Home treatment for Fabry disease: practice guidelines based on 3 years experience in The Netherlands

Gabor E. Linthorst¹, Anouk C. Vedder¹, Els E. Ormel¹, Johannes M. F. G. Aerts² and Carla E. M. Hollak¹

¹Internal Medicine/Clinical Haematology, ²Department of Biochemistry, Academic Medical Centre, Amsterdam, The Netherlands

Abstract

Introduction. Recently, chronic supplementation with α-galactosidase A (αGal A) has been approved as a treatment modality for Fabry disease. The aim of the current study was to investigate the feasibility of home therapy for Fabry disease during a follow-up of >3 years and to make a proposal for practice guidelines.

Methods. Based on experience in previous clinical trials, an algorithm for home treatment eligibility was developed. The number of successful and uneventful infusions was recorded, as well as adverse and infusion-associated events. The presence and titre of recombinant human (rh)-αGal A antibodies were monitored every 3 months.

Results. Thirty of the 36 patients eligible for home treatment received a total of 1418 infusions at home (median 44 infusions, range 1–108), between March 2001 and July 2005. Mean age was 44.7 years (17–71). Seventeen patients receiving home treatment (57%) were male. The majority of patients (27 out of 30, 90%) undergoing home treatment received 0.2 mg/kg agalsidase α or β. Six male patients developed an infusion-associated event, of which three developed these at home. All patients with an infusion-associated event were anti-rh-αGal A IgG positive at 3 months, but three patients with rh-αGal A antibodies did not develop side effects. Antibody titres between these patients did not differ. None of the events was life-threatening or necessitated urgent admission.

Conclusion. Home treatment with rh-αGal A for Fabry disease with 0.2 mg/kg for males and both 1.0 and 2.0 mg/kg for females is feasible and safe, and reduces both the burden related to chronic intravenous therapy and health care costs. Whether this can also be applied for male patients treated with 1.0 mg/kg has not yet been determined.

Keywords: non-diabetic renal diseases; treatment
available in Europe. These preparations are used in clinical practice at two different dosages (0.2 and 1.0 mg/kg, respectively). Direct comparison of the two products from the phase II/III clinical trials is hampered by the differences in design and dosing regimens [6].

In clinical studies with both preparations, a high prevalence (50–90%) of occurrence of IgG antibodies to rh-αGal A in male (and rarely female) patients has been reported [3,4,7]. These antibodies may lead to infusion-associated adverse events, such as fever and chills. The aim of the current study was to investigate the pros and cons of home therapy for Fabry disease during a 2 year period and to make a proposal for practice guidelines. This study was not meant to document which enzyme preparation is best suited for home treatment, but rather to establish the conditions under which home treatment would be safe and feasible. The protocol for home treatment is part of an ongoing clinical trial concerning a head to head comparison of agalsidase α (Replagal, TKT Inc., Cambridge, MA) and agalsidase β (Fabrazyme, Genzyme Corp., Cambridge, MA) at a dose of 0.2 mg/kg.

Patients and methods

**Patients**

All patients attended the Lysosomal Storage Disease Out-patient Clinic at our hospital. Patients had a confirmed diagnosis of Fabry disease either by reduction of enzyme activity (in males) or by mutation analysis of the αGal A gene (in females). All patients (except one) were 18 years or older. Patients were treated with agalsidase α at a dose of 0.2 mg/kg or agalsidase β at a dose of 0.2 or 1.0 mg/kg. The choice of these treatments is part of another clinical study [8]. None of the patients had received a kidney transplant or was using any corticosteroids.

### Table 1. Scheme for infusion rate and antibody analysis for patients with different treatment strategies

<table>
<thead>
<tr>
<th></th>
<th>Male patients</th>
<th>Female patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2 mg/kg</td>
<td>1.0 mg/kg</td>
</tr>
<tr>
<td><strong>Infusion volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(diluted in 0.9% NaCl)</td>
<td>100</td>
<td>500 (250)</td>
</tr>
<tr>
<td><strong>Infusion scheme</strong></td>
<td>150 ml/h</td>
<td>50 ml/h increasing every 30 min to 100, 150, 250.</td>
</tr>
<tr>
<td><strong>Home treatment feasible?</strong></td>
<td>Yes</td>
<td>Probable, under investigation. ~3 h (if IgG is negative after 12 months, decrease to 90 min)</td>
</tr>
<tr>
<td><strong>Infusion time</strong></td>
<td>40 min</td>
<td>3 h (if IgG is negative after 12 months, decrease to 90 min)</td>
</tr>
<tr>
<td><strong>No. of infusions in hospital</strong></td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td><strong>IgG antibody analysis</strong></td>
<td>Every month, when on home treatment, every 3 months</td>
<td>Every month, when on home treatment, every 3 months</td>
</tr>
</tbody>
</table>

For all subjects, if an adverse event occurs, the next infusion is to be carried out in hospital in order for the event to be witnessed. The next infusions should be with premedication (see Figure 1). Home infusions are only to be continued after two event-free infusions.

