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Home infusion program with enzyme replacement therapy for Fabry disease: The experience of a large Italian collaborative group

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ABSTRACT

Fabry disease (FD) [OMIM 301500] is an X-linked lysosomal storage disorder caused by a deficiency of the lysosomal enzyme alpha-galactosidase A, resulting in progressive multisystem accumulation of globotriaosylceramide (Gb3). Although the introduction of Enzyme Replacement Therapy (ERT) resulted in a variety of clinical benefits, life-long intravenous (IV) treatment with ERT with an every other week schedule, may interfere with daily life activities and impact on QoL. We report here a multicentric, observational, longitudinal data analysis on a large cohort of 85 Italian FD patients (45 males, 40 females) from 11 out of 20 Italian regions, who received a cumulative number of 4269 home infusions of agalsidase alfa. For the whole cohort, the average duration of home therapy was 1 year and 11 months (range 3 months–4 years and 6 months), and during this period, compliance to treatment (number of infusions performed vs scheduled) reached 100%. The EQ-5 VAS scale was administered to patients to evaluate the self-reported QoL, 58% of patients showing an increase of EQ-5 VAS score at follow up compared to baseline (home treatment start) or remaining stable. A mild increase of average disease severity, measured through Mainz Severity Score Index (MSSI), was found during hospital treatment ($p < 0,007$), while it remained stable between the first home therapy infusion and last follow up. Interestingly, 4 out of 7 (57%) patients, showing an improvement in FD-related clinical status after starting home

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therapy, had previously a sub-optimal compliance to treatment during the period of hospital treatment management. Only 4 adverse non serious reactions (0,093%) were reported totally in 2 patients during home treatment.

We conclude that home infusions in eligible patients with FD are safe, contribute to improve treatment compliance and therapeutic clinical outcomes, and may have a positive impact on self-perceived QoL.

1. Introduction

Fabry disease (FD) [OMIM 301500] is an X-linked lysosomal storage disorder caused by a deficiency of the lysosomal enzyme alpha-galactosidase A [E.C.3.2.1.22], resulting in progressive accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids (galabiosylceramide) in lysosomes within tissues and organs throughout the body. Reported incidence, ranging from 1 in 476,000 to 1 in 117,000 [1,2] in the general population, may underestimate the true prevalence: newborn screening initiatives have found a prevalence of the disease as high as 1 in ~3100 newborns in Italy [3]. Due to the X-linked inheritance, the disease primarily affects males, but females can be affected as well [4–7] and both sexes can display symptoms during childhood [8–12]. The most frequent symptoms complained by pediatric patients with FD are episodes of recurrent pain in hands and feet (acroparesthesias), and gastrointestinal symptoms (mainly abdominal pain and diarrhea), manifestations that interfere with child's well-being and school performance and have a severe impact on quality of life (QoL) [8,12,13]. With age, progressive damage to vital organ systems develops in both genders [14], leading to multi-organ failure and even more reducing QoL [13] although the clinical expression of the disease has a wide inter- and intra-familial variability [15]. Additionally, end-stage renal disease and life-threatening cardiovascular or cerebrovascular complications limit life-expectancy [16,17].

The introduction of Enzyme Replacement Therapy (ERT), available since 2001, as a specific therapeutic option for patients with FD, resulted in a variety of clinical benefits including improved renal pathology and cardiac function, reduced severity of neuropathic pain and improved pain-related QoL as well as significantly improved life-expectancy [18,19]. In order to monitor disease progression and patients' response to ERT, Mainz Severity Score Index (MSSI) has been developed as a clinical scoring-system specific for FD, which reflects disease's severity and it has been validated as a sensitive tool to allow monitoring treatment response in individual patients [22].

Despite the encouraging clinical outcomes achieved with ERT, a lifelong intravenous (IV) treatment with an every other week schedule, may interfere with daily life activities and negatively impact on QoL. The availability of a home treatment option for patients with FD, resulted in a safe and practicable way to improve patient experience and reduced the “burden of treatment”. In addition, home treatment is associated with improved adherence to treatment and with a significant and positive impact on QoL [20,21].

