HK J Paediatr (new series) 2004;**9**:231-239

Specific Treatment for Lysosomal Storage Disorders: Enzyme Replacement Therapy, Bone Marrow Transplant and Others

SYR ***LEE***, STS ***LAM***, DKK ***NG***, KY ***CHAN***, KW ***NG***

Abstract In this article, we review specific therapies that tackle the basic biochemical defects of lysosomal storage diseases. These include bone marrow transplantation, substrate deprivation therapy, enzyme replacement therapy and enzyme enhancement therapy. We particularly update the progress of development of enzyme replacement therapy, which plays a major role in the treatment of lysosomal storage diseases. Nowadays, enzyme products have been developed and marketed for treatment of Gaucher disease, Fabry disease, mucopolysaccharidosis I and currently there are ongoing trials of enzyme replacement for the treatment of glycogen storage disease II, mucopolysaccharidosis II and VI and Niemann-Pick B disease. Enzyme replacement therapy has a definite role in treatment of lysosomal storage diseases as it can ameliorate the signs and symptoms of the diseases. However, there are certain limitations. Enzyme replacement therapy is ineffective in improving or preventing neurological involvement. Response to treatment is slow in some situations, for example, bone involvement in Gaucher disease. It may also be unpredictable in other situations, for example, lung involvement in Gaucher disease. Hence, there is room for incorporation of other treatment modalities. One example is provided by mucopolysaccharidosis type I, in which bone marrow transplantation has a definite role as it prevents psychomotor retardation when carried out before significant brain damage occurs.

Key words Bone marrow transplant; Enzyme enhancement therapy; Enzyme replacement therapy; Lysosomal storage diseases; Substrate reduction therapy

Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Kwai Chung, N.T., Hong Kong, China

SYR **LEE** （李誠仁） *FHKAM, MRCP(UK)*
KY **CHAN** （陳國燕） *FHKAM, FRCP*

Clinical Genetic Service, Department of Health, Hong Kong, China

STS **LAM** （林德深） *FHKAM, FRCP*

Department of Paediatrics, Kwong Wah Hospital, 25 Waterloo Road, Kowloon, Hong Kong, China

DKK **NG** （吳國強） *FHKAM, FRCP*

Private Practice

KW **NG** （吳鋈煒） *FHKAM*

Correspondence to: Dr SYR **LEE**

Received December 15, 2003

Introduction

Lysosomal storage diseases (LSDs) are disorders in which the basic pathology lies in the abnormal storage of compounds in lysosomes. In the majority of cases, this results from genetic defects encoding enzymes, that catalize breakdown of the storage compounds. Otherwise, this could result from defects in transport of storage compounds out of lysosomes or defects of transport of enzymes into lysosomes. Until 1980, treatment available was basically symptomatic, which could not alter the course of the metabolic diseases. Since 1980 treatment modalities that tackle the basic biochemical defects and could potentially modify the disease process have been developed and are now employed in the treatment of LSDs. They include bone marrow transplantation, substrate deprivation therapy, enzyme replacement therapy and enzyme enhancement

therapy. The aim of this article is to review these specific treatment modalities for LSDs. The first part of this article gives the general overview of these treatment modalities whereas the latter part of the review is on how individual LSDs could be better managed in the era when these treatment modalities are beginning to become available. At present, another important field of development, gene therapy for LSD is still at the stage of animal experiments[1] and is beyond the scope of this review article.

Bone Marrow Transplantation

Bone marrow transplantation revolutionised the treatment of LSD. The first bone marrow transplant for LSD was performed in a patient with Hurler syndrome in 1980.[2] Bone marrow transplantation theoretically provides continual source of enzymes from the engrafted donor cells. The fact that some marrow cells are capable of crossing the blood-brain barrier and differentiate into microglial cells implies that bone marrow transplantation can potentially prevent psychomotor retardation of LSD if done early in the course of the diseases.[3] However, outcome after bone marrow transplantation in terms of slowing or halting of disease progression is quite variable in different LSDs.[4] Besides, bone marrow transplantation carries a significant mortality and high rate of failure of engraftment. In a large European cohort, the mortality related to the procedures was 10% if an human leukocyte antigen-identical sibling marrow donor was available and 20-25% if mismatched tissue was used.[4] The chance of failure of engraftment was 28.5%.

