Home treatment with enzyme replacement therapy for mucopolysaccharidosis type I is feasible and safe


Summary Objective: Intravenous enzyme replacement therapy (ERT) with recombinant α-L-iduronidase may ameliorate the non-neurological symptoms in patients with mucopolysaccharidosis type I (MPS I). Since home-based ERT for Gaucher and Fabry diseases has been reported to be safe and successful, we investigated the feasibility and safety of home therapy in patients with MPS I. Setting: This two-centre study included 17 ERT-treated MPS I patients between 1 and 35 years of age. A patient was allowed to transfer to home treatment after a minimum period of 6 months of in-hospital administration of ERT and after a self- or home nurse-supported home setting was arranged. Results: Thirteen out of 17 patients transferred to home treatment with a median time to transfer of 13 months (range 7–40 months). Two patients preferred to continue ERT in the hospital, whereas for two other patients the transfer to home was hampered for practical reasons. All patients who received ERT at home were assisted by either a relative or a nurse. In total over 1000 home infusions were performed and no serious complications were observed. Two infusion-associated reactions were observed, both within the first 3 months of in-hospital administration of ERT. All patients except one developed antibodies against the recombinant enzyme, but this was not associated with the development of hypersensitivity reactions. Conclusion: ERT for MPS I applied at home is safe and might alleviate the burden of life-long intravenous treatment in these patients.

Abbreviations
ERT enzyme replacement therapy
GAG glycosaminoglycan
(r)IDUA (recombinant) α-L-iduronidase
LSD lysosomal storage disorder
MPS I mucopolysaccharidosis type I
PAC porth-a-cath

Introduction
Lysosomal storage disorders (LSDs) are a group of inborn errors of metabolism comprising more than 50
different diseases. The majority of the diseases are caused by the deficiency of a single lysosomal enzyme. One of the therapeutic strategies for LSDs is based on the delivery of the deficient lysosomal enzyme by repeated infusions. This approach was first established for Gaucher disease, in which supplementation of purified beta-glucocerebrosidase was shown to be highly effective (Barton et al 1991). More recently, enzyme replacement therapy (ERT) has been developed for Fabry disease, Pompe disease and mucopolysaccharidosis types I, II and VI (MPS I, II and VI).

In MPS I the deficiency of a-L-iduronidase (IDUA; EC 3.2.1.76) results in the accumulation of specific glycosaminoglycans (GAGs) in the lysosomes. The resulting multisystemic disease is highly variable in phenotypic expression. Patients who suffer from the most severe neuronopathic phenotype, the so-called Hurler syndrome (MPS IH; OMIM 607014), exhibit severe symptoms early in life, including mental retardation, airway obstruction, hepatosplenomegaly and skeletal disease. Patients who are classified as having the non-neuronopathic Scheie syndrome (MPS IS; OMIM 607016) have less extensive disease, characterized by connective-tissue and skeletal complications, cardiac valve abnormalities and upper airway-related symptoms. The Hurler-Scheie syndrome (MPS IH/S; OMIM 607015) displays an intermediate phenotype.

ERT has been approved in the USA and Europe since 2003 for the treatment of the non-neurological manifestations of MPS I. Weekly intravenous supplementation of recombinant IDUA (rIDUA) results in improvement of various disease parameters, such as hepatosplenomegaly and vital capacity (Kakkis et al 2001; Wraith et al 2004). However, ERT probably involves life-long intravenous treatment, which may have a strong negative effect on the quality of life. Fortunately, several years of experience with ERT in Gaucher and Fabry diseases have demonstrated that home treatment with ERT may be safe and successful (Linthorst et al 2006; Schiffmann et al 2001, 2006). In MPS I the recommended infusion time is 3–4h. Although this is relatively long, it probably should not preclude home treatment.

The aim of the present study was to investigate the feasibility and safety of home therapy for MPS I patients in the Netherlands.

