A revised home treatment algorithm for Fabry disease: Influence of antibody formation

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A B S T R A C T
Background: Enzyme replacement therapy for Fabry disease, consisting of biweekly infusions, interferes daily life. Home treatment proved beneficial. We evaluated a previously reported home treatment algorithm aiming to shorten the period of in-hospital infusions, while ascertaining patient safety.

Methods: Retrospective analysis on clinical records of treated Fabry patients. Potentially predictive factors for infusion associated reactions (IARs) were studied: agalsidase antibodies, agalsidase product and dose, FOS-SSI scores, and GLA activity and mutation. A questionnaire evaluated patient satisfaction and compliance.

Results: Seventy-nine patients were included (41 males, 46% agalsidase antibody positive (AB+)). 85% received home treatment. Home treatment complications were erroneous fast infusion rates (n=4) causing IARs and, rarely, venous access problems. The single SAE was unrelated to home treatment. IgG antibody status was significantly associated with IARs (80% vs. 26% p-value<0.01). Negative antibody status did not preclude IARs. Except for three AB+ patients, all first IARs occurred within 13 infusions. IARs occurred more frequently in patients using agalsidase beta 1.0 mg/kg/eow than agalsidase alpha or beta 0.2 mg/kg/eow, but the time to first IAR did not differ between groups. Four AB+ males experienced IARs after a dose increase. Compliance between home and in-hospital treatment was similar. Most patients preferred home treatment.

Conclusion: In this study home therapy for Fabry disease was safe and improved patient satisfaction. We propose a revised algorithm which allows safe home-treatment in all male patients after 13 instead of 26 infusions, irrespective of ERT preparation or dose. Furthermore, AB+ patients with dosage increase may experience new or increased IARs, necessitating in-hospital observations.

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1. Introduction

Fabry disease (OMIM 301500) is a rare X-linked lysosomal storage disorder caused by deficiency of the lysosomal enzyme α-galactosidase A (αGal A) [1]. Since 2001 enzyme replacement therapy (ERT) is available as a treatment for Fabry disease. In the European Union there are two enzyme preparations available (agalsidase alpha at a dose of 0.2 mg/kg/every other week (eow) and agalsidase beta 1.0 mg/kg/eow). In the USA only agalsidase beta received marketing approval. ERT in Fabry disease has to be given life-long, biweekly and irrespective of ERT preparation or dose. Furthermore, AB+ patients with dosage increase may experience new or increased IARs, necessitating in-hospital observations.

Home treatment is preferred by Fabry disease patients [6,7], has a positive effect on quality of life [8] and reduces health care costs.

In Fabry disease infusion associated reactions (IARs) occur frequently and it is suggested that these are for a large part correlated to the formation of antibodies towards the infused enzyme [9]. In the pivotal trials, 57% of the males on agalsidase alpha [10] and 88% on agalsidase beta [11] demonstrated anti-agalsidase antibodies (from now on referred to as AB+). While most of the IARs appear mild and consist mainly of fever and chills, their occurrence may hamper the establishment of a safe home treatment environment. In addition, rare cases of anaphylactic reactions towards agalsidase beta have been described [12–14]. It is therefore of importance to gain insight into who are the patients at risk to develop IARs.

A previous study in 2006 by our group established an algorithm to aid in the decision when patients could safely transfer from in hospital to home treatment [3]. The aim of this study was to evaluate the safety of this algorithm and to shorten the period of in-hospital infusions. Therefore, we explored factors predictive for the occurrence of IARs and possible differences in severity of IARs in the in-hospital or in the at home treated patients (including anti-agalsidase antibodies, type or dosage of enzyme therapy, αGal A activity, αGal A mutation and baseline FOS-SSI scores). In addition we studied the (self-reported) compliance of at-home versus in-hospital treatment.

Abbreviations: AB, antibodies; αGal A, alpha-galactosidase A; FD, Fabry disease; ERT, enzyme replacement therapy; IARs, infusion associated reactions; SIARs, serious infusion associated reactions; SAE, serious adverse event.