*Excluding the time needed to wash the lines with NaCl after infusion is finished.

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**Protocol for home treatment**

The rationale of this protocol was based on the following observations: infusion-associated events were correlated with the presence of rh-αGal A antibodies [7]. Patients were most likely to develop these antibodies during the first 3–6 months of treatment [3,4]. Only male patients were believed to develop antibodies, since they often do not express any αGal A protein at all and therefore will generate an immune response towards rh-αGal A. Infusion-associated reactions in patients treated in our hospital did not occur during the following infusions when they were given 5 mg dexamethasone orally 1 h before infusion [7].

A detailed protocol on infusion guidelines is listed in Table 1. The accompanying algorithm is shown in Figure 1. Patients are trained to prepare the infusions according to the manufacturer’s recommendations and learn to create i.v. access using a butterfly needle during the first infusion in our hospital. Patients were only allowed to continue infusions at home once they showed that they were able to prepare and administer the infusions accurately. If so, female patients, with proven residual enzyme activity, treated with either 0.2 or 1.0 mg/kg, are able to continue their infusions at home. Male patients treated with a dose of 0.2 mg/kg are allowed to continue treatment at home after they have received the first 10 infusions in the hospital. If a patient develops an infusion-associated event during in-hospital treatment, premedication is given at the next infusions.

Patients receive stock vials for 3 months, which they store in a separate container in their own refrigerator. Following transition to home treatment, patients are required to perform five infusions at home during office hours, in case they require assistance with applying venous access. After this, patients are free to determine the time of infusion. In addition, patients are instructed to report every reaction that occurs during or after an infusion. If these reactions are considered to be possibly related to the rh-αGal A administration, patients are required to have their next infusion in a hospital (not necessarily ours) so that the adverse event can be witnessed. In cases where a local hospital is used, the local general practitioner and/or local treating specialists are contacted to explain the procedure. Patients treated
at home are not routinely prescribed rescue medication (such as corticosteroids, adrenalin or antihistamines).

Adverse events, infusion-associated reactions and complications.

Infusion-associated events were defined as fever, chills or other reactions that occurred during or within 4 h after the administration of rh-2Gal A. Patients who developed a decrease in blood pressure or difficulty breathing were checked by IgE analysis, to rule out an anaphylactic reaction to the treatment product (either agalsidase α or β). Adverse events were events that occurred 4 h after administration or during any other time between two infusions. Complications were defined as events that occurred during home treatment that normally would not have occurred when treated in a hospital.

Premedication

Standard premedication is not given to the patients. Patients who developed rigours and/or fever after an infusion were treated with 5 mg dexamethasone orally 1 h before the next infusion. The infusion rate is not changed. Patients should have at least two event-free infusions in the hospital before they can continue home treatment. Treatment with 5 mg dexamethasone is continued for 6 months, after which the dose is tapered by 1 mg every two infusions. If the infusion-associated event recurs, the dose is increased to the lowest dose on which the event did not occur or is increased to 5 mg. This dose is continued for 6 months, after which tapering can be reconsidered. An algorithm for start and tapering of premedication with dexamethasone is shown in Figure 2.

Determination of β-Gal A antibodies

A detailed description of the enzyme-linked immunosorbent assay (ELISA) for determination of 2Gal A antibodies has been published elsewhere [7]. Briefly, 96-well ELISA plates (Nunc, Maxisorp, Denmark) were coated overnight at room temperature with agalsidase α (Replagal, TKT Inc.) or agalsidase β (Fabrazyme, Genzyme Corp.). Serial dilutions of serum taken at 3 month intervals are incubated after extensive washing and blocking the plate for 1 h with 4% gelatin. For detection of antibodies, peroxidase-labelled goat anti-human IgG antibody is used. The antibody titre was determined by the maximum dilution at which the post-exposure serum had an absorbance at least twice that of the baseline sample of that patient at the same dilution.