Methods

Patients

In the Netherlands, the treatment and follow-up of patients with MPS I is centralized at two facilities: the Academic Medical Center (AMC) in Amsterdam and the Erasmus Medical Center (EMC) in Rotterdam. All patients with a confirmed diagnosis of MPS I demonstrated by reduced IDUA activity and mutation analysis and eligible for treatment with rIDUA were included in this study. Children under the age of 2 years were only included when haematopoietic stem cell transplantation was not feasible. Patients were included from January 2002 until November 2006.

Home treatment protocol

The patients received rIDUA (Aldurazyme, Genzyme Corp, Boston, MA, USA) at a dose of 100 IU/kg (0.58 mg/kg). All children (age <18 years) received a port-a-cath (PAC) before or shortly after initiation of ERT. Adult patients received infusions through a peripheral vein.

Before initiation of home treatment, patients received ERT in the hospital for a minimum period of 6 months. This was based on the rationale that hypersensitivity reactions mainly occur within the first 6 months of treatment (Kakkis et al 2001). In addition, seroconversion usually occurs within the first 3 months
of ERT in patients who develop IgG antibodies and is generally followed by a decline in antibody titres in the following 3 months (Kakavanos et al 2003; Kakkis et al 2001; Wraith et al 2004).

In patients opting for home treatment, based on the preference of the patient and/or the partner, either home nursing service was arranged or the parents or partner were trained to create intravenous access. In the latter case, a skilled nurse trained the person who was going to perform the reconstitution of the rIDUA. For patients from one of the participating centres (EMC) who had a PAC, the rIDUA was reconstituted in the hospital pharmacy. Patients from the EMC without a PAC and all patients from the AMC received a stock of vials sufficient for 3 months of ERT. Vials had to be stored in a separate box in the refrigerator at home. Reconstitution at home was performed by either a home nurse or a relative. If reconstitution was performed by a relative, that person was extensively educated about the procedure and ensuring full sterility of the solution. The appropriate dosage of rIDUA was diluted in 100 ml and 250 ml for patients weighing under and over 20 kg, respectively. Initially, the patients received pre-medication with an antihistaminergic drug for 6 months (clemastine 0.025 mg/kg i.v. in children or 1 mg orally in adults). In all patients, the pre-medication was withdrawn at least 2 months before they were transferred to their home setting. Standard pre-medication was later completely withdrawn from the protocol at the beginning of 2005.

Vials had to be retained during the time of the infusion procedure, as batch information might be needed in case of potential adverse events. The vials, needles and other potentially contaminated waste were disposed of in a medical disposal container. Waste was handled by the home nursing service or the local pharmacy.

During the first month of home treatment, the patient and or parents were asked to administer ERT during regular office hours in case assistance was required. All patients received instructions regarding procedures in case of technical problems or the suspicion of an adverse event. If a suspected adverse event should occur, the infusion was to be interrupted immediately and the general practitioner, who was informed about the switch to home treatment and the potential adverse events, was to be contacted. Parents and patients were instructed to report all possible side-effects and complications to their treating physician. Home protocols were personalized and included contact information of the home nursing service, general practitioner and the academic nurses and specialists involved.

IgG anti-rIDUA antibody detection

Blood samples were obtained at baseline and every 3 months thereafter. The samples were spun at 3000 rpm for 10 min and serum was stored at −80°C. Antibodies against rIDUA were detected using an ELISA system with 1 μg of rIDUA per well, 4% gelatin buffer as blocking agent and peroxidase-conjugated goat antibodies to human IgG (1:250 000). A solution of tetramethylbenzidine (0.1 mg/ml) and 0.003% H₂O₂ in sodium acetate (100 mmol/L; pH 5.2) was used for the colorimetric reaction, which was then blocked with H₂SO₄ (1 mol/L). The absorbance was measured at 450 nm in an ELISA reader (Titer-Tek, Huntsville, AL, USA). The titre was determined by the dilution at which 50% of the maximum absorbance was observed. A titre <1/32 was defined as negative.