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2. Patients and methods

2.1. Patients

All patients had a confirmed diagnosis of Fabry by reduced αGal A activity (in males), or by mutation analysis (in males and females). Patients were treated with agalsidase alpha 0.2 mg/kg/eow, with agalsidase beta 0.2 mg/kg/eow (as part of a different study [15]) or agalsidase beta 1.0 mg/kg/eow. Due to a recent worldwide shortage of agalsidase beta some patients switched to a lower dose of agalsidase beta (0.5 or 0.25 mg/kg/eow) or to agalsidase alpha [16]. All Dutch Fabry patients who were treated with ERT either in hospital or at home were included, only excluding those who were treated with ERT before home-therapy was available or who were part of an ongoing clinical trial.

As stated in the earlier protocol home therapy was initiated in those patients physically and mentally capable to administer ERT and with event free final two infusions [3]. Patients (or family member/friend) were trained to prepare the infusions according to the manufacturer’s recommendations and learn to create intravenous access using a butterfly needle during the infusions in our hospital (no anesthetics were used). Patients were only allowed to continue infusions at home once they (or a family member/friend) showed that they were able to prepare and administer the infusions accurately. Following transition to home treatment, patients were required to perform 5 infusions at home during office hours, in case they required assistance with applying venous access. When patients were not able to establish venous access but did prefer home therapy or when infusion duration was above 90 min, nursing care at home was arranged.

According to the Dutch law this study does not require formal approval by our hospital’s Ethical Committee because of the retrospective and non-interventional nature of the study.

2.2. Methods

We reviewed clinical records from July 1999 to October 2011 of ERT treated patients to investigate the occurrence of IARs. A questionnaire was sent to all ERT treated patients in September 2011. The questionnaire contained questions on treatment setting (home/hospital, help of a nurse, (reason of) change of treatment location), compliance (median number and reason of missed infusions per year), establishment of venous access (percentage of successful venous access at once, median number of failed attempts), patient satisfaction (advantages and disadvantages, suggestion for improvements), infusion associated reactions (adverse event type, date, recurrence rate, what did you do when an adverse event occurred) and premedication (type, date, tapering).

Potential predictive factors for the occurrence of infusion associated reactions were explored. The following factors were identified: anti-agalsidase antibody status (AB) and time of emergence of AB (IgG and IgE), GLA mutation, baseline FOS-MSSI and leukocyte antibody status (AB) and time of emergence of AB (IgG and IgE). Reactions were explored. The following factors were identified: adverse event type, date, recurrence rate, what did you do when an adverse event occurred). We devalued by neutralization assay only, as described elsewhere [17]. IgE analysis was requested if a patient developed a (possible) anaphylactic reaction and was carried out by the manufacturer of the enzyme preparation used for that particular patient.

2.3. Infusion associated reactions (IARs)

All symptoms occurring during or up to 4 h after ERT infusions were considered an IAR. Serious IARs were IARs which needed medical treatment (i.e. medication: paracetamol, tavegil, dexamethasone, or lowering of infusion rate). We defined IARs as a serious adverse event (SAE) when life threatening or requiring hospitalization or intervention or resulting in significant disability or death. A complication of home treatment was defined as an IAR that occurred during home treatment but unlikely to have occurred during in-hospital treatment.

2.4. Premedication

Patients with a witnessed IAR, suggestive for an IgG antibody mediated response, were treated with 5 mg dexamethasone orally 1 h before the next infusion. After 6 months tapering was attempted reducing the dose by 1 mg every two infusions. If an IAR re-occurred, the dose was increased to the lowest dose at which no IAR occurred. This dose was carried on for 6 months after which tapering was again reconsidered [3].

2.5. Agalsidase antibodies

Initially, serum samples were evaluated for the presence of anti-agalsidase IgG antibodies by ELISA [9] and/or for neutralizing activity every three months during the first year of therapy and yearly thereafter for males, and yearly for females. As all antibody positive (AB +) patients demonstrated neutralizing activity [9] subsequent analyses were carried out by neutralization assay only, as described elsewhere [17].

