juvenile patients with Niemann-Pick disease type C: long-term data from a clinical trial. Mol Genet Metab 2010; 99: 351-7.

82 Schlander M, Beck M. Expensive drugs for rare disorders: to treat or not to treat? The case of enzyme replacement therapy for mucopolysaccharidosis VI. Curr Med Res Opin 2009; 25: 1285-93.