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Agalsidase-β should be proposed as first line therapy in classic male Fabry patients with undetectable α-galactosidase A activity

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ABSTRACT

Background: Fabry disease (FD) is a rare X-linked lysosomal storage disease caused by mutations in the α-galactosidase A (*GLA*) gene leading to deficiency of α-galactosidase A (α-gal A). This results in progressive multisystemic glycosphingolipid accumulation, especially globotriaosylceramide (Gb3) and globotriaosylsphingosine (Lyso-Gb3). Enzyme replacement therapy with two recombinant enzymes, agalsidase-α and –β is approved for two different dosages. However, little is known about which enzyme is more effective in decreasing the metabolite load in male and female patients with the classic form of the disease.
Methods: In this prospective observational study, 14 consecutive adult Fabry patients (10 males) with a classic *GLA*-mutation, were switched from agalsidase–α to agalsidase–β at the respective licensed doses. Lyso-Gb3 levels were measured before the switch and for a period of 12 months after the switch in dried blood spots by tandem mass spectrometry.
Results: Mean age at start of the switch was 36.7 ± 14 years. Plasma Lyso-Gb3 levels decreased from 27.2 ± 17.9 ng/mL before the switch to 16.8 ± 10.5 ng/mL after the switch (mean reduction of 30.1%; $p = 0.004$). The decrease was maximal in the subgroup of 7 male patients with no or very low residual enzyme activity (mean reduction of 40.4%). However, two females with high residual enzyme activity also showed a reduction >30% after the switch. In male patients, the reduction of plasma Lyso-Gb3 correlated negatively with the residual α-gal A activity: $r = -0.803$; $p = 0.009$.
Conclusion: Agalsidase-β at licensed dose is significantly more effective than agalsidase-α to reduce Lyso-Gb3 levels in classic Fabry patients, and should be used as first line therapy in classic males with no residual enzyme activity.

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1. Introduction

Fabry disease (FD) (OMIM#301500) is an X-linked metabolic disorder resulting from pathogenic variants in the *GLA* gene, that lead to α-galactosidase A (α-Gal A) deficiency [1,2]. The consequence is a progressive accumulation of glycosphingolipids, specifically globotriaosylceramide (Gb3) and globotriaosylsphingosine (Lyso-Gb3), mainly in cardiac, endothelial and renal cells. The disease affects hemizygotes more severely and earlier than heterozygotes, according to Lyonization, also called X-inactivation [3]. Two major phenotypes, classic and later-onset, have been identified [1,4–6]. The classic phenotype is caused by absent or minimal (<3% of mean normal) residual α-Gal A activity, with the early childhood-onset of acroparesthesias, angiokeratoma, cornea verticillata and hypohidrosis. In adulthood, the increasing glycosphingolipid-load provokes direct cellular toxic effects, promotes cell proliferation, and induces inflammatory and fibrogenic response. These pathogenic mechanisms result in hypertrophic cardiomyopathy, chronic nephropathy, early strokes, and premature death [7–10]. In the later-onset phenotype, the most prevalent form of the disease, patients have a relatively high residual α-Gal A enzyme activity

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(up to 25% of mean normal), and no accumulation of Gb3 in endothelial cells. Males experience a normal childhood but, as adults, may develop a cardiomyopathy similar to that of the classic form, and, more rarely, a nephropathy [4,11,12].

FD is characterized by a slow progression, punctuated by clinical events of variable occurrence and severity according to sex, age and type of mutations (>1000 different pathogenic variants identified), even for the same mutation or family, making any long-term prognosis or prospects for therapeutic response very difficult to anticipate [12]. Since 2001, disease specific therapies include two recombinant human enzymes, agalsidase-α derived from human fibroblasts (Replagal®; Takeda Pharma AG at a licensed dose of 0.2 mg/kg/eow), and agalsidase-β derived from Chinese ovary hamster cells (Fabrazyme®; Sanofi Genzyme at a licensed dose of 1.0 mg/kg/eow) [5,13]. In addition, since 2016, the oral pharmacological chaperone migalastat, an imino-sugar, (Galafold®; Amicus), has also been approved for patients with amenable missense mutations [14]. So far, it is unclear, which of the two enzyme replacement therapy (ERT) preparations, approved at two different dosages, is more effective in decreasing the metabolite load. The question arises in particular in patients with the more severe classic phenotype. The deacylated Lyso-Gb3, one of the major metabolites in FD, accumulates in body tissues and liquids in FD patients [15]. It is used as a diagnostic biomarker of FD although normal levels of Lyso-Gb3 can be found in heterozygotes with cardiac variant [16]. Lyso-Gb3 levels also help to discern between both phenotypes of the disease, and represent a risk parameter for severe clinical outcomes [17,18]. Finally, plasma Lyso-Gb3 has also been used as a biomarker for therapy monitoring in FD [19].