3. Results

3.1. Patient characteristics

Of the 86 patients eligible for this study, 79 were included, of which 8 aged below 18 years (see Table A for patient characteristics). We excluded seven patients; 5 children were included in an ongoing clinical trial with agalsidase [18], 1 patient stopped treatment before home treatment was available, and 1 patient received medical care in another hospital.

3.2. Home treatment

Eighty-five% (n = 67 of 79) of patients received home treatment. Of the patients on home treatment, 45 (67%) received treatment without supervision of a medical professional (of which n = 9 received help from a friend or family member) and 22 (33%) had (in some cases temporarily) assistance by a specialized nurse. Five patients switched from home treatment to in hospital treatment (in 3 because of problems with venous access and in 2 because of dosage increase). Of the 11,120 infusions 76% (n = 8399) was administered at home. Of all home infusions 89% (n = 7480 infusions) were performed without any medical assistance.

In line with the 2006 Dutch home infusion algorithm [3], females transferred to home treatment as soon as they were able to adequately perform administration without medical assistance (median in hospital 3 infusions 4, range 1 – 66). Males transferred to home treatment depending on ERT dose; after a median of either 10 (range 2 – 32, (agalsidase beta and alpha 0.2 mg/kg/eow)), or 40 (range 13 – 274) in hospital infusions (agalsidase beta 1.0 mg/kg/eow). Six males started home treatment before the algorithm was adopted, which resulted in earlier initiation of home therapy and thus a reduced number of in-hospital infusions (< 26 infusions).
3.3. Anti-agalsidase antibodies (AB)

Of the males 46% developed anti-agalsidase AB (AB+), which all had cGal A neutralizing effects in vitro. All AB+, but one, seroconverted after 3 months of ERT, of 1 patient data concerning timing of seroconversion was missing. None of the females developed antibodies. Antibody negative patients (AB− males) remained negative despite dose increases or treatment preparation changes (e.g. from agalsidase beta 0.2 mg/kg/eow to 1.0 mg/kg/eow (n=2) or agalsidase alpha 0.2 mg/kg/eow to agalsidase beta 1.0 mg/kg/eow (n=1)). However, antibody titres increased in 4 of 9 AB+ patients (males) transferring to a higher dose of ERT.

3.4. Infusion associated reactions (IARs)

3.4.1. Agalsidase IgG positive patients

Eighty-nine% (n=17 of 19) of the AB+ males reported IARs (see Table B). Of these 17 patients, 5 were treated with agalsidase alpha 0.2 mg/kg/eow, 3 with agalsidase beta 0.2 mg/kg/eow and 9 with agalsidase beta 1.0 mg/kg/eow. The pattern of IARs was not consistent between individual patients. Some experienced recurrent chills sometimes coinciding with fever, while others experienced urticaria, skin rash or aspecific gastro-intestinal complaints. Also a few patients reported shivers or a sensation of fever which could not be objectified by a doctor or nurse. None of these IARs were considered to be serious adverse events. In 14 patients the ensuing infusions were managed by premedication (dexamethasone 5 mg, clemastine 1 mg, paracetamol 1000 mg) or by reducing infusion rate.

We wondered whether IARs of AB+ were distinguishable from AB− patients by a recurrent nature. Indeed, 12 of the 17 AB+ patients experienced recurrent IARs (1 patient missing data). The early initiation of dexamethasone in one AB+ patient might have masked the reoccurrence of IARs.

All, but 3, AB+ patients, developed the first IAR within 13 infusions of ERT (median 10 weeks, range 5–83). One patient developed his first IAR (chills) after 42 weeks, 1 experienced chills and fever after 57 weeks and 1 patient experienced a rash after 88 weeks of treatment. These IARs were managed with premedication following the infusion. In 7 patients the first IAR happened at home (first IAR occurrence after 10 weeks (n=2), 15, 23, 27, 58 and 83 weeks) of which none were considered an SAE. Four of these patients started home therapy early (i.e. before 26 weeks) because the algorithm was implemented afterwards. Time to first adverse IAR did not differ between patients treated with agalsidase alpha or beta, or preparation dose.

