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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