Recently, Goker et al. reported plasma Lyso-Gb3 reductions up-to 6 months after switching from agalsidase-α to agalsidase-β, and concluded that agalsidase-β has a greater pharmacodynamics effect on Lyso-Gb3 and Gb3 levels [20]. In a registry study, Arends and colleagues found that the decrease in plasma Lyso-Gb3 was more robust following treatment with agalsidase-β than agalsidase-α [21]. Likewise, in an observational study, Lenders and colleagues reported decreasing Lyso-Gb3 levels in patients re-switched from agalsidase-α to agalsidase-β [22,23]. In both latter studies, the initial switch from agalsidase-β to agalsidase-α was due to worldwide shortage of agalsidase-β. Conversely, Smid et al. observed an increase in plasma Lyso-Gb3 levels in their patients switched from agalsidase-β to agalsidase-α, or to a reduced agalsidase-β dose after one year of shortage, suggesting recurrence of disease activity [24]. However, in these studies, data were partly collected following different protocols, and Lyso-Gb3 was only available in a subset of patients and measured in different laboratories. Standardization of the methods is still needed in order to obtain comparable Lyso-Gb3 measurements [25].

The aim of our study was to assess the biochemical response in classic patients, switched from a stable treatment of agalsidase-α to agalsidase-β, at the respective licensed doses, in particular in male patients with the most severe phenotype, i.e. with no residual enzyme activity. To address this, Lyso-Gb3 levels were repeatedly determined before and after switching and measured in a single laboratory with the same standards of technical methods.

2. Methods

2.1. Study participants and clinical work-up

The study was conducted in accordance with the principles of the Helsinki Declaration. Informed consent for collecting clinical data and blood samples for biobanking was obtained from all patients.

The study population consisted of all patients followed at the two specialized Fabry centers in Switzerland, Lausanne and Zurich, whose therapy was switched from agalsidase-α to agalsidase-β, since Lyso-Gb3 measurements became routinely available for the clinical use. Between June 2016 and November 2021, 14 patients with classic FD were switched from the licensed dose of 0.2 mg/kg body weight of recombinant agalsidase-α (Replagal) to 1 mg/kg body weight agalsidase-β (Fabrazyme), administered intravenously every 14 days, respectively. No patient was switched from agalsidase-β to agalsidase-α during this period of time.

All patients had a confirmed *GLA* mutation diagnosis. The phenotype was classified based on genotype and residual α-Gal A enzyme activity in males. All mutation-based phenotyping of this cohort was reported in previous studies [18,25,26]. Patients presented for their routine annual examinations at the FD center when the therapy switch was discussed and conducted. The decision to switch, which took place after the shortage, has been made between the patient and the treating physician following a discussion on pros and cons of a higher infused dose of agalsidase-beta. For each patient, ERT was initiated according to the written local guidelines as reported previously [27]. All clinical data used for the present analyses were extracted from medical records, and the adverse events were evaluated during annual examinations as reported previously [27].

2.2. Lyso-Gb3 measurement

Lyso-Gb3 concentrations in dried blood spots (DBS) were measured at routine annual examinations before the switch (agalsidase-α period), and monthly for 1 year after the switch (agalsidase-β period). The blood samples were collected during home infusion visits and sent to the laboratory. The duration of the agalsidase-β period was 12 months. A mean value, including all the Lyso-Gb3 assays, was calculated individually for the agalsidase-α period. As plasma Lyso-Gb3 levels stabilize 3 months after an enzymatic switch, during the agalsidase-β period, the mean value of Lyso-Gb3 for each patient was calculated as of the 4th month after the switch, [19]. At the end of the agalsidase-β period, the decision to continue ERT with agalsidase-β or to re-switch to agalsidase-α was discussed with each patient based on their Lyso-Gb3 levels decrease and treatment tolerance.