Four out of nine AB+ patients in which the dose was increased from 0.2 mg/kg/eow agalsidase alpha (n=1) or agalsidase beta (n=3) to agalsidase beta 1.0 mg/kg/eow experienced increased or new IARs. These included a swollen tongue and urticaria during the second infusion (n=1) after switch; or chills during the third (n=2) and eighth infusion (n=1) after switch, respectively. None of the AB− male patients (n=3) in whom the dose was increased developed subsequent antibodies or IARs.

In three patients IgE analysis was performed, with clinical suspicion for a histaminergic reaction in only one patient (swollen tongue and urticaria, no hypotension). In all three patients IgE analysis was negative.

3.4.2. Agalsidase IgG negative patients

Twenty-six% (n=16 of 60) of the AB− patients (12 males) developed IARs (see Table B), which significantly differed from the AB+ patients (p<0.01). They were treated with agalsidase alpha 0.2 mg/kg/eow (n=6), with agalsidase beta 0.2 mg/kg/eow (n=3) and with agalsidase beta 1.0 mg/kg/eow (n=7). In contrast to the IARs of the AB+, the IARs were less frequent and tended to be milder. Similar to AB+ patients, IARs of most AB− patients were recurrent, but recurrence rate was much lower as compared to that of AB+ patients. Three AB− patients experienced IARs (chills, shivers and fever) in which a relation to IgG antibodies was considered. One male patient experienced chills and fever after 56 weeks of treatment (agalsidase beta 1.0 mg/kg/eow). For the next infusions he was pre-treated with dexamethasone (5 mg, clemastine 1 mg, paracetamol 1000 mg) or by reducing infusion rate.

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In three patients IgE analysis was performed, with clinical suspicion for a histaminergic reaction in only one patient (swollen tongue and urticaria, no hypotension). In all three patients IgE analysis was negative.
to contact the hospital after the occurrence of an IAR. 9 AB + patients did not mention IARs because they considered the symptoms too mild. The occurrence of the first IAR was unclear in these patients, as the IAR was mentioned in the questionnaire, but patients were unable to recall when this IAR had occurred. One patient developed a serious adverse event. During an infusion air was trapped in the infusion system and was already possibly partially infused upon discovery by the supervising nurse (patient received infusions at home by a specialist nurse). Because the patient complained of slight dyspnea she was taken to the emergency department of a local hospital. Here it was speculated that symptoms could have been caused by an air embolus, though no further additional examinations or treatment was performed and the patient was discharged 1 h later.

3.4.3. Other possible predictors for the development of serious IARs

We investigated whether alpha-galactosidase activity, baseline FOS-SSI score, GLA mutation type and ERT preparation or dose, were predictive for the occurrence of serious IARs (Table C). Sixteen (15 males) patients developed a serious infusion associated reaction (SIAR) which required medical intervention the same or the following infusion (dexamethasone only n = 5, dexamethasone in combination with clemastine or paracetamol n = 5, clemastine only or in combination with paracetamol n = 3, paracetamol only n = 1, lowering of infusion rate only n = 2). In total 16 patients experienced an SIAR (15 males), occurring at a median of 10.6 weeks (range 5.4–113). For these analyses only males were included. The SIAR + female (AB −) reported subjective sensations of fever, for which her infusion rate was diminished. Two SIAR + male patients were already using premedication before IARs occurred because they were included in a clinical trial.

There is a significant difference in the occurrence of SIARs between AB + and AB − male patients (p < 0.01). Alpha-galactosidase A activity was not predictive for the occurrence of serious IARs in males. Baseline FOS-SSI scores tended to be higher in the SIAR + males than the SIAR − males, but scores demonstrated significant overlap. GLA mutations were categorized in 4 groups: nonsense, missense, deletions/insertion and splice site mutations, while excluding splice site mutations (n = 1) and deletion insertions (n = 5) because groups were too small. The odds ratio for a missense mutation vs. nonsense mutation for the development of SIAR + was 0.23 CI (0.06–1.21) p = 0.08.