Results

Patients

From March 2002 to December 2006 17 MPS I patients, 11 children and 6 adults (Table 1) were started on long-term ERT in the Netherlands. Thirteen patients were transferred successfully to home therapy. Four patients (patients 14–17) still received ERT in the hospital. Two of them preferred to continue hospital-based ERT since both lived very close to a hospital (patients 14 and 17). The two other patients who are still on hospital-based ERT (siblings, patients 15 and 16) preferred to start home treatment but obtaining peripheral venous access was very difficult in one of them and appropriate assistance at home has not been able to be arranged so far.

Cumulatively, 1020 home infusions have been performed in 13 patients. Patients were transferred to home treatment after a median period of 13 months (range 7–40). Venous access was achieved by either a home nurse or a parent and in one case by a spouse (Table 1). In 13 patients blood samples were available
for IgG antibody studies. In all except one, IgG anti-
rIDUA antibodies were detected 3 months after
initiation of ERT (Table 1). After 12 months of
ERT, antibody titres had declined in all patients.

Side-effects, complications and technical difficulties

One MPS IS patient (patient 8) suffered from an
infection of the PAC within one week after placement.
She recovered well after antibiotic treatment and
removal of the PAC. After this complication the child
preferred peripheral venous access. To achieve this, a
home nurse assists the parents and the child.

One patient (patient 13) experienced chills during
the second month of hospital-based treatment, which
disappeared spontaneously without any change in pre-
medication. After 4 months the pre-medication could
be discontinued without recurrence of symptoms.
After 12 months of home treatment, she experienced
temporary difficulties with the insertion of the infusion
needle.

Another patient (patient 7) experienced a possible
adverse reaction after 3 months of hospital-based
ERT, characterized by shortness of breath and tran-
sient hypoxaemia. The symptoms resolved after the
infusion was interrupted. No signs or symptoms
developed after restarting of the infusion. The infusion
rate was reduced during subsequent infusions and
increased again to the normal rate at a later stage with-
out recurrence of side-effects.

Repetitive technical problems, such as the failure to
achieve intravenous access, were not reported in any
of the patients receiving home therapy.

Compliance and patient satisfaction

In one MPS IH patient (patient 1), ERT was discon-
tinued after 2 months of home treatment because of
relentless neurological deterioration. All other 12
patients still receive ERT at home (median period of
home therapy 22 months, range 12–35).

A high level of satisfaction was reported by all
parents and patients during the visits at the outpatient
clinic. This included feelings of comfort regarding
safety and the advantages of more flexibility and
independence. Children and adults reported that home
treatment allows for better balance with their schooling
or work. The compliance was calculated on the basis of
the drug prescriptions, which were checked with the
patient or parent before delivery, allowing assessment
of the number of vials used over a certain period of
time. The compliance was estimated to be >95%.

Two adult MPS I patients (patients 13 and 16)
changed to a biweekly infusion scheme of 100 U/kg
after 44 and 22 months of ERT, respectively, based on
stability of the disorder in relation to the burden of the
frequent infusions. No clinical deterioration or increase
in urinary GAGs was observed within 6 months of
follow-up. In three patients (patients 8, 13 and 14) the
rate of infusion was increased to 100 ml/h after they had

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**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th>ID</th>
<th>Phenotype</th>
<th>Age at initiation of ERT (years)</th>
<th>Months of ERT at the hospital</th>
<th>Months of ERT at home</th>
<th>Anti-rIDUA IgG antibodies</th>
<th>Complication/months after initiation of ERT</th>
<th>Person performing procedure</th>
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*aIgG antibodies: (++), titre >1/500; (+), titre >1/32 and <1/500; (−), titre <1/32; n.d., not determined.*
been receiving ERT for more than one year. No side-effects were observed.

Discussion

Our study shows that ERT can be satisfactorily and safely administered at home in both children and adults with MPS I. More than 1000 home infusions did not result in any infusion-related reaction or prolonged technical difficulties.

