Review

FABRY DISEASE: Switch from enzyme replacement therapy to oral chaperone migalastat. What do we know today?

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Abstract: Fabry disease is a lysosomal storage disorder caused by the deficiency of the α-galactosidase-A enzyme. Cardiac, renal, and neurological involvement significantly reduces life expectancy. Until a few years ago, treatment options for Fabry disease were limited to enzyme replacement therapy with agalsidase alfa or beta administered by intravenous infusion every 2 weeks. Migalastat (Galafold®) is an oral pharmacological chaperone that increases enzyme activity of "amenable" mutations. The safety and efficacy of migalastat were supported in the phase III FACETS and ATTRACT studies, compared to available enzyme replacement therapies; showing a reduction in left ventricular mass, and stabilization of kidney function and plasma Lyso-Gb3. Similar results were confirmed in subsequent extension publications, both in patients who started migalastat as their first treatment and in patients who were previously on enzyme replacement therapy and switched to migalastat. In this review we describe the safety and efficacy of switching from enzyme replacement therapy to migalastat in patients with Fabry disease and "amenable" mutations, referring to publications available to date.

Keywords: Fabry disease, globotriaosylceramide, α-galactosidase-A, enzyme replacement therapy, chaperone therapy, migalastat.

INTRODUCTION

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Fabry disease (FD, OMIM 301500) is a rare, X-linked, lysosomal storage disorder caused by the absence or deficiency of the α-galactosidase-A enzyme (α-gal-A, EC 3.2.1.22) [1]. The result is the complex glycolipids accumulation in body fluids and different tissues, mainly globotriaosylceramide (GL-3 or Gb3) and globotriaosylsphingosine (Lyso-Gb3) [1,2]. FD can be classified into a classic and a non-classic or later-onset phenotype also called an adult variant. Patients with the classic disease have an undetectable or very low enzyme activity (<3% of normal value), and develop organic complications early in life, including stroke, hypertrophic cardiomyopathy, and renal failure [2,3]. The disease in women may be more variable; from practically asymptomatic to severely affected as in men, regarding the percentage of cells that express the healthy or mutated X chromosome (Lyon hypothesis) [4,5]. The later-onset phenotypes are associated with higher residual enzyme activity, being the patients generally less affected, with manifestations limited to a single organ; cardiac or renal variant [2,3]. For male patients α-gal-A activity testing is diagnostic, but the confirmation of the mutation is important to determine the disease phenotype. In female patients, the presence of a GLA gene mutation is required as the plasma enzyme activity is often within the normal range [2].

Current therapeutic options include enzyme replacement therapy (ERT); agalsidase alfa (Replagal®, Takeda), and agalsidase beta (Fabrazyme®, Sanofi), both therapies are administered by intravenous infusion every 2 weeks. A novel alternative that overcomes some limitations of ERT, the pharmacological chaperone migalastat (Galafold®, Amicus), has been approved in the European Union in 2016 and the United States in 2018, for patients with FD and “amenable” mutations [6]. Migalastat is an imino-sugar that selectively and reversibly binds to “amenable” mutant forms of the enzyme α-gal-A, facilitating proper trafficking to lysosomes to metabolize the accumulation of Gb3 [6,7]. It is estimated that between 35 and 50% of FD mutations are “amenable” to migalastat (mainly missense mutations) [8]. The efficacy of the pharmacological chaperone migalastat was evaluated in two pivotal multicenter phases III studies; FACETS [9] and ATTRACT [8], and in subsequent open-label extension studies. This review aims to describe the safety and

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efficacy of switching from enzyme replacement therapy to migalastat in FD patients and “amenable” mutations, referring to publications available to date.

SWITCHING FROM ENZYME REPLACEMENT THERAPY TO MIGALASTAT

After a bibliographic search in different electronic databases (MEDLINE, EMBASE, SCOPUS, Cochrane, Latindex, and Google academic) regarding the switch from ERT to the pharmacological chaperone migalastat, five publications were found. The terms used for searching were “Fabry disease” and “enzyme replacement therapy” and “migalastat” and “switch”. The characteristics of these publications are shown in Table 1.

Table 1. Characteristics of the publications.