Assays were performed by highly-sensitive electrospray ionization liquid chromatography tandem mass spectrometry (ESI LC-MS/MS) using a modified method based on Gold et al [28], and as recently described [16,29]. A 7-point serum calibrator and an internal standard for Lyso-Gb3 quantification (covering the analytic range from 0 to 120 ng/mL; lower limit of quantification: 0.3 ng/mL), and three level controls (3, 30 and 100 ng/mL) for quality control were used (ARCHIMED Life Science GmbH, Vienna, Austria; www.archimedlife.com). Lyso-Gb3 values above 3.0 ng/mL were considered pathological. The reference range (0.0–3.5 ng/mL) was defined as the prediction interval that included 95% of a reference group values: cut-off ≤1.1 ng/mL. The Lyso-Gb3 determination was assessed for stability in 3 affected males, in which the results of the DBS levels remained well reproducible one month later, with a coefficient of variation ≤9% [29]. Taking in account this variation, a reduction in a given patient ≥15% of Lyso-Gb3 level after the switch, was considered arbitrarily as therapeutically significant.

2.3. Dosage of α-Gal A activity

A-Gal A enzyme activity was measured in leukocytes, which was initially determined at the time of diagnosis and subsequently updated according to the methodological evolution of the assay (Universtäts Kinderspital Zürich). Residual A-Gal A enzyme activity is presented in this publication as percentage of the mean normal value.

2.4. Statistical analysis

Statistical analyses were performed using Graph Pad Prism version 9. Descriptive statistics were used for demographics and clinical parameters. Categorical variables were expressed as proportions, or mean ± standard deviation. Two tailed, parametric, paired *t*-tests were used to

compare means before and after treatment switch. Correlation was evaluated with the Pearson r coefficient. All statistical tests were two-sided, a *p*-value below 0.05 was considered significant.

3. Results

3.1. Baseline characteristics

The demographic and baseline clinical characteristics of the study population at the time of the switch are shown in Table 1. Patients came from ten unrelated families, carrying classic mutations. The mean age of the population (9 males and 5 females) was 36.7 ± 14 years. In six male patients, residual α-Gal A activity in leucocytes was undetectable. In the five female patients, residual α-Gal A activity was between 25.7 and 85.6% of mean normal. All patients had multisystem involvement. Three patients (2 males, 1 female) received previously a kidney transplantation. Overall, eGFR calculated using the chronic kidney disease epidemiology collaboration formula on the basis of creatinine (CKD-EPI) remained stable 12 months after the switch: 89.7 ± 28.6 mL/min/1.73m^2 (range: 134–43) vs 87.4 ± 26.6 (range: 128–44); $p = 0.12$, as did the protein to creatinine ratio in a urine sample: 29.9 ± 49.0 mg/mmol (range: 6–74) vs 45.1 ± 69.4 (range: 2–221); $p = 0.15$. At the time of the switch, 5 patients (3 males, 2 females) had a left ventricular hypertrophy (LVH) defined as a left ventricular mass index (LVMi) > 78 g/m^2 in males, and >70 g/m^2 in females, using cardiac MRI. The mean LVMi before the switch was 86.1 ± 33.8 g/m^2 (range: 49–176). During the switch period, there was no clinical events in terms of arrhythmia, myocardial infarction, progression to chronic kidney disease (CKD) stage 5 (eGFR <15 ml/min/1.73m^2), transient ischemic attack, stroke, or death.

The mean duration of the agalsidase-α period was 8.4 ± 5.0 years (range: 1.1–16.8). Mean plasma Lyso-Gb3 level of the Fabry population decreased significantly from 27.2 ± 17.9 ng/mL (range: 5.0–52.4) before the switch, to 16.8 ± 10.5 ng/mL (range: 4.0–44.8) after the switch: $p = 0.01$ (Figs. 1–2), corresponding to a mean reduction of 30.1% (range: 4–60). The mean reduction of Lyso-Gb3 level was 33.5%, and 24.0% respectively, in the subgroup of 9 males (range: 4–60; $p = 0.003$), and in the subgroup of 5 females (range: 16–35; $p = 0.01$) (Fig. S1). However, the decrease was maximal (40.4%; range: 25–60) in the subgroup of 7 males with no or very low (<1% of mean normal) α-Gal A residual activity.

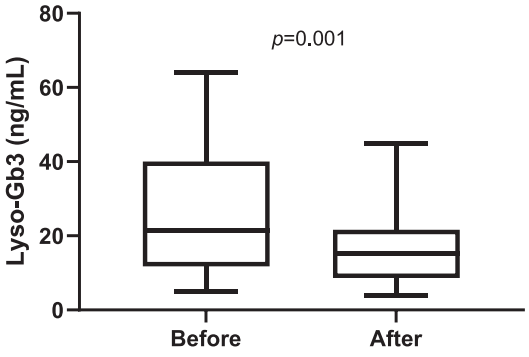

Fig. 1. Mean plasma Lyso-Gb3 levels (ng/mL) in the $N = 14$ patients, before and after the switch from agalsidase-α to agalsidase-β.