The odds for developing an SIAR was significantly higher for patients treated with agalsidase beta 1.0 mg/kg/eow vs. agalsidase alpha 0.2 mg/kg/eow: 10.7 (95% CI 2.1–54.7, p = 0.0044). There was no difference between agalsidase beta 0.2 mg/kg/eow vs. agalsidase alpha 0.2 (95% CI 0.3–16.6, p = 0.5) or agalsidase beta 1.0 mg/kg/eow vs. agalsidase beta 0.2 mg/kg/eow 5.0 (95% CI 0.7–35.5, p = 0.17).

### Table C

<table>
<thead>
<tr>
<th>Predictor</th>
<th>SIAR+</th>
<th>SIAR−</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of IgG antibodies</td>
<td>93.3%</td>
<td>6.7%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Alpha-galactosidase activity</td>
<td>1.39 (0–7.3)</td>
<td>2.72 (0–13.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>% lower limit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOS-SSI baseline</td>
<td>7.8 (−2.19)</td>
<td>3.0 (−22.22)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Mutation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missense</td>
<td>4 (22%)</td>
<td>18 (78%)</td>
<td>0.08*</td>
</tr>
<tr>
<td>Nonsense</td>
<td>6 (86%)</td>
<td>7 (14%)</td>
<td></td>
</tr>
<tr>
<td>Deletion/insertion</td>
<td>4 (80%)</td>
<td>7 (20%)</td>
<td></td>
</tr>
<tr>
<td>Splice site</td>
<td>4 (80%)</td>
<td>2 (50%)</td>
<td></td>
</tr>
<tr>
<td>ERT preparation/dose:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha 0.2 mg/kg/eow</td>
<td>3 (19%)</td>
<td>16 (81%)</td>
<td></td>
</tr>
<tr>
<td>Beta 0.2 mg/kg/eow</td>
<td>2 (40%)</td>
<td>5 (60%)</td>
<td></td>
</tr>
<tr>
<td>Beta 1.0 mg/kg/eow</td>
<td>10 (67%)</td>
<td>5 (33%)</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

* Missense vs. nonsense mutation.

b Agalsidase beta 1.0 mg/kg/eow vs. agalsidase alpha 0.2 mg/kg/eow.

### 3.5. Patient home treatment questionnaire for the evaluation of home treatment complications, compliance and patient satisfaction

A questionnaire was sent to 71 of the 79 patients of which 69 (97%) were returned. Of these patients 62 (90%) people started on home therapy. In the home treatment setting venous access was established by a medical professional in 29%, a family member in 16% or by patients themselves in 55%. Successful establishment at first attempt did not differ between home and hospital (90% range 1–100 at home vs. 95% 20–99 at the hospital, p = 0.4).

With a mean of 1.06 missed infusion per year at home (range 0–10) without medical assistance, 0.65 at home with medical assistance (range 0–5) and 0.73 in hospital (range 0–2) there was no difference in missed infusions (p = 0.39).

Four patients reported an IAR after erroneously infusing at a too high rate at home without medical supervision (2 chills, 2 rash) of which 3 patients were AB + and 1 was AB −. The following infusions were without IARs. These IARs were classified as a complication of home treatment as they might not have occurred during in hospital treatment or when performed under supervision of a nurse.

Freedom to determine date and time of infusion (59%), lack of need to travel (54%) and performing infusion in a private environment (61%) were the most reported benefits of home treatment. Most reported disadvantages were: absence of medical backup when experiencing difficulties (38%), problems establishing venous access (24%), compliance (21%) and infusion materials occupying a lot of space (17%).

### 4. Discussion

This study, based on long-term experience of a large Fabry cohort, confirms the safety of home treatment for Fabry disease, irrespective of agalsidase product or dosage. This enabled us to simplify the algorithm for home treatment of Fabry disease published in 2006 (Fig. A) [3]. Although earlier literature assumed [19] that home treatment improves therapy compliance, we found evidence that compliance of home treatment is equivalent to in hospital treatment.