On the basis of our five year experience with home treatment for FD, we first aimed at assessing the impact of home therapy with agalsidase alfa on improvement in QoL in a large cohort of Italian patients with FD, in comparison with standard hospital-based ERT. The second objective was to evaluate if the benefit of home therapy could positively influence the clinical progression of FD as calculated by MSSI, and if higher levels of compliance with home-treatment than hospital-based ERT could contribute to the stabilization in MSSI score, thus reflecting an additional positive effect on the progression of the disease.

2. Patients and methods

2.1. Fabry@Home program

The Home Therapy program, called Fabry@Home, involves a professional team consisting of a treating physician and a registered nurse. The nurse visits patients with FD every 2 weeks to perform the infusion of agalsidase alfa at the in-label dosage of 0,2 mg/kg in 40 min, according to drug indication and SmPc. The nurse is responsible for checking drug vial condition before administration, recording details of administered vials (number of vials and batch numbers), controlling for vital signs before and after administration and any adverse reactions during and after infusions. The nurse remains at the patient's side until the infusion is completed and post-infusion vital signs are recorded. The nurse dedicated to the infusion of agalsidase alfa is in real-time remote contact with the physician of the team who is immediately notified in case of an adverse event. This is in order to warrant that any adverse event during the infusion is timely and properly addressed. Patients who underwent any adverse reaction have been subsequently evaluated for a premedication treatment with antihistaminics and/or corticosteroids before the following infusions, in accordance with the treating physician of the Fabry clinic who is charge of periodically following the patient up in order to monitor the progression of disease, response to treatment and safety.

To be eligible to enter the Home Therapy program, each patient is required to fulfill the following criteria:

- At least eight ERT infusions for FD, at least three of which with agalsidase alfa, at his local Fabry clinic or infusion center;
- -Stable clinical conditions (no deteriorating target organ damage, i.e. renal, cardiovascular, cerebrovascular damage);
- No evidence of adverse reactions to ERT reported during the last four infusions.
- Each patient has to sign an informed consent before joining the home infusion program.

2.2. Patients and data collection

Patients with FD who have been treated with agalsidase alfa in the home therapy program for a period of at least 3 months were enrolled in the study. June 2013 has been chosen as a cut off time for the data collection and analysis.

All patients enrolled in the study gave informed consent and the study was approved by the local Ethical Committee.

In order to evaluate the self-reported QoL and health-related status, the EQ visual analogue scale (VAS) of the EQ-5 questionnaire was administered to each patient at the time of entering the home therapy program (before the first home infusion) and prospectively at the last follow up during the home treatment. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled “Best imaginable health state” (100) and “Worst imaginable health state” (0). This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

In addition, on the basis of the information contained in medical records, MSSI was retrospectively calculated for each patient at the time of the diagnosis, at the time of entering the home therapy program and at the last follow up with the aim of assessing clinical conditions and response to treatment. MSSI was published in 2004 for use in patients with Fabry disease [22] and is composed of four sections that cover the general, neurological, cardiovascular and renal signs and symptoms of FD. Each section includes a group of signs and symptoms that are associated with FD, and these are weighted according to their contribution to the morbidity of the disease. MSSI was associated to a

Table 1
Baseline characteristics of patients.