At the end of the agalsidase-β period, 11 patients (78%; 7 males and 4 females) with a decrease in plasma Lyso-Gb3 level of at least 15%, decided to continue the treatment with agalsidase-β. Two male patients, with a reduction ≤15% were re-switched to agalsidase-α. A female patient with a reduction of Lyso-Gb3 < 20%, complaining of headache under agalsidase-β, was re-switched to agalsidase-α.

No serious adverse event was reported during the agalsidase-β period (total: 364 infusions).

3.2. Correlation

In the subgroup of male patients, the reduction of Lyso-Gb3 negatively correlated with the residual α-Gal A enzyme activity: $r = -0.8033$; $p = 0.009$ (Fig. 3).

4. Discussion

This study shows that plasma Lyso-Gb3 levels, in male and female patients with classic FD, and on stable long-term treatment with agalsidase-α at a licensed dose, decreased significantly after a switch to agalsidase-β at a licensed dose (Figs. 1 and 2). The percent of reduction of Lyso-Gb3 level was considered as significant (≥15%) in 7 classic males with no or very low residual α-Gal A activity (<1% of mean normal) (Fig. 3). In the subgroup of classic male patients, we found an inverse correlation between the residual α-Gal A activity and

Table 1
Clinical and biochemical characteristics of the Fabry population.

	Age	Mutation	Clinical manifestations	α-Gal activity	Mean Lyso-Gb3 Period 1	Mean Lyso-Gb3 Period 2	Lyso-Gb3 Reduction
Males	years			(% MN)	ng/mL	ng/mL	(%)
1	23	c.125 T > C	G3bA1,GI,AC,CV	0	22.3	13.0	42
2	53	c.136C > T	LVH,G2A3,WML,S,GI,AN,CV	0	31.9	19.4	39
3	28	c.488G > T	G1A1,WML, AC,AN	4.0	13.8	13.2	4
4	20	c.658C > T	G1A1,WML,AC,AN,CV	0	42.0	24.7	41
5	31	c.680G > A	G1A1,WML,HL,GI,AC,AN	0.7	39.4	21.5	46
6	22	c.743_744delTA	G1A1,GI,AC,AN,CV	0	29.5	22.1	25
7	23	c.743_744delTA	G1A1,GI,AC,AN,CV	0	52.4	21.2	60
8	51	c.743_744delTA	LVH,LE,TX,WML,HL,AC,AN,CV	0	64.1	44.8	30
9	62	c.1285delC	LVH,LE,PM,ID,TX,WML,S,HL,AN,CV	4.0	20.4	17.5	15
Females							
1	50	c.467C > A	LVH,PM,G2A1,WML,S,HL,GI,CV	85.6	11.3	9.1	19
2	51	c.488G > T	LVH,LE,G2A1,WML,HL,GI	83.9	5.0	4.2	16
3	27	c.743_744delTA	G1A2,GI,AC,CV	56.0	5.8	4.0	31
4	46	c.1047G > A	TX,WML,S,HL,GI,CV	39.2	11.9	7.8	35
5	42	c.1168insT	G2A2,WML,AC,CV	25.7	14.8	12.4	17

LVH: left ventricular hypertrophy; LE: late enhancement; PM: pacemaker; ID: internal defibrillator; eGFR mL/min (CKD-EPI) according to KDIGO 2012: G1: >90, G2: 60–89, G3a: 45–59, G3b: 30–44, G4: 15–30, G5: <15; urinary proteine to creatinine ratio mg/mmol: A1: <15, A2: <15–50, A3: >50; TX: renal transplantation; WML: white matter lesions; S: stroke; HL: hearing loss; GI: gastrointestinal; AC: acroparesthesia; AN: angiokeratoma; CV: cornea verticilata.
Period 1: agalsidase-α treatment; period 2: agalsidase-β treatment; MN: mean normal.