Complications of home treatment were rare. Four patients administered agalsidase too fast, causing chills and rash, but these IARs were not serious and subsequent infusions were event free. In one patient on home treatment, air was discovered in the infusion system that had been partially already infused. While the event was considered an SAE, it occurred at home under supervision of a specialized nurse, and was therefore not deemed a complication of home treatment. While individual patients without supervision were equally successful as medical personnel in obtaining venous access, a few patients reported failed attempts up to 8 times. This is reflected by the high percentage of patients (38%) mentioning absence of medical backup as a drawback of home therapy. Therefore, in the revised algorithm we mandate patients to consult their general practitioner or the local ER when a maximum of four failed attempts are reached, for which a standard medical letter is made to facilitate rapid service.

To determine the safety of home treatment and optimize the home treatment algorithm we sought for predictive factors for the development of infusion associated events (IARs). Since agalsidase antibodies are implicated in the generation of infusion associated adverse events, we evaluated antibody status in all patients. Indeed, anti-agalsidase IgG antibodies were significantly associated with the occurrence of IARs and IAR that required medical intervention (SIARs). In addition, the AB − group experienced IARs that were mild and most often did not necessitate medical intervention. However, two AB − males demonstrated IARs comparable to what is observed in AB + patients (e.g. fever, chills, shivers), a finding also reported by others [20]. Therefore, antibody status was not fully predictive for the occurrence of serious IARs. Why some AB − patients develop similar IARs as AB + patients remains unclear.

We decided that a period of 6 months (13 infusions) is sufficient for a safe transfer to home treatment because this study showed
that IgG antibodies develop within 6 months of therapy (the majority within 3 months) and most IARs in the AB+ group occurred within this timeframe. This can be substantiated by literature [21]. Although the timing of a transfer to home treatment was based on IgG antibody status, the measurement of IgG antibodies was not implemented in the new algorithm for practice purposes: whenever a male patient with an unknown AB status presents with (serious) IARs within 6 months after start of therapy, we suggest that this patient should be regarded as AB+. Results of AB assessments are usually not readily available (if at all measurable in some centers). Nevertheless, measurement of antibodies is highly recommended since it can endorse or reject the use of pre-medication. In addition, this study shows that AB+ patients may be at risk to develop IARs following an increase in dose (0.2 mg/kg/eow to 1.0 mg/kg/eow). Therefore, AB+ patients who are subject to new dose increases (e.g. from 0.2 mg/kg/eow agalsidase alpha or beta to agalsidase beta 1.0 mg/kg/eow) should receive their first infusions in the hospital.

Similar to AB+ patients, more severely affected Fabry males (e.g. those with higher FOS-SSI scores) and those using agalsidase beta 1.0 mg/kg/eow were at higher risk of developing IARs. But again these factors were not fully predictive or IAR occurrence, as FOS-SSI scores were highly dispersed between patients and IARs also occurred on agalsidase alpha or agalsidase beta 0.2 mg/kg/eow. Subsequently, in the revised algorithm neither preparation nor dose is taken into account.

Finally, it comes to no surprise that the estimated treatment costs per year per patient are favorable for home treatment [22,23]. Costs for in-hospital treatment in The Netherlands are estimated to be € 10,712 (including infusion material, excluding agalsidase cost) versus € 4654 home treatment with medical assistance and € 260 for home treatment without medical assistance. In the Dutch situation where 85% of the studied patients receives home treatment, half a million euro is saved every year.

Our study is limited by as small sample size. We can by no means exclude the possibility that SAEs, especially severe IgE mediated reactions, could occur during home-therapy. So far, only seven cases of severe IgE mediated SAEs have been described with the use of agalsidase beta [12].

Given that approximately 2650 patients have been treated with agalsidase beta (personal communication from Genzyme), the chance of development of IgE mediated SAEs is less than 0.3%. Since most IARs occur during the first 6 months, especially in males, the chances will be even less. However, easy access to medical care needs to be provided as a general rule and protocols for management of IARs should be in place.