Results

Patients

Of the 39 patients [22 (56%) male] who receive or have received enzyme supplementation therapy, 36 were eligible for home treatment. Three patients had not yet finished the protocol-required period of in-hospital infusions and therefore were not eligible. A total of...
30 patients (86% of eligible patients) administered treatment at home, without any medical supervision. Of the six patients not on home treatment, five were unwilling to carry out the procedure and one received his treatment during dialysis. Between March 2001 and July 2005, these patients received a total of 1418 infusions at home (median 44 infusions, range 1–108). Mean age was 44.7 years (17–71). All 18 male patients on home treatment received 0.2 mg/kg agalsidase \( \alpha \) or \( \beta \). Three female patients received 1.0 mg/kg agalsidase \( \beta \) and the remaining 10 females on home treatment received 0.2 mg/kg agalsidase \( \alpha \) or \( \beta \).

Infusion-associated events, adverse events and complications

A total of six patients developed an infusion-associated event, of which four occurred during a hospital infusion (see Table 2). No patient developed an anaphylactoid reaction. All patients with an infusion-associated event were male. In all cases, chills, followed by fever, was the main symptom. Hypotension did not develop in these patients. Patient 1 developed these symptoms during infusion 6. He refused to have his follow-up infusions done at the hospital and shortly thereafter decided to discontinue treatment due to lack of motivation. Patient 2 developed chills 1 h after start of infusion 10, but had erroneously infused himself at double the infusion rate (this was considered to be a complication). His next infusions (at the prescribed infusion rate) were unremarkable. Patient 3 developed chills 1 year after start of treatment during a home infusion. His next infusion was observed in the hospital and the symptoms recurred. He was treated with dexamethasone 5 mg orally before infusion, after which he had two event-free infusions in the hospital and he subsequently continued treatment at home. Patient 4 developed chills after the tenth infusion at the hospital shortly after arriving home (~90 min after start of the infusion). Per protocol, the next two infusions (11 and 12) were performed at his local hospital, without any adverse events. Subsequently, he continued treatment at home, without any further problems. Patient 5 and 6 developed chills at infusion 9 and 5, respectively, while receiving their infusion in the hospital. They were treated with dexamethasone.

Table 2. Characteristics of patients with an infusion-associated reaction

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Infusion number (months)</th>
<th>Treatment</th>
<th>Time to IgG+ (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 (3)</td>
<td>Agalsidase ( \alpha ) (Replagal) 0.2 mg/kg</td>
<td>3</td>
<td>Discontinued treatment for personal reasons</td>
</tr>
<tr>
<td>2</td>
<td>10 (5)</td>
<td>Agalsidase ( \beta ) (Fabrazyme) 0.2 mg/kg</td>
<td>3</td>
<td>Single occurrence, no premedication needed</td>
</tr>
<tr>
<td>3</td>
<td>25 (11)</td>
<td>Agalsidase ( \beta ) (Fabrazyme) 0.2 mg/kg</td>
<td>3</td>
<td>Pre-treatment with dexamethasone 5 mg, recurrence of adverse events upon tapering of dexamethasone dose</td>
</tr>
<tr>
<td>4</td>
<td>10 (5)</td>
<td>Agalsidase ( \alpha ) (Replagal) 0.2 mg/kg</td>
<td>3</td>
<td>Single occurrence, no premedication needed, subsequently tapered and discontinued</td>
</tr>
<tr>
<td>5</td>
<td>9 (4)</td>
<td>Agalsidase ( \alpha ) (Replagal) 0.2 mg/kg</td>
<td>3</td>
<td>Pre-treatment with dexamethasone 5 mg, subsequently tapered and discontinued</td>
</tr>
<tr>
<td>6</td>
<td>5 (2)</td>
<td>Agalsidase ( \beta ) (Fabrazyme) 0.2 mg/kg</td>
<td>3</td>
<td>Pre-treatment with dexamethasone 5 mg</td>
</tr>
</tbody>
</table>
5 mg orally 1 h before an infusion, and continued treatment at home after two event-free infusions in the hospital. Patient 5 also noted erythema of the face the day after an infusion, which was considered an adverse event. The erythema slowly resolved during the rest of the day. Over a period of months, this event regressed.

Apart from one infusion-associated event due to an erroneously high infusion rate, no other complications occurred because of treatment at home. Minor discomfort occurred only if more than one attempt was needed to establish venous access. No infections or phlebitis occurred. Mild bruising was reported, but never required patients to seek medical attention.