	Sex	Age (years)	Angiokeratomas Y/N	Cornea verticillata Y/N	Gastrointestinal symptoms Y/N	Hypohidrosis Y/N	Acroparesthesia Y/N	Pain Y/N	Dizziness Y/N	TIA/stroke Y/N	Cardiac involvement Y/N	Renal involvement Y/N
1	M	60	Y	Y	N	Y	Y	Y	N	N	Y	Y
2	M	48	N	N	Y	Y	Y	N	N	N	Y	N
3	M	57	N	Y	Y	Y	Y	Y	Y	N	Y	Y
4	F	27	N	N	Y	Y	Y	N	N	N	N	N
5	F	23	N	N	Y	Y	Y	N	N	N	N	N
6	M	50	N	Y	Y	N	Y	N	Y	N	Y	Y
7	M	29	N	N	N	N	N	N	N	N	Y	Y
8	F	60	N	N	N	N	N	N	N	N	N	N
9	M	52	Y	N	N	Y	Y	Y	N	N	Y	Y
10	M	41	N	N	N	N	N	N	N	N	Y	Y
11	M	32	Y	N	Y	N	Y	N	N	N	N	Y
12	F	65	N	N	N	N	N	N	N	N	N	N
13	M	41	Y	N	N	Y	N	N	N	N	N	N
14	F	59	Y	N	N	N	N	N	N	N	Y	N
15	F	65	Y	N	Y	N	N	N	Y	N	N	N
16	F	48	Y	N	N	Y	Y	N	N	N	N	N
17	F	44	N	N	N	Y	N	N	N	N	N	Y
18	M	12	N	Y	Y	Y	Y	Y	N	N	N	N
19	M	57	Y	N	N	N	Y	Y	N	N	Y	Y
20	M	28	Y	N	Y	N	Y	Y	N	N	N	N
21	F	64	N	N	N	N	N	N	N	N	N	N
22	M	37	Y	N	N	N	N	N	N	N	N	N
23	F	68	Y	Y	Y	Y	Y	Y	N	N	Y	Y
24	M	51	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
25	M	36	Y	Y	Y	Y	Y	Y	N	N	Y	Y
26	M	54	Y	N	N	N	N	N	N	N	Y	Y
27	M	69	N	N	N	Y	N	N	N	N	Y	Y
28	M	68	N	N	N	N	N	N	N	N	Y	N
29	M	47	N	N	Y	N	N	Y	N	N	N	N
30	M	22	N	N	Y	Y	Y	Y	N	N	N	N
31	M	12	Y	Y	Y	Y	N	N	N	N	N	N
32	F	50	N	Y	N	N	Y	Y	N	N	Y	Y
33	M	28	Y	Y	Y	Y	Y	N	N	N	Y	N
34	F	48	N	Y	N	Y	Y	N	N	N	N	Y
35	M	57	N	Y	N	N	N	N	N	N	N	Y
36	M	18	Y	Y	Y	N	Y	Y	N	N	N	N
37	M	20	Y	Y	Y	N	Y	Y	N	N	N	N
38	M	23	Y	Y	Y	Y	Y	N	N	N	N	N
39	F	50	Y	Y	Y	N	Y	N	N	N	Y	Y
40	F	56	Y	Y	N	N	Y	Y	N	N	Y	Y
41	M	54	N	N	N	N	N	N	N	N	Y	N
42	F	31	Y	N	N	Y	Y	Y	N	N	N	N
43	F	71	Y	N	N	Y	Y	Y	N	N	Y	Y
44	F	27	0	Y	N	N	Y	Y	N	N	N	N
45	F	74	Y	N	Y	N	N	N	N	N	N	N
46	F	67	Y	Y	Y	Y	Y	Y	N	N	Y	Y
47	F	59	Y	Y	Y	Y	Y	Y	N	N	Y	Y
48	M	49	Y	Y	Y	N	N	Y	N	N	Y	Y
49	f	60	Y	Y	N	N	N	N	N	N	Y	N
50	m	41	Y	N	Y	Y	Y	N	N	N	Y	Y
51	m	50	N	Y	Y	Y	Y	Y	Y	N	Y	Y
52	m	48	Y	N	N	Y	Y	N	N	N	Y	Y
53	f	18	N	N	Y	N	Y	N	N	N	Y	N

(continued on next page)