Enzyme Replacement Therapy

Enzyme Replacement Therapy (ERT) follows the observation in 1970s that many lysosomal enzymes can be secreted and then sequestrated by lysosomes in distant tissues. Mannose-6-phosphate receptors present on numerous cell membranes bind lysosomal enzymes with mannose-6-phosphate residues and facilitate the uptake of lysosomal enzymes.[5] Early tissue-culture experiments showed that exogenous enzymes could gain access to and degrade the accumulated intracellular substrates.[6-8] Even with achievement of 1-5% of normal cellular activity after supplying exogenous enzymes, these in vitro studies showed that storage substances dwindled. After these early exciting discoveries in 1970s, the progress in the 1980s was relatively slow. It was due to the difficulty of manufacturing large quantities of purified lysosomal enzymes and the lack of animal models of some human LSDs. The first enzyme available for treating LSDs was Alglucerase, (Ceredase, Genzyme Corporation, Boston, USA) for Gaucher disease. It was extracted from placentae. Effectiveness and safety were proven by clinical trials[9,10] leading to the approval by Food and Drug Administration (FDA) in the United States of America and the Evaluation of Medical Products (EMEA) in Europe in 1991.

In 1990s, advances in clinical genetics sped up the development of enzyme replacement therapy. Firstly, by means of genetic engineering, production of large quantities of recombinant enzymes became feasible. Secondly, knock-out mouse models for LSDs became technologically possible providing animal models of LSDs for pre-clinical trials. Hence, since the successful production of imiglucerase (Cerezyme, Genzyme Corporation, Boston, USA) by recombinant technology in 1996 replacing alglucerase in the market, several other lysosomal enzymes produced by recombinant DNA technology went into pre-clinical and clinical trials. Enzymes developed for treatment of Fabry disease and mucopolysaccharidosis type I were approved in Europe and USA in the early 2000s. Currently, clinical trials of ERT are going on for mucopolysaccharidosis type II[11] and type VI[12] and Pompe disease.[13,14] Preclinical studies in knockout mice or other naturally occurring animal models are under way for several other disorders including Niemann-Pick B disease,[15] galactosialidosis,[16] Wolman disease[17] and mucopolysaccharidosis VII.[18,19]

The study of pharmacokinetics and pharmacodynamics of exogenous enzymes for treatment of Gaucher disease deepened the understanding of how exogenous enzymes work in the body. Exogenous enzymes once given intravenously are rapidly taken up into cells resulting in a short serum half-life of around 10-20 minutes.[20] However, exogenous enzymes are not uniformly taken up. The efficient and preferential uptake of exogenous enzymes into certain compartments of the bodies leads to rapid clearance of enzymes in the bloodstream and deprives the availability of enzymes for uptake into less accessible compartments. One illustrative example of this preferential uptake in different tissues can be seen in ERT for Gaucher disease. Response to ERT in Gaucher disease is greater in liver and spleen than in bone[21,22] and lung.[23]

ERT has always enjoyed good reputation for its safety. Infusion related reactions like utricarial rash, chills and rigors, headache are common but not serious. It is due to

the development of antibodies against the exogenous enzymes. Slowing infusion rate lessens the severity of such reactions. Life-threatening reaction was reported only once in a patient with mucopolysaccharide type I during enzyme infusion.[24] The patient who had pre-existing airway compromise developed upper airway obstruction on enzyme infusion requiring tracheostomy.

Fortunately, other than causing infusion related reactions, antibodies developing during the course of ERT are rarely neutralising and effectiveness of ERT is usually not hampered as a result. The exception to this general rule was first noted in the phase I/II trial of ERT for Pompe disease. Two of the three patients developed antibodies during ERT, which were believed to be neutralising as appearance of antibodies coincided with the deterioration of gross motor function after an initial period of improvement.[14]

It was found that development of antibodies is correlated with the residual enzyme activities in patients. In a trial in which ERT was offered for 15 female heterozygotes having severe manifestations of Fabry disease, none developed antibodies.[25] This is presumably due to the existence of one normal locus on the other X chromosome in female heterozygotes and thus presence of residual enzyme activities. In Gaucher disease with most patients having some enzyme activity only 15% patients developed antibodies against exogenous enzyme on ERT.[22] Conversely, in classical Fabry disease with most patients having little or none enzyme activity, 80% did.[26,27] On the other hand, almost all patients receiving ERT for the treatment of mucopolysaccharidosis type I developed antibodies.[28]

One intrinsic problem of ERT is that ERT has so far not been effective in the treatment of neurological manifestations of LSDs, as exogenous enzymes cannot penetrate the blood-brain barrier. So application and development of other treatment modalities remains important.