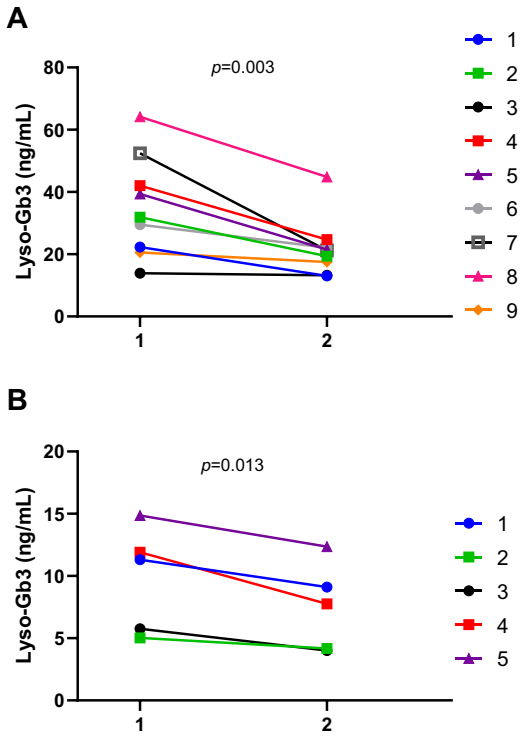

Fig. 2. (A): Reduction of mean plasma Lyso-Gb3 levels (ng/mL) in the $N = 9$ classic male patients from period 1 (agalsidase-α period) to period 2 (agalsidase-β or switch period). (B): Reduction of mean plasma Lyso-Gb3 levels (ng/mL) in the $N = 5$ classic female patients from period 1 (agalsidase-α period) to period 2 (agalsidase-β or switch period).

the reduction of Lyso-Gb3 levels after the switch to agalsidase-β (Fig. 2). These observations suggest that agalsidase-β is more effective than agalsidase-α in reducing the accumulated substrates in the subgroup of classic male patients with the most severe phenotype, i.e. with no or very few residual α-Gal A activity. Interestingly, two female patients with a reduced α-Gal A activity also showed a significant decrease in Lyso-Gb3 levels after the switch to agalsidas-β. No male or female patient showed an increase of Lyso-Gb3 levels after the switch. At the end of the agalsidase-β period, 11 patients (78%) decided to continue the treatment with agalsidase-β, due to a significant reduction of their Lyso-Gb3 level.

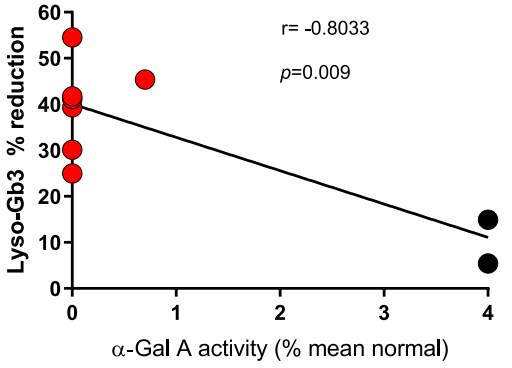

Fig. 3. Inverse correlation found in the $N = 9$ classic males between the residual α-Gal A activities and percent of Lyso-Gb3 levels decrease after the switch from agalsidase-α to agalsidase-β. The red points correspond to the patients who continued at the end of the switch period the treatment with agalsidase-β

Since the commercialization of agalsidase-α and agalsidase-β in 2001, the question of their comparative effectiveness has arisen. Given the wide phenotypic heterogeneity in Fabry patients, the very slow disease progression, and difficulties to conduct head-to-head studies, the results of the few observational comparative studies had not yet made it possible to formally answer this question [30]. On the one hand, a meta-analysis of the switch studies, published during the worldwide shortage of agalsidase-β, reported discordant clinical results after switching from agalsidase-β 1.0 mg/kg to agalsidase-β 0.5 or 0.2 mg/kg or agalsidase-α 0.2 mg/kg. They concluded that the effect of both ERT preparations was likely similar [31]. However, in these various studies, taking into account the slow progression of the disease, the duration of patient follow-up was relatively short, to allow for the conclusion of the superiority of one of the two recombinant enzymes. On the other hand, a large meta-analysis of relevant trials analyzing long-term clinical results of both recombinant enzymes found that the occurrence of renal, cardiovascular and cerebrovascular events favored agalsidase-β over agalsidase-α. A linear regression showed that Fabry patients treated with agalsidase-α were more likely to present higher rates of composite endpoints compared to those treated with agalsidase-β [32]. At present, a broad consensus exists among specialists to start ERT as early as possible in males with the classic form of FD, i.e. before the point of no return [15,33,34]. The latter directly depends on the appearance of inflammatory lesions and irreversible fibrotic organ damage, closely related to the progressive sphingolipid substrate accumulation [7]. Given the slow progression of FD, and potential for severe multi-organ damage, a biomarker or surrogate endpoint is needed in clinical practice to evaluate the risk of progression and therapeutic response.