Table 1 *(continued)*

	Sex	Age (years)	Angiokeratomas Y/N	Cornea verticillata Y/N	Gastrointestinal symptoms Y/N	Hypohidrosis Y/N	Acroparesthesia Y/N	Pain Y/N	Dizziness Y/N	TIA/stroke Y/N	Cardiac involvement Y/N	Renal involvement Y/N
54	f	17	N	N	N	N	Y	Y	N	N	N	Y
55	f	57	N	Y	N	N	N	N	N	N	Y	Y
56	m	41	Y	Y	Y	N	Y	Y	N	N	N	N
57	f	60	N	N	N	Y	Y	Y	N	N	Y	N
58	m	24	Y	N	Y	Y	Y	Y	N	N	Y	N
59	f	40	Y	N	Y	N	N	N	N	N	Y	Y
60	m	47	Y	N	N	N	N	N	N	N	Y	Y
61	f	72	Y	Y	Y	N	N	N	N	N	Y	N
62	m	44	Y	N	N	Y	Y	Y	Y	N	Y	Y
63	m	42	Y	N	N	Y	Y	Y	N	N	Y	Y
64	m	54	Y	Y	Y	Y	Y	Y	N	N	Y	Y
65	f	40	N	N	Y	Y	Y	Y	N	N	N	N
66	m	32	N	Y	Y	Y	Y	Y	N	N	N	N
67	m	41	N	N	N	N	Y	N	N	N	N	N
68	f	28	N	Y	Y	N	Y	Y	N	N	Y	Y
69	m	31	N	N	Y	N	N	N	N	N	N	N
70	f	50	Y	Y	Y	N	Y	Y	Y	N	Y	N
71	f	61	N	Y	Y	Y	Y	Y	Y	N	Y	Y
72	m	39	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
73	f	50	N	Y	N	Y	Y	Y	Y	N	Y	Y
74	f	23	N	Y	N	Y	Y	Y	Y	N	N	Y
75	f	27	N	N	Y	Y	Y	Y	Y	N	N	Y
76	f	71	N	N	N	Y	N	N	N	N	Y	N
77	f	53	N	Y	N	N	Y	N	N	N	N	N
78	f	30	Y	N	Y	Y	Y	N	N	N	N	N
79	f	48	Y	N	Y	N	Y	Y	N	Y	N	N
80	f	29	N	Y	N	Y	Y	N	Y	N	Y	Y
81	f	62	N	Y	N	Y	Y	N	N	N	Y	N
82	m	36	Y	Y	Y	Y	Y	N	N	N	Y	Y
83	m	30	Y	Y	Y	Y	Y	N	N	N	N	Y
84	m	33	Y	Y	Y	Y	Y	N	N	N	Y	Y
85	m	41	Y	Y	Y	Y	Y	N	Y	N	N	Y

mild disease severity for values between 0 and 20, moderate for values between 20 and 40, and severe for values higher than 40.

Finally, adherence to the infusion schedule during the previous 12 months and the number of requests for leaving the home therapy program raised by patients or treating physicians were assessed as indirect effectiveness indicators of home infusion program. Adherence to treatment was calculated considering a compliance of 95–100% for those patients who missed 0 to 1 infusions, 90–95% for those who missed 2 infusions, 80–90% for those who missed from 3 to 5 infusions, < 80% for those who missed > 5 infusions compared to the previous year before entering the home therapy program. Data on adherence to treatment during home therapy were compared with those observed during the last six months of hospital treatment, as reported by treating physicians or self-reported by patients at the time of entering the home treatment program. As safety indicators, the number of adverse events reported during the home treatment were considered and compared with that observed during the hospital treatment.

2.3. Statistical analysis

Descriptive statistical analysis was applied. For comparisons, non-parametric tests (Wilcoxon two-sample test, Friedman test) were used as appropriate. $p < 0,05$ was considered significant.