Substrate Deprivation Therapy

Substrate deprivation therapy makes use of small molecules that inhibit synthesis of storage substances in LSDs. The inhibition of synthesis of storage substances coupled with the remaining enzyme activities results in the gradual disappearance of storage substances in cells. Theoretically these small molecules can be taken up into the central nervous system and potentially can treat LSDs with involvement of central nervous system. N-butyldeoxynojirimycin (OGT 918, Oxford Glycosciences, Abingdon, Oxfordshire) is the first of such small molecules marketed in Europe. It inhibits ceramide-specific glucosyltransferase preventing the formation of glucocerebroside, the storage compound in Gaucher disease. Clinical trial demonstrated some success in ameliorating clinical signs.[29] However, the experience of this drug is limited so far and it has not been shown to be efficacious in treating neurological manifestation of Gaucher disease. It was stated that ERT remains the mainstay of treatment of Gaucher disease and OGT 918 should be considered as an alternative to enzyme replacement therapy for patients who find enzyme treatment unacceptable.[29]

Enzyme Enhancement Therapy

In some LSDs, mutations cause misfolding of enzyme protein and thus impairing transport of enzymes into lysosomes from endoplasmic reticulum. Chaperones are low-molecular weight molecules that help unfold the proteins and thus enhance the residual enzyme activity. Based on this principle, a patient with the cardiac variant of Fabry disease who had severe heart complications was treated with galactose infusions (1 g/kg) three times weekly.[30] There was marked clinical improvement obviating cardiac transplantation. This is an area with great potential for development. As chaperones are small enough to cross blood-brain barrier, there is hope that neurological manifestations of LSDs could be effectively treated by chaperones and this awaits confirmation by clinical studies.

Lysosomal Storage Diseases in Hong Kong

Literature revealed showed that the following LSDs exist in Hong Kong: mucopolysaccharidosis type I,[31] II[31] and VI,[31] mucolipidosis type II,[32] Niemann-Pick C,[32] Gaucher disease[23] and Fabry disease.[33,34] In the hospital of the first author, recently a patient was diagnosed GM1-gangliosidosis. Hence, advance in the treatment of LSD is relevant to the situation in Hong Kong. The following section explores how LSDs could be best treated in the light of development of specific treatment modalities mentioned. We focus only on several LSDs, which are amenable to the specific treatment modalities.

Gaucher Disease

Gaucher disease is an autosomal recessive disease due to the deficiency of glucocerebrosidase resulting in accumulation of glucocerebroside in lysosomes. Patients present with hepatosplenomegaly and pancytopenia. Bone involvement results in bone pain, decreased bone density, collapse or fracture of bones. Asymptomatic lung involvement is common. The disease is classified into type I, type II and type III depending on neurological involvement. Type I is the non-neuronopathic form. Patients with type II disease have acute neurological deterioration and often die early as a result of degenerative brain disease. Type III is the neuoronopathic form with subacute onset.

It is already known that some correlation exists between severity of disease and phenotype.[35,36] For example, L444P is associated with severe clinical manifestations, early onset and neurological involvement whereas N370S is associated with mild phenotype. The prediction of severity by genotype may have an important bearing on the initial dosing of ERT.

In the past before ERT was available, bone marrow transplantation was tried in some patients with improvement of clinical features.[4] However, bone marrow transplantation was unable to prevent development of neurological manifestation and is not advantageous to ERT as far as neurological involvement is concerned. Ever since ERT becomes available, bone marrow transplantation is seldom performed because of high mortality rate.

Before ERT was available, splenectomy was occasionally done to control thrombocytopenia. However, it was noted that bone involvement was hastened after splenectomy.[37] Nowadays, patients on ERT rarely need splenectomy since platelet count usually rises to a safe level.

The effectiveness of ERT shown by initial small-scale clinical trials were further confirmed by a report of 1028 patients with type I Gaucher disease after 2 to 5 years of treatment.[22] Haemoglobin became normal or near normal within 6 to 12 months with sustained response in five years. Thrombocytopenia improved gradually. For patient having spleen removed, platelet count returned to normal within 6 to 12 months. However, for patients with intact spleen and low baseline platelet count less than 60,000/mm, normalisation of platelet count was usually not achieved. However, platelet count usually rose to a safe level. Hepatomegaly decreased by 30% to 40% and splenomegaly decreased by 50% to 60% but rarely to volumes below five times of normal size. In patients with pretreatment bone pain or bone crises, 52% were pain free and 94% reported no additional crises after 2 years. The incomplete clinical response was due to the fact that irreversible damage like avascular necrosis had happened. Hence, this illustrates the importance of starting ERT before any irreversible damage sets in.