Author	Uni/Multi-center	Follow-up	n total	n switch	Both genders	Classic and later-onset
Hughes et al.	Multicenter	18 months	52	34	Yes	Yes
Müntze et al.	Unicenter	12 months	14	6	Yes	Yes
Feldt-Rasmussen et al.	Multicenter	12 months	46	15	Yes	Yes
Riccio et al.	Unicenter	12 months	7	7	No	Yes
Lenders et al.	Multicenter	24 months	54	33	Yes	Yes

In phase III ATTRACT study [8] the principal objective was to evaluate the migalastat effects on kidney function among FD “amenable” patients previously treated with ERT (agalsidase alfa 0.2 mg/kg or agalsidase beta 1 mg/kg), moreover cardiac effects, disease substrate, patient-reported outcomes, and safety were assessed. A total of 60 patients between 18-72 years (56% female) were randomized; for different reasons, 52 patients (34 in the group of ERT switch to migalastat and 18 in the group that remained on ERT) finished the 18-month randomization phase. Most of the patients included in this study had multiple-organ involvement by FD, considering their baseline characteristics and medical reports. The kidney results have demonstrated that migalastat has a similar effect to ERT, stabilizing renal function in terms of proteinuria and glomerular filtration rate

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(GFR) loss. Regarding cardiac outcomes, the results have shown a significant decrease in the left ventricular mass index (LVMi) from baseline to month 18 in FD patients treated with migalastat. In the analysis of events, the frequency in the migalastat group was 29% versus 44% in the ERT group. Patients experienced no changes in their quality of life after the switch from ERT to migalastat; the SF-36 v2 and Brief Pain Inventory scores remained stable during the study for both groups of treatment. The results have also shown stabilization of plasma Lyso-Gb3 among migalastat group patients. Finally, migalastat was generally safe and well tolerated throughout the ATTRACT study.

In 2019, Müntze et al. published the first real-world data about chaperone therapy with migalastat for treating FD patients [10]. In this prospective single-center study, migalastat efficacy and biomarkers changes were evaluated after 1 year of treatment on 14 FD patients (mean age of 55 ± 14 years); 6 of these patients were from ERT switch (agalsidase alfa 0.2 mg/kg or agalsisdase beta 1 mg/kg) to migalastat. Regarding Fabry-specific biomarkers, patients evidenced a significant α-gal-A activity increase (0.06-0.2 nmol/minute/mg protein; $p = 0.001$) in both female and male patients, and plasma Lyso-Gb3 was decreased in naive treatment patients and stable in patients who switched from ERT to the pharmacological chaperone migalastat. After 1 year of migalastat treatment follow-up, a significant reduction in LVMi (137-130 g/m2; $p = 0.037$) was observed, and biomarkers hs-troponin T and NT-ProBNP remained stable. This cardiac hypertrophy reduction was associated with higher α-gal-A activity. In this study, kidney function decreased after 1 year of migalastat, but part of the cohort started migalastat and angiotensin-converting enzyme inhibition simultaneously.

Long-term efficacy and safety of the pharmacological chaperone migalastat have been reported in the open-label extension to 30 months of the phase 3 ATTRACT study by Feldt-Rasmussen et al. [11]. In this extension period, patients who received the pharmacological chaperone migalastat continued receiving migalastat (Group 1 or MM), and patients who received ERT were switched to start migalastat treatment (Group 2 or EM). A total of 46 patients who completed the ATTRACT study continued into the 12 months extension period; 31 patients in group 1 (MM) and 15 in group 2

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(EM). Renal results over 30 months of treatment evidenced that eGFR (estimated GFR) remained stable with migalastat in both groups, with mean annualized rates of change of −1.7 in group 1 (MM) and −2.1 mL/min/1.73 m2 in group 2 (EM). A reduction in cardiac mass was observed with migalastat treatment in group 1 (MM) in patients with left ventricular hypertrophy at baseline, but cardiac mass remained stable in Group 2 (EM) during ERT treatment in this subgroup of patients. During the open-label extension period, few patients experienced new Fabry-associated clinical events and no new safety concerns were informed.