Another limitation of this study is its retrospective nature, relying on medical records and patient narratives during regular outpatient clinic appointments. To evaluate whether we missed any IARs in the medical records we attempted to evaluate IARs in the patient questionnaire. It appeared that patients had difficulties remembering frequency and timing of IARs and this may have caused underreporting. Only few IARs in females were not reported in the medical files (data not shown), of which none proved to be serious. Following the revision of the home treatment algorithm patients are now obliged to keep a detailed log on date of infusion, infusion duration, IARs, missed infusions and number of attempts needed to establish venous access.

In conclusion, this study endorses that home therapy for Fabry disease is safe and improves patient satisfaction with excellent compliance. Antibodies are significantly associated with (serious) IARs. Antibodies and most first IARs in the AB+ patients occur within 6 months after start of therapy. The revised algorithm deviates from the earlier algorithm: home-treatment can now safely be initiated in all male patients after 13 infusions instead of 26 infusions, irrespective of ERT preparation or dose. In addition, AB+ patients in whom ERT dose increased may experience new or increased IARs, necessitating in-hospital observations.

Authors’ contributions

BES performed acquisition, statistical analysis and interpretation of data, and drafting of the manuscript. SH performed acquisition of data and drafting of manuscript. GEL, CEMH participated in the design of the study, interpretation of the data and helped to draft the manuscript. FW revised the manuscript. All authors have read and accepted the manuscript.

Fig. A. New home treatment algorithm for agalsidase alpha and beta. Eligible for home treatment are those Fabry patients who are physically and mentally capable to administer ERT at home. Patients are mandated to keep a monitoring log on date of infusion, infusion duration, IARs, missed infusions and number of attempts needed to establish venous access. Patients are advised to consult their general practitioner or the local hospital for aid when they failed the establishment of venous access after four times.

Given that approximately 2650 patients have been treated with agalsidase beta (personal communication from Genzyme), the chance of development of IgE mediated SAEs is less than 0.3%. Since most IARs occur during the first 6 months, especially in males, the chances will be even less. However, easy access to medical care needs to be provided as a general rule and protocols for management of IARs should be in place.

Another limitation of this study is its retrospective nature, relying on medical records and patient narratives during regular outpatient clinic appointments. To evaluate whether we missed any IARs in the medical records we attempted to evaluate IARs in the patient questionnaire. It appeared that patients had difficulties remembering frequency and timing of IARs and this may have caused underreporting. Only few IARs in females were not reported in the medical files (data not shown), of which none proved to be serious. Following the revision of the home treatment algorithm patients are now obliged to keep a detailed log on date of infusion, infusion duration, IARs, missed infusions and number of attempts needed to establish venous access.

In conclusion, this study endorses that home therapy for Fabry disease is safe and improves patient satisfaction with excellent compliance. Antibodies are significantly associated with (serious) IARs. Antibodies and most first IARs in the AB+ patients occur within 6 months after start of therapy. The revised algorithm deviates from the earlier algorithm: home-treatment can now safely be initiated in all male patients after 13 infusions instead of 26 infusions, irrespective of ERT preparation or dose. In addition, AB+ patients in whom ERT dose increased may experience new or increased IARs, necessitating in-hospital observations.

Authors’ contributions

BES performed acquisition, statistical analysis and interpretation of data, and drafting of the manuscript. SH performed acquisition of data and drafting of manuscript. GEL, CEMH participated in the design of the study, interpretation of the data and helped to draft the manuscript. FW revised the manuscript. All authors have read and accepted the manuscript.
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None.

Ethical approval

According to the Dutch law this study does not require formal approval by our hospital’s Ethical Committee because of the retrospective and non-interventional nature of the study.

Competing interests

B.E. Smid once received a travel support from Shire. C.E.M. Hollak and G.E. Linthorst received reimbursement of expenses and honoraria for lectures on the management of lysosomal storage diseases from Genzyme Corporation, Shire, Actelion and Amicus Therapeutics. All honoraria are donated to the Gaucher Stitching, a national foundation that supports research in the field of lysosomal storage disorders. F.A. Wijburg has received honoraria for presentations and board meetings, travel expenses to meetings and honoraria for consultancy work from Genzyme Corp., Shire HGT and BioMarin and has received unrestricted educational grants and research grants from Genzyme.

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