Study on children showed that in addition to the above benefits, ERT appears to normalise growth and possibly puberty.[37] Delayed puberty was prevented when ERT was started in the first decade of life.[38]

Organs respond differently to ERT. Skeletal response to ERT is slower than haematological and visceral changes.[39] Response of lung involvement to ERT is unpredictable.[23] ERT is ineffective in treating neurological involvement due to the inability of penetration of the enzyme into the blood-brain barrier.

Considering the phenotypic heterogeneity among children, even between siblings with the same genotype,[40] it is anticipated that response to ERT would vary accordingly. The dosing of ERT should therefore be individualised.

The response to ERT is gauged by monitoring the status of different organs. It takes months for the liver and spleen to shrink while bone improvement becomes evident in 2 years and this should be taken into account when monitoring response.[41] Magnetic resonance imaging (MRI) of bone and dual X-ray absorptiometry (DEXA) scan are helpful tool in monitoring bone involvement. Bone complication sometimes occurs despite improvement of visceral symptoms on ERT. This underscores the importance of regular evaluation of bone involvement by MRI and DEXA scan to pick up bone problems before they surface clinically and adjustment of dose accordingly.

When the response is not satisfactory, increasing dosage should be tried. Patients with Gaucher disease commonly received 30-60 Units/kg/2 weeks. Higher doses (90 Units/kg every 2 weeks up to 240 Units/kg/ 2 weeks) have been tried for pulmonary involvement,[23] severe bone crisis[42] or neurological involvement.[43] When disease is under control, doses could be reduced to see if resolution of signs and symptoms could be maintained. However, doses should not be reduced to less than 15 Units/kg every 2 weeks than, which is regarded as the minimal effective dose.

Treating children with Gaucher disease merits special consideration. The starting dose for children with Gaucher disease is 30-60 Units/kg every 2 weeks[41,44] and dosage should not be decreased to less than 30 Units/kg/2 weeks[41] as disease with onset in childhood represents the severe form of the disease. Besides, in childhood before the full development of skeleton, using higher doses to maximise growth potential is important, let alone the prevention of

osteopenia, fracture of long bones, collapse of vertebrae and avascular necrosis, all of which are detrimental to the attainment of final height.

Concerning the dosing frequency, biweekly infusion is the most popular. Frequent low dose infusion regimen delivering 2.5 Units/kg 3 times a week (equivalent to an overall dose of 15 Units/kg/2 weeks) was tried in the hope that this could be as effective as higher doses given biweekly and that total cost could be reduced.[45] However, 62% of patients developed new bone lesions on this regimen illustrating that there is no advantage of low dose frequent infusion. On the other hand, trial exploring the possibility and efficacy of spacing the infusion from 2 weekly to three weekly was done but the result showed that hepatosplenomegaly returned as a result of this dosage change.[46] Hence, biweekly infusion should be the most appropriate frequency of treatment given the current evidences.

In Hong Kong, a Chinese girl with Gaucher disease without overt neurological signs and symptoms started to receive ERT since the age of three.[23] This is the first reported case of ERT in Hong Kong. Interested readers may refer to the original article.

Fabry Disease

Fabry disease is an X-linked glycosphingolipid storage disorders that is caused by the deficient activity of lysosomal alpha-galactosidase A, resulting in accumulation of glycolipids, mainly globotriaosylceramide, GL-3 in endothelial, perithelial and smooth-muscle cells of blood vessels, cardiac myocytes, autonomic spinal ganglia, glomerular endothelium and epithelial cells of glomeruli and tubuli of the kidney. The symptoms include severe pain in the extremities, hypohidrosis and angiokeratoma. Renal involvement usually presents with proteinuria progressing eventually to renal failure. Cardiac manifestations include coronary artery disease, valvular disease and conduction abnormalities. Patients can die early because of cerebrovascular disease. Ocular findings are important in aiding diagnosis: engorged conjunctival and retinal vessels and corneal opacities.

Following the phase I/II clinical trial yielding preliminary promising results in terms of safety and probable efficacy,[47] two phase III clinical trials of ERT showed that there was marked improvement of renal and cardiac biopsies in terms of decreased GL-3 deposition in endothelium.[26,27] There was slowing of deterioration in renal function.[27] In these short-term studies, efficacy of improvement of pain was not proven beyond doubt as both the placebo group and the treatment group experienced the same rate of reduction of pain scores at the end of the studies. The marked pathological improvement in numerous vital organs after ERT leads us to believe that ERT should be able to drastically improve mortality and morbidity of Fabry disease related to coronary heart disease and cerebrovascular accident, which awaits long-term follow-up findings and confirmation

Since Fabry disease is an X-linked condition, female heterozygotes in general are less affected than male patients. However, most female heterozygotes have at least some symptoms and severe manifestations are occasionally seen. In an open-label study of ERT for female patients with severe symptoms, 15 subjects were treated for 55 weeks.[25] Benefits in terms of improved quality of life, maintenance of renal function, improved electrocardiograph and echocardiograph results were demonstrated.