The deacylated derivative of Gb3, Lyso-Gb3, has been shown to serve as a pharmacological marker since it significantly and rapidly decreases after ERT initiation [19]. After ERT switch, a stabilization of plasma Lyso-Gb3 levels occurs in a similar manner within the first 3 months [19] [20,21]. Moreover, Lyso-Gb3 is associated with the disease severity, major organ manifestations, disease phenotype and seems to be prognostic of severe clinical events [18,25,35,36]. Importantly, it has been shown in a population of classic FD males that Lyso-Gb3 levels decrease to a greater degree if ERT is started at a younger age, [37]. In addition, recent studies have shown a dose-dependent Gb3 clearance in podocytes in favor of agalsidase-β at 1 mg/kg of body weight, compared to a reduced dose of agalsiadase-β or to agalsidase-α at the licensed dose [38–40]. As previously suggested, antibody titers do not appear to significantly influence plasma Lyso-Gb3 levels in classic males after a switch [20,22,24]. Practical criteria for surrogate markers identified recently include accurate, repeated measurements, available to the clinician at a reasonable cost and within a short turnaround time, information that is not already available from a careful clinical assessment, and measurements that aid in medical decision making [41]. Based on these clinical studies, Lyso-Gb3 meets these practical criteria for patients with the classic form of the disease [42]. As for ERT in males with the classic form of FD " the best is as early as possible", regarding Lyso-Gb3 levels, the best should be the lowest possible in order to delay the point of no return. In fact, the highest Lyso-Gb3 levels are measured in classic male patients, with no residual enzyme activity, and who have the most severe phenotype of the disease. This subgroup of patients is the most suitable for evaluating the dose effect of each enzyme preparation. Our findings help to answer this question.

Our data appear to be in line with previous research on Lyso-Gb3. Based on our findings, agalsidase-β may be particularly effective in reducing the Lyso-Gb3 levels in classic males with the most severe phenotype, i.e. with no or very low (<1% of mean normal) residual enzymatic activity. Consequently, agalsidase-β should be proposed as first-line therapy in these patients. Unexpectedly, some symptomatic classic heterozygous women, regardless of their residual enzyme activity, have also showed a significant decrease in their Lyso-Gb3 levels. Interestingly, their mutation, in hemizygous relatives, was associated

with no residual enzymatic activity. This observation suggests, as in classic males, a dose effect in their cells carrying the mutated X-chromosome. Therefore, we propose to test the effects of both enzymes on Lyso-Gb3 levels successively for 3 months in symptomatic females of this subgroup of heterozygous patients. Agalsidase-β should also be proposed as first-line therapy in heterozygous females with a Lyso-Gb3 additional reduction ≥15%, compared to levels on agalsidase-α.

A key advantage of our study is that Lyso-Gb3 measurements were performed at a single laboratory with the same standards of technical methods employed. However, a relatively low number of study participants were included, which is a common problem in rare diseases and different therapy modalities. Another limitation is the lack of a head-to-head comparison of both ERT preparations in terms of clinical events. However, in this perspective, a prospective study lasting 25–30 years would be necessary to connect our results with definitive clinical significance. Such a study would be a challenge for an investigator-initiated study. Currently, plasma Lyso-Gb3 remains the most appropriate biomarker in the classic patients, based on its plausibility, construct validity, reliability, and responsiveness to treatment. It is, therefore, appropriate in a therapeutic and prognostic approach to decrease Lyso-Gb3 values as low as possible in classic male and female patients.

In conclusion, based on literature and findings of this study, we have decided in the Swiss Fabry centers to propose agalsidase-β as first-line therapy in classic males with no or very low (<1% of mean normal) residual enzyme activity, and in classic heterozygotes who experienced an additional reduction ≥15% in Lyso-Gb3 levels under agalsidase-β, compared to levels under agalsidase-α.

Author contributions

AN, and FB performed study design, data interpretation, and drafted the manuscript. OD performed the statistical analysis and the figures, and revised the manuscript. UH, and PM participated in the study design, and revised the manuscript. VM performed data acquisition and revised the manuscript. All authors read and approved the final manuscript.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2022.08.003.

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