Riccio et al. reported in 2020 a single-center observational study in Italy, about switching from ERT (agalsidase alfa 0.2 mg/kg or agalsisdase beta 1 mg/kg) to migalastat in 7 adult male patients (18-66 years) with “amenable” FD mutations; 5 classic and 2 later-onset variants [12]. Neurologic, cardiac, and renal function, health status, α-gal-A activity, and Lyso-Gb3 were evaluated, by comparing retrospective data at baseline (pre-ERT) and after one year of ERT, with prospective data after one year of migalastat treatment. The results have shown a significant improvement in LVMi ($p = 0.028$) and proteinuria ($p = 0.048$) with the pharmacological chaperone migalastat vs ERT, and the migalastat treatment led to a decrease in plasma Lyso-Gb3 levels and an increase in α-gal-A activity. Adverse effects were similar in 28% for both treatments (migalastat and ERT). In conclusion, the switch was safe and well tolerated in this study.

A prospective 24 months observational multicenter study with migalastat on FD patients has been published by Lenders et al. last year [13]. Fifty-four adult patients (33 previously treated with ERT) were studied after 12 and 24 months of migalastat treatment; analyzing cardiovascular and renal function, disease severity, and changes in plasma Lyso-Gb3. FD signs and symptoms remained stable ($p > 0.05$). A reduction in LVMi was observed after 24 months of migalastat treatment (-7.5 ± 17.4 g/m2, $p = 0.0118$), particularly in males with cardiac hypertrophy at baseline. Renal results have evidenced a moderate eGFR loss, but it was mostly in patients with renin-angiotensin-aldosterone system inhibitors or aldosterone receptor blockers, which would indicate a higher baseline involvement. Lyso-Gb3 and α-gal-A activity persisted stable during the 24 months. Finally,

the authors highlight the safety of migalastat treatment, suggesting regular monitoring of clinical response in FD patients.

DISCUSSION

This is the first review about the safety and efficacy of switching from ERT to the oral chaperone migalastat in patients with FD and “amenable” mutations, referring to publications available to date. The conclusions summary of these reports, in favor of migalastat treatment, is shown in Table 2. A total of 95 patients from switch were included in the studies analyzed (Table 1). In 2019 Hughes et al. published a research letter describing the experience from the Phase III ATTRACT study in switching from ERT to migalastat [14]. The conclusion was that patients with FD and “amenable” mutations who have received ERT can be safely switched to the oral chaperone migalastat. A recent review concluded that to date, the main useful biomarker for Fabry nephropathy monitoring in patients receiving migalastat is eGFR using equations with plasma creatinine [15].

ERT was the only therapeutic alternative available for FD patients for several years. Currently, new therapeutic approaches have been introduced including chaperone therapy, substrate reduction therapy, and gene therapy. There are different reasons why the pharmacological chaperone migalastat is an attractive option for the treatment of patients with FD and “amenable” mutations. First of all, migalastat is an oral treatment that avoids intravenous ERT infusions, and consequently possible associated complications (e.g., headaches, allergic reactions, anaphylaxis, etc.) [6]. In addition, pharmacological chaperones are not immunogenic, and would not be expected to have tolerability issues similar to those described for the different recombinant enzyme therapies [16]. Moreover, as a small molecule, it would have the ability to cross the blood-brain barrier in humans, as shown in mice [17]. Migalastat, being an oral therapy, allows more sustained and stable α-gal-A levels than ERT [16].

In our experience in Argentina to date, we have a follow-up of a cohort of 20 patients, both with migalastat as initial therapy and also with the switch from ERT to migalastat. No significant pharmacological adverse effects or serious clinical events (cardiac, renal, or cerebrovascular) have

been reported in our population during the initial follow-up (preliminary data not published to date). In conclusion, due to its proven efficacy in the reduction of LVMi, and stabilization of renal function and disease biomarkers, migalastat is a safe alternative for switching from ERT or initiating therapy in patients with FD and “amenable” mutations.

Table 2. Conclusion summary of the publications.

Author	Conclusions in favor of migalastat treatment
Hughes et al.	• Stabilization of renal function • Decrease in the left ventricular mass index • Stabilization of plasma Lyso-Gb3
Müntze et al.	• Increase in α-gal-A activity • Decrease in the left ventricular mass index • Stabilization of plasma Lyso-Gb3
Feldt-Rasmussen et al.	• Stabilization of renal function • Decrease in the left ventricular mass index
Riccio et al.	• Increase in α-gal-A activity • Stabilization of renal function • Decrease in the left ventricular mass index • Stabilization of plasma Lyso-Gb3
Lenders et al.	• Decrease in the left ventricular mass index

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