Certainly, ERT should be given early to patients with Fabry disease if resources allow before irreversible pathology sets in. When the disease progresses to the stage of chronic renal failure, it will obviously be too late as established renal pathology will be irreversible by whatever treatment. Enzyme enhancement therapy has also been shown to dramatically improve the cardiac condition of a case of cardiac variant of the disease (described in previous section).

Mucopolysaccharidosis I

Mucopolysaccharidosis I is an autosomal recessive disease due to deficiency of alpha-L-iduronidase. This results in the storage of mucopolysaccharides in the body. Patients have coarse facial features and macroglossia. Patients with severe disease (Hurler disease) have mental deficiency. Chest deformity, flexion contractures of joint, carpal tunnel syndrome, valvular defects of heart contribute to morbidity and mortality. Patients die in first decade of life. Patients with intermediate severity of the disease (Hurler-Scheie) do not have mental deficiency but have short life span dying in the second decade of life. Patient with the mildest form of the disease called Scheie disease have mild clinical features and long life span.

Bone marrow transplantation early in life before occurrence of significant brain damage prevents neurological deterioration in addition to improvement of visceral features.[48,49] It is because donor marrow cells are

able of entering the brain and differentiate into neuroglial cells. During follow-up of patients who received bone marrow transplantation, it was found that they invariably developed severe dysostosis multiplex later in life. This probably reflects the inefficacy of bone marrow transplantation in preventing all complications and in particular bone problem. Hence, bone marrow transplantation does not provide an ultimate answer to the management of the disease.

In a phase I/II trial of recombinant human alpha-L-iduronidase 10 patients (aged 5 to 22 years) were treated for 26 weeks and later extended to 152 weeks. A number of clinical improvement was observed.[50-52] Eight out of 10 patients had normal size of liver and spleen by 26 weeks and all showed significant decrease in size of spleen and liver at the end of the study. The rate of growth in height and weight increased by a mean of 85 and 131 percent respectively in the six prepubertal patients. The mean maximal range of motion of shoulder flexion and elbow extension increased significantly. The number of episodes of apnoea and hypopnoea during sleep decreased by 61 percent. Exercise tolerance measured by New York Heart Association Functional Class improved substantially over time (p value versus baseline: 0.063 by week 12, 0.008 by week 26 and 0.002 by week 52).

In a phase III trial with open label extension, 45 Mucopolysaccharidosis I patients were recruited. One patient was clinically assessed as having Hurler form, 37 Hurler-Scheie, and 7 Scheie. Patients were randomised into receiving alpha-L-iduronidase or placebo.[53] By the end of 6 months, patients in the treatment group had significantly improved forced vital capacity (p=0.016) and exercise tolerance as indicated by increased 6-minute walk distance (p=0.066, which was almost statistically significant). It was followed by a six-month open-label extension study, in which all patients received alpha-L-iduronidase. The placebo group who subsequently received alpha-L-iduronidase in this period caught up in exercise tolerance and performance of forced vital capacity. Allergic reactions were frequent (32%). One patient who had pre-existing airway compromise had anaphylaxis and airway obstruction requiring tracheostomy.

Alpha-L-iduronidase is unable to cross blood-brain barrier and is not useful in treating or preventing neurological involvement. Hence, timely diagnosis and bone marrow transplantation before significant psychomotor retardation sets in remains important despite the availability of ERT. Alpha-L-iduronidase probably offers hope to those patients who do not receive bone marrow transplant and have disabling illness.

Glycogen Storage Disease Type II (Pompe Disease)

The mode of inheritance is autosomal recessive. It is due to deficiency of alpha-1,4-glucosidase resulting in storage of glycogen in the myocardium and skeletal muscles. Patients presenting in infancy die of heart failure in the first year. Patients presenting later in life have muscle weakness but with minimal or no cardiac involvement. They may die of respiratory failure as involvement of respiratory muscles progresses. Presentation in adulthood is compatible with prolonged life.

Two phase I/II single center, open label trials enrolled four and three infants respectively for the treatment with recombinant human enzyme.[13,14] Survival beyond one year with marked improvement of cardiac function was possible for all patients, which was an very important endpoint as historical cohort showed that death within the first year of life was almost invariable.[54] The response of skeletal muscle to ERT was less consistent. Two of the three patients in a phase I/II trial had deterioration of gross motor function after an initial period of improvement while the other had continual improvement in gross motor function.[14] Antibodies to alpha-glucosidase were coincidentally detected in these two patients and was attributed to be the cause of ineffectiveness of ERT for improvement of skeletal muscle. In these short studies muscle biopsy also failed to reveal clearance of glycogen regardless of clinical improvement in gross motor function.[14,15] Explanation of this is difficult, as the contribution of lysosomal versus cytoplasmic glycogen to the total glycogen content of the muscle is unknown.