3. Results

Each patient evaluated in the study was home treated for a period of at least 3 months. These 85 patients represent the 35% of the total number of patients treated in Italy with agalsidase alfa at the time of the analysis and originally came from 21 Fabry Clinics across Italy. This cohort was composed of 45 males (53%; mean age: 40.6 years; range 12–69 years) and 40 females (47%; mean age: 48,8 years; range 17–74 years). Five patients (5,8%) entered the home treatment program before the age of 18 (mean 13,6 years; range: 10–16 years). Patients who were enrolled in the home treatment program had started ERT 4 years before (average treatment duration; range 4 months–11 - years and 6 months). Seventeen out of 85 patients (20%) started ERT with agalsidase beta and then were switched to agalsidase alfa according to standard clinical practice and treating physician decision without undergoing adverse events. For the whole cohort, the average duration of home treatment was 1 year and 11 months (range 3 months–4 years and 6 months). Ten out of 85 patients (11,7%) abandoned the home treatment program after at least 3 months due to the following reasons: death for incoming acute cardiac complications (3 patients), treating physician decision (4 patients), bureaucratic and administrative issues due to the decision of one Italian region to withdraw the consent for the home patients (2 patients). No patient asked to leave the home treatment program except one showing psychiatric disturbances. The cohort of FD patients treated at home within the program included also 2 pregnant women. One female patient and four male patients underwent kidney transplantation before the beginning of home therapy. A total of 4269 infusions (mean: 50 infusions/patient; range: 7–118) was performed for the whole cohort during the observation. Seventy-four out of 85 patients (87%) were treated by the same nurse during the whole period of home treatment, while 11 out 85 patients (13%) have been infused by more than one nurse during the observation. The home infusion program was available in 11 out of 20 Italian regions (55%). In Table 1 clinical baseline characteristics of the 85 patients are reported.

3.1. EQ-5 VAS

To evaluate the self-reported QoL and health related status, the EQ-5 VAS was administered to patients enrolled in the study immediately before initiating home therapy and at last follow up. Complete data regarding EQ-5 VAS was available for 72 out of 85 patients (85%) (initial and follow up data missing for 1 and 12 patients, respectively). We found no statistically significant difference regarding average self-reported health-related status between pre home treatment and the last follow up (mean: 70). However, among all 72 patients, 42 (58%) showed an increase of EQ-5 VAS score at follow up compared to baseline (before starting home infusions), reflecting an improvement of health status, or remained stable (20 and 22, respectively). On the contrary 30 patients (42%) reported a worsening of their health-related status. In the group of patients who experienced an improvement of EQ-5 VAS (20 patients) the average of EQ5-VAS increased of 21,5. In addition, EQ-5 VAS score ranged between 20 and 100 at baseline and between 60 and 100 at follow up, thus standing for an increase of self-reported health-related status after home therapy start in patients with lower score at baseline. This is confirmed by the calculation of the interquartile range (IQR) which showed two overlapping values (= 20) in the two groups (EQ5-VAS at baseline vs EQ5-VAS at follow up) indicating a homogeneous dispersion of the values. No differences regarding gender and age at treatment initiation have been observed.

3.2. Mainz Severity Score Index (MSSI)

MSSI was calculated at three time points: the time of diagnosis, immediately before starting home therapy and at last follow up. MSSI data was available at the time of diagnosis, at the time of starting home therapy and at the last follow up for 73 (86%), 75 (88%), 74 (87%) patients out of 85, respectively, being the other records lost. At the time of diagnosis, MSSI ranged from 1 to 55 (mean 16,1, median 13,0); at the time of entering the home therapy program it ranged from 2 to 56 (mean 18,6, median 16,0) while at last follow up it ranged between 2 and 54 (mean 19,3, median 16.0).

During the hospital treatment period occurring between diagnosis and home therapy start, 10 out 73 patients (14%) showed a progression of disease by switching from a mild to a moderate disease status or from a moderate to a severe status. Only one patient showed a clinical status amelioration while the remaining 63 patients (85%) showed no change in disease severity according to MSSI. On the other end, after starting the home therapy program, 10 out of 74 patients (14%) showed a progression of disease, while 7 out of 74 patients (9%) registered an improvement of clinical status related to FD by switching from a severe to a moderate class or from a moderate to a mild class according to MSSI. Fifty-seven out of 74 patients (77%) showed no progression of disease and remained stable between starting home therapy and follow up.

Interestingly, 4 out of 7 (57%) patients, showing an improvement in FD-related clinical status after starting home therapy, had previously a sub-optimal compliance to treatment during the period of hospital treatment management (< 95%).

Generally, for all 74 patients, average disease severity as calculated by MSSI showed a slight increase in the timeframe between the diagnosis and immediately before starting home therapy ($p < 0,007$) while it remained stable between the first home therapy infusion and last follow up.