**Premedication and tapering**

Four patients of the six that had an infusion-associated event have been treated with 5 mg dexamethasone, which suppressed the events in all. No other premedication was required. In two patients, the dosage was slowly tapered and they currently no longer require premedication. One patient has not yet reached the 6 month period after which tapering is allowed. One patient (patient 3) had recurrence of his infusion-associated events when the dexamethasone dose was 1 mg. His next infusion was performed with 2 mg dexamethasone, but his symptoms still occurred. His dose was increased to 5 mg and his next infusions were event free.

**Antibody analysis**

All patients with infusion-related events had developed IgG antibodies at month 3 of treatment (after six infusions). Interestingly, the development of adverse reactions did not always coincide with the emergence of antibodies, nor did it coincide with the IgG titre [7]. However, in contrast, not all patients with IgG antibodies had infusion-associated events. Three male patients also developed IgG antibodies (all tested positive at month 3) but remained without infusion-associated events during the studied period (treatment periods 2.5, 3 and 4 years, respectively). The anti-agalsidase titres of these patients were in the same range as in patients with an infusion-associated event. Since no patient developed an anaphylactoid reaction, IgE antibodies were not analysed.

**Patient satisfaction and compliance**

Most (30 out of 36) patients eligible for home treatment preferred to transfer their treatment to their home. In particular, patients who were in full-time work or attending school appreciated the possibility of administering the infusions at a self-determined time. Compliance was estimated based on the registration of the number of vials used during a certain period of time. On the basis of this, we estimate that >95% of infusions were actually performed. The only problem encountered at home was difficulties in establishing venous access. In a few cases, this required the help of the general practitioner. One patient was again instructed in establishing venous access at our hospital because of repeated failures to do so at home. In none of the patients who had trouble with establishing venous access once or repeatedly was home treatment discontinued for this reason.

**Discussion**

Following the success of home treatment in patients with Gaucher disease, we studied this approach in Fabry disease. We show that in male patients treated with 0.2 mg/kg, and female patients at doses of both 0.2 and 1.0 mg/kg, home treatment is feasible and safe.

Although Fabry disease has similarities to Gaucher disease with respect to its underlying defect and therapeutic approach, the issues regarding home therapy are very different. The most important issue is the more frequent occurrence of infusion-associated events in Fabry disease, during treatment with rh-αGal A. This is due to the emergence of anti-rh-αGal A antibodies, which occurs in 50–90% of male patients usually during the first 12 months of treatment, compared with only 12% in Gaucher disease [3,4,9]. In our study, all patients who developed an infusion-associated event had IgG antibodies. However, not all patients with anti-agalsidase IgG antibodies developed an infusion-associated event. Therefore, screening for antibody formation in male patients may be useful to identify patients at risk for infusion-associated events, but does not predict if such an event is likely to occur. In another study, we showed that the IgG titre does not correlate with the occurrence or severity of an infusion-associated event [7].

Most patients develop the infusion-associated events during the first 6 months of treatment, a finding that is substantiated in this study. Four out of six patients developed an infusion-associated event during the first 10 infusions. One patient had a self-induced event due to an increased infusion rate, and one patient had their event ~1 year after start of therapy. This patient had already developed anti-agalsidase IgG antibodies at month 3 and it is unclear as to why he developed infusion-associated events after 1 year. The fact that in another study prolonged treatment with 1.0 mg/kg agalsidase β reduced antibody titres in more than half of the patients indicates that these adverse events will not recur while on home treatment [10].

Though patient satisfaction and cost reduction were not specifically addressed, home treatment has substantial positive effects on both issues, as has been demonstrated by others [5]. Temporary difficulties with establishing venous access in a few patients did not lead to cessation of home treatment. We are currently studying the feasibility of safe administration of 1.0 mg/kg agalsidase β in male patients at home,
following the algorithm shown in this study. In conclusion, using our criteria, home treatment with rh-αGal A for Fabry disease with 0.2 mg/kg in males and both 1.0 and 0.2 mg/kg in females is feasible and safe, and reduces both the burden related to chronic intravenous therapy and health care costs.

Acknowledgements. This study was supported financially by the Dutch Medical Insurance Board and was made possible by the cooperation of the Dutch Fabry patients.

Conflicts of interest statement. G.E.L., A.C.V. and C.E.M.H. have been involved in clinical trials with agalsidase β. The authors do not serve as consultant to, hold stock in or receive money from Genzyme Corp. or TKT Inc.

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Received for publication: 4.2.05
Accepted in revised form: 20.9.05