There was a phase I/II clinical trial on late onset glycogen storage disease type II and was published only in abstract form.[55] According to the brief report, totally three patients received ERT. Two patients aged 32 and 16 years were ventilator dependent and wheelchair bound. Their lung function improved on ERT. Another patient aged 12 years who had been wheelchair bound for 4 years started to walk again after receiving ERT. The result of this report was obviously very encouraging.

So far, the results of phase I/II clinical trials for Pompe disease are promising. We are looking forward to the results of the phase III clinical trial, which has already been started.

Mucopolysaccharidosis II (Hunter Disease)

Hunter disease is an X-linked condition due to the deficiency of Iduronate-2-sulfatase. The clinical picture closely resembles that of Hurler disease but there is no corneal clouding. There is also a mild form of the disease with mild symptoms and long survival. Unlike Hurler disease, result of bone marrow transplant in ameliorating visceral signs or prevention of psychomotor retardation was not impressive.[56] This might be due to poor donor selection.[56] However, enthusiasm for bone marrow transplant died down. Actually one renowned center in United Kingdom has abandoned further attempt of bone marrow transplant for this disease (personal communication with Dr. Vellodi, Consultant, Great Ormond Street Hospital for Sick Children, London, United Kingdom).

A phase I/II was carried out on 12 patients with Hunter disease[11] and was published in abstract form. The brief report showed that there was improvement in exercise tolerance and range of movement of joints after ERT.

Conclusion

ERT has a definitive role in the treatment of LSD as it is capable of reducing storage materials thus altering the natural course of LSD in a positive way. Any benefits, however, are only possible if irreversible damage to organs has not occurred. This underscores the importance of early start of ERT. However, its ineffectiveness in ameliorating symptoms in some organs, the brain in particular, speaks for the need for incorporation of other treatment modalities like bone marrow transplant and further research, like gene therapy and substrate deprivation treatment. The metabolic clinicians should keep up with the rapid development of ERT as quite a number of new enzymes are currently under clinical trials and approval should not be too distant in the future.

References

1. Cabrera-Salazar MA, Novelli E, Barranger JA. Gene therapy for the lysosomal storage disorders. Curr Opin Mol Ther 2002;4: 349-58.
2. Hobbs JR, Hugh-Jones K, Barrett AJ, et al. Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation. Lancet 1981;2:709-12.
3. Krivit W, Peters C, Shapiro EG. Bone marrow transplantation as effective treatment of central nervous system disease in globoid cell leukodystrophy, metachromatic leukodystrophy, adrenoleukodystrophy, mannosidosis, fucosidosis, aspartylglucosaminuria, Hurler, Maroteaux-Lamy, and Sly syndromes, and Gaucher disease type III. Curr Opin Neurol 1999;12:167-76.
4. Hoogerbrugge PM, Brouwer OF, Bordigoni P, et al. Allogeneic bone marrow transplantation for lysosomal storage diseases. The European Group for Bone Marrow Transplantation. Lancet 1995; 345:1398-402.
5. Kornfeld S. Lysosomal enzyme targeting. Biochem Soc Trans 1990;18:367-74.
6. O'Brien JS, Miller AL, Loverde AW, Veath ML. Sanfilippo disease type B: enzyme replacement and metabolic correction in cultured fibroblasts. Science 1973;181:753-5.
7. Porter MT, Fluharty AL, Kihara H. Correction of abnormal cerebroside sulfate metabolism in cultured metachromatic leukodystrophy fibroblasts. Science 1971;172:1263-5
8. Cantz M, Kresse H. Sandhoff disease: defective glycosaminoglycan catabolism in cultured fibroblasts and its correction by beta-N-acetylhexosaminidase. Eur J Biochem 1974; 47:581-90.
9. Barton NW, Furbish FS, Murray GJ, Garfield M, Brady RO. Therapeutic response to intravenous infusions of glucocerebrosidase in a patient with Gaucher disease. Proc Natl Acad Sci U S A 1990;87:1913-6.
10. Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency--macrophage-targeted glucocerebrosidase for Gaucher's disease. N Engl J Med 1991; 324:1464-70.
11. Muenzer J, Towle D, Calikoglu M, McCandless S. A phase I/II clinical study evaluating the safety and clinical activity of enzyme replacement therapy in mucopolysaccharidosis II (Hunter syndrome). In Abstract of the 52nd annual meeting of the American Society of Human Genetics, October 15-19, 2002. Baltimore, Maryland, USA. Am J Hum Genet 2002;71(4 Suppl): 582.
12. Harmatz P, Whitley CB, Waber L, et al. Enzyme replacement therapy in mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). J Pediatr 2004;144:574-80.
13. Van den Hout JM, Reuser AJ, de Klerk JB, Arts WF, Smeitink JA, Van der Ploeg AT. Enzyme therapy for pompe disease with recombinant human alpha-glucosidase from rabbit milk. J Inherit Metab Dis 2001;24:266-74.
14. Amalfitano A, Bengur AR, Morse RP, et al. Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. Genet Med 2001;3:132-8.
15. Miranda SR, He X, Simonaro CM, et al. Infusion of recombinant human acid sphingomyelinase into niemann-pick disease mice leads to visceral, but not neurological, correction of the pathophysiology. FASEB J 2000;14:1988-95.
16. Bonten EJ, et al. Effective enzyme replacement therapy of murine galactosialidosis using insect cell-expressed PPCA and neuraminidase. In Abstract of the 52nd annual meeting of the American Society of Human Genetics, October 15-19, 2002. Baltimore, Maryland, USA. Am J Hum Genet 2002;71(4 Suppl): 420.