3.3. Safety and compliance to treatment

Compliance to treatment (number of infusions performed vs scheduled) reached 100% in patients during the home therapy program while during hospital management, compliance had been of 95–100% for 44 patients, 90–95% for 13 patients, 80–90% for 4 patients and < 80% for 11 patients. Data was not available for two patients.

During hospital treatment, 4 patients had discontinued infusions at least for a period of time, while during home treatment only one patient incurred in a temporary interruption of infusions, which involved only one infusion and had no effect on the determination of total compliance.

A total of 4 adverse reactions out of 4269 infusions (0,093%) were

reported in 2 patients during home treatment. All reactions were considered related to treatment and not serious, consisting of cutaneous rash which subsided in all patients spontaneously or after administration of antihistaminics. No anaphylactic reactions were observed.

4. Discussion

A patient-centric home infusion program has been implemented in Italy since 2008 for patients with FD treated with agalsidase alfa, in order to avoid frequent travels and hospital admissions to receiving periodical IV infusions of ERT.

Our multicentric, observational, longitudinal data analysis on a large cohort of Italian FD patients and a large number of delivered infusions (4269) in the home therapy setting, showed that ERT administration at home is safe and that the home infusion program can positively influence treatment compliance by reducing the number of therapy interruptions and improve the adherence to in-label dose-regimen and treatment schedule. In the present study, compliance to treatment was measured by the patient-reported percentage of lost infusions as reported by Linthorst et al. [23] in a previous experience. As mentioned, during the home therapy program, compliance reached 100% while during hospital treatment > 20% of patients had a compliance lower than 90%, meaning that at least one infusion out of ten was lost. As a direct consequence, we can argue that improved compliance to ERT could result, in the long term, in a positive effect on treatment outcome, as shown by the trend of disease severity as indicated by the MSSI score: while median MSSI score slightly, even if significantly, increased during the timeframe of hospital treatment, it remained stable after the home therapy treatment start, up to the last follow up. This was, to our opinion, directly correlated to the ameliorated compliance to treatment regimen. In fact, patients who experienced an improvement in disease-related status, as assessed by the MSSI score, after entering the home infusion program, had previously a suboptimal adherence while on hospital treatment. However, a longer duration of hospital treatment compared to home infusion (average: 4 years vs 1 years and 11 months) should be taken into account as it may have had a role in slightly determining a disease progression independently from the treatment setting.

The number of adverse events recorded during home treatment, that were not higher than expected, all of mild intensity and managed at home without recourse to hospital, clearly demonstrates that home infusions can be considered at least as safe as infusions administered in a hospital setting. The home infusion program called Fabry@Home involves a professional team consisting of a treating physician and a registered nurse who is dedicated to the infusion of agalsidase alfa. The nurse is in real-time remote contact with the physician, who is immediately notified in case of an adverse event that is timely and properly addressed. In addition, stringent eligibility criteria for patients entering the home infusion program are observed, including no adverse events occurred during the last 4 infusions in a hospital setting, thus providing further safety warranty for patients.

The slight increase in MSSI during the hospital treatment and the clinical severity of the disease did not preclude the possibility of those patients to access the Fabry@Home program, including for kidney transplant patients and pregnant women, ensuring a setting which was more comfortable but still safe despite patient's clinical conditions.

In addition, patients who joined the home infusion program, experienced a subjective amelioration of their self-reported health-related status (QoL). Even if no statistically significant changes occurred in EQ-5 VAS, the minimum value of the score was 60 after home treatment start compared to 20 during hospital treatment. This result may be a direct consequence of the improvement or stabilization of self-reported QoL that 58% of patients experienced following home infusion start, probably due to the lack of hospitalization related to treatment administration.

5. Conclusions

The availability of a home care model, built around patient needs and his daily habits, may allow an improvement of treatment compliance by reducing the number of treatment interruptions and allowing a better adherence to treatment dose and schedule for FD. We conclude that home infusions in eligible patients with FD are safe and contribute to improve treatment compliance and therapeutic clinical outcomes and may have a positive impact on self-perceived QoL.

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