In our cohort, only two patients experienced an infusion-associated reaction during the initial hospital-based ERT period. None of the patients experienced an infusion-associated reaction after 3 months of ERT. In two previous studies no correlation between clinical side-effects and the induction of anti-rIDUA antibodies was detected (Kakkis et al 2001; Wraith et al 2004). In a placebo-controlled trial similar incidences of infusion-associated reactions were reported in the placebo and treatment group (Wraith et al 2004). Almost all patients in our study developed IgG antibodies towards rIDUA, which seems not to be associated with significant infusion-associated reactions. In our opinion, therefore, the presence of antibodies should not exclude the initiation of home treatment in patients with MPS I. This differs from the situation in Gaucher and Fabry diseases. While in patients with Gaucher disease only a minority (approximately 13%) of patients develop IgG antibodies, seroconversion is associated with a higher incidence of adverse events (Rosenberg et al 1999; Starzyk et al 2007). In Fabry disease the majority of male patients develop IgG antibodies towards rIDUA, which seems not to be associated with significant infusion-associated reactions. In our opinion, therefore, the presence of antibodies should not exclude the initiation of home treatment in patients with MPS I. This differs from the situation in Gaucher and Fabry diseases. While in patients with Gaucher disease only a minority (approximately 13%) of patients develop IgG antibodies, seroconversion is associated with a higher incidence of adverse events (Rosenberg et al 1999; Starzyk et al 2007). In Fabry disease the majority of male patients develop IgG antibodies towards rIDUA, which seems not to be associated with significant infusion-associated reactions. In our opinion, therefore, the presence of antibodies should not exclude the initiation of home treatment in patients with MPS I.

In MPS I, most adult patients with Fabry or Gaucher disease are indeed able to perform the whole procedure by themselves.

Follow-up of MPS I patients in our centres is scheduled every 3 months, allowing for evaluation of the practical aspects of home treatment and the efficacy of treatment. All patients who transferred ERT to their home setting feel completely satisfied with the new situation. As in patients with Fabry disease, the compliance is very high (Linthorst et al 2006).

Finally, cost reduction might be another advantage of home treatment. In Gaucher disease, cost reduction was previously reported to be 90% of infusion-related costs when a three-times-a-week schedule was applied (Zimran et al 1993). However, this is not the case in MPS I with an ERT dosage frequency of once a week. We estimated cost reduction to be only £120 per month per patient in the Netherlands, which, compared to the costs of the recombinant enzyme, is negligible.

Legal aspects of intravenous home treatment will vary between different countries. In the Netherlands, patients, relatives and caregivers are allowed to give intravenous medication at home after completing an extensive educational programme and after competence has been assessed by a registered professional. The procedure, completion of the procedure, assessment of competence and the fact that potential complications and legal issues have been discussed and understood need to be clearly documented in the patient’s chart. From that moment, the competent

allows for education of the patient or parent and the arrangement of an adequate home setting.

All children in our study received a PAC. Unfortunately, one child suffered from a PAC infection. After its removal, no new PAC was inserted. Supplying lifelong intravenous treatment through a PAC implies a significant risk of infection, such as reported for patients with congenital coagulation disorders (McMahon et al 2000). However, creating peripheral venous access in children can be difficult because of the lack of cooperation and the small vessel size. In children, a PAC may ameliorate the burden of the high-frequency intravenous treatment (Crowley 2003). Parents should be extensively educated about the proper use of a PAC and the signs of infection or malfunction.

Creating peripheral intravenous access might also be difficult in adult patients with MPS I owing to the underlying disorder with multiple contractures and deformity of the extremities. In one adult MPS IS patient in our study this indeed hampered the transfer to home therapy. Moreover, the concomitant morbidity results in a high proportion of patients who require assistance at home. In contrast to our experience in MPS I, most adult patients with Fabry or Gaucher disease are indeed able to perform the whole procedure by themselves.

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person is legally responsible for this medical procedure. A checklist, such as proposed by Dobson, might facilitate the procedure (Dobson 2001). It is important to stress that extensive education, monitoring of the treatment and feedback by an experienced team consisting of the treating specialist, a general practitioner and a home nurse are obligatory to make home therapy a success.

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References