17. Du H, Schiavi S, Levine M, Mishra J, Heur M, Grabowski GA. Enzyme therapy for lysosomal acid lipase deficiency in the mouse. Hum Mol Genet 2001;10:1639-48.
18. Vogler C, Levy B, Galvin NJ, et al. Enzyme replacement in murine mucopolysaccharidosis type VII: neuronal and glial response to beta-glucuronidase requires early initiation of enzyme replacement therapy. Pediatr Res 1999;45:838-44.
19. Sands MS, Vogler CA, Ohlemiller KK, et al. Biodistribution, kinetics, and efficacy of highly phosphorylated and non-phosphorylated beta-glucuronidase in the murine model of mucopolysaccharidosis VII. J Biol Chem 2001;276:43160-5.
20. Desnick RJ, Schuchman EH. Enzyme replacement and enhancement therapies: lessons from lysosomal disorders. Nat Rev Genet 2002;3:954-66.
21. Gaucher disease. Current issues in diagnosis and treatment. NIH Technology Assessment Panel on Gaucher Disease. JAMA 1996; 275:548-53.
22. Weinreb NJ, Charrow J, Andersson HC, 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.
23. Lee SY, Mak AW, Huen KF, Lam ST, Chow CB. Gaucher disease with pulmonary involvement in a 6-year-old girl: report of resolution of radiographic abnormalities on increasing dose of imiglucerase. J Pediatr 2001;139:862-4.
24. Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J. A phase 3 study of rhIDUA enzyme replacement therapy for MPS I. 7th International Symposium on MPS and related disease, Paris, France (2002).
25. 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.
26. Eng CM, Guffon N, Wilcox WR, 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.
27. Schiffmann R, Kopp JB, Austin HA 3rd, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001;285:2743-9.
28. Kakavanos R, Turner CT, Hopwood JJ, Kakkis ED, Brooks DA. Immune tolerance after long-term enzyme-replacement therapy among patients who have mucopolysaccharidosis I. Lancet 2003;361:1608-13.
29. Pastores GM, Barnett NL. Substrate reduction therapy: miglustat as a remedy for symptomatic patients with Gaucher disease type 1. Expert Opin Investig Drugs 2003;12:273-81.
30. Frustaci A, Chimenti C, Ricci R, et al. Improvement in cardiac function in the cardiac variant of Fabry's disease with galactose-infusion therapy. N Engl J Med 2001;345:25-32.
31. Pang CP, Law LK, Mak YT, et al. Biochemical investigation of young hospitalized Chinese children: results over a 7-year period. Am J Med Genet 1997;72:417-21.
32. Tang NL, Hui J, Law LK, et al. Overview of common inherited metabolic diseases in a Southern Chinese population of Hong Kong. Clin Chim Acta 2001;313:195-201.
33. Lam CW, Mak YT, Lo YM, Tong SF, To KF, Lai FM. Molecular genetic analysis of a Chinese patient with Fabry disease. Chin Med J (Engl) 2000;113:186-8.
34. Tse KC, Chan KW, Tin VP, et al. Clinical features and genetic analysis of a Chinese kindred with Fabry's disease. Nephrol Dial Transplant 2003;18:182-6.
35. Sibille A, Eng CM, Kim SJ, Pastores G, Grabowski GA. Phenotype/genotype correlations in Gaucher disease type I: clinical and therapeutic implications. Am J Hum Genet 1993; 52:1094-101.
36. Zimran A, Sorge J, Gross E, Kubitz M, West C, Beutler E. Prediction of severity of Gaucher's disease by identification of mutations at DNA level. Lancet 1989;2:349-52.
37. Kaplan P, Mazur A, Manor O, et al. Acceleration of retarded growth in children with Gaucher disease after treatment with alglucerase. J Pediatr 1996;129:149-53.
38. Kauli R, Zaizov R, Lazar L, et al. Delayed growth and puberty in patients with Gaucher disease type 1: natural history and effect of splenectomy and/or enzyme replacement therapy. Isr Med Assoc J 2000;2:158-63.
39. Hermann G, Pastores GM, Abdelwahab IF, Lorberboym AM. Gaucher disease: assessment of skeletal involvement and therapeutic responses to enzyme replacement. Skeletal Radiol 1997;26:687-96.
40. Van Weely S, Van Leeuwen MB, Jansen ID, et al. Clinical phenotype of Gaucher disease in relation to properties of mutant glucocerebrosidase in cultured fibroblasts. Biochim Biophys Acta 1991;1096:301-11.
41. Baldellou A, Andria G, Campbell PE, et al. Paediatric non-neuronopathic Gaucher disease: recommendations for treatment and monitoring. Eur J Pediatr 2004;163:67-75.
42. Larsen EC, Connolly SA, Rosenberg AE. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 20-2003. A nine-year-old girl with hepatosplenomegaly and pain in the thigh. N Engl J Med 2003;348:2669-77.
43. Vellodi A, Bembi B, de Villemeur TB, et al. Management of neuronopathic Gaucher disease: a European consensus. J Inherit Metab Dis 2001;24:319-27.
44. Charrow J, Andersson HC, Kaplan P, et al. Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: consensus recommendations. J Pediatr 2004;144:112-20.
45. Zaizov R Frish A, Cohen IJ. Lower-dose, high-frequency enzyme replacement therapy in children with type 1 Gaucher disease: experience at the Schneider Children's Medical Center of Israel. Semin Hematol 1995;32(3 Suppl 1):39-44.
46. Perez-Calvo J, Giraldo P, Pastores GM, Fernandez-Galan M, Martin-Nunez G, Pocovi M. Extended interval between enzyme therapy infusions for adult patients with Gaucher's disease type 1. J Postgrad Med 2003;49:127-31.
47. Eng CM, Banikazemi M, Gordon RE, et al. A phase 1/2 clinical trial of enzyme replacement in fabry disease: pharmacokinetic, substrate clearance, and safety studies. Am J Hum Genet 2001; 68:711-22.
48. Guffon N, Souillet G, Maire I, Straczek J, Guibaud P. Follow-up of nine patients with Hurler syndrome after bone marrow transplantation. J Pediatr 1998;133:119-25.
49. Vellodi A, Young EP, Cooper A, et al. Bone marrow transplantation for mucopolysaccharidosis type I: experience of two British centres. Arch Dis Child 1997;76:92-9.
50. Kakkis ED, Muenzer J, Tiller GE, et al. Enzyme-replacement

therapy in mucopolysaccharidosis I. N Engl J Med 2001;344: 182-8.
51. Kakkis E, Jonas A, Muenzer J, et al. A phase 1/2 study of enzyme replacement therapy of Aldurazyme in MPS I. International Symposium on Clinical Management of MPS I, Naples, Italy, 2003.
52. Brooks DA. Alpha-L-iduronidase and enzyme replacement therapy for mucopolysaccharidosis I. Expert Opin Biol Ther 2002;2:967-76.
53. Beck M, Wraith JE, Clarke LA, Kolodny EH, Pastores GM, Muenzer J. A phase 3 study of rhIDUA enzyme therapy for MPS I (abstract). J Inherit Metab Dis 2002;25(Supp 1):120.
54. van den Hout HM, Hop W, van Diggelen OP, et al. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. Pediatrics 2003;112:332-40.
55. Van der Ploeg AT, et al. Preliminary findings in patients with late onset Pompe's disease treated with recombinant human alpha-glucosidase from rabbit milk (Abstract). J Inherit Metab Dis 2002:25:118.
56. Vellodi A, Young E, Cooper A, Lidchi V, Winchester B, Wraith JE. Long-term follow-up following bone marrow transplantation for Hunter disease. J Inherit Metab Dis 1999;22:638-48.