



REVIEW

Effects of Current Therapies on Disease Progression in Fabry Disease: A Narrative Review for Better Patient Management in Clinical Practice

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ABSTRACT

Fabry disease (FD) is a rare lysosomal storage disorder that is characterized by renal, neurological, and cardiovascular dysfunction. Four treatments are currently available for patients with FD; three enzyme replacement therapies (ERTs; agalsidase alfa, agalsidase beta, and pegunigalsidase alfa) and one pharmacological chaperone (migalastat). This review focuses on the evidence for the benefits of ERTs and migalastat, and provides an overview of their impact on disease manifestations

and quality of life (QoL). Agalsidase beta is associated with renal, neurological, and cardiovascular benefits, and may prevent renal disease progression. Agalsidase alfa provides stabilizing effects across all main organ systems, although minor sex-specific differences exist in patients with more advanced baseline disease. The benefits of agalsidase alfa and agalsidase beta are similar but depend on the extent of baseline disease. Some data indicate that agalsidase beta may be preferable over the longer term. Both agalsidase alfa and agalsidase beta are associated with improved gastrointestinal and pain symptoms, as well as improved QoL. Patients with advanced end-organ

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damage tend not to respond as optimally to ERTs as those who initiate ERTs before irreversible organ fibrosis develops, highlighting the need for early treatment initiation. Migalastat, which is only approved for patients with amenable missense gene variants, generally stabilizes renal parameters and provides cardiovascular benefits. Migalastat also improves diarrhea and pain, and stabilizes QoL (although ERT may be more effective for pain management), but the neurological effects of migalastat have not been studied. Real-world data raise concerns about effective in vivo amenability of some genetic variants. Future studies with direct treatment comparisons in patients with FD are needed.

Keywords: Agalsidase alfa; Agalsidase beta; Cardiovascular outcomes; Enzyme replacement therapy; Fabry disease; Neurological outcomes; Pegunigalsidase alfa; Quality of life; Renal outcomes

Key Summary Points

Fabry disease (FD) is a rare lysosomal storage disorder that is characterized by renal, neurological, and cardiovascular dysfunction.

Treatments available for patients with FD include enzyme replacement therapies (ERTs; agalsidase beta, agalsidase alfa, and pegunigalsidase alfa) and a pharmacological chaperone (migalastat).

The benefits of agalsidase alfa and agalsidase beta are similar but depend on the extent of baseline disease.

Migalastat is only approved in patients with an amenable α -galactosidase mutation, and generally stabilizes renal parameters and provides cardiovascular benefits, although real-world data raise concerns about the effective in vivo amenability of some genetic variants.

Despite the therapeutic benefits of available options, no treatments can considerably reverse the major organ damage caused by FD progression.

INTRODUCTION

Fabry disease (FD) is a rare, X-linked, lysosomal storage disorder that results from deficient α -galactosidase A (α -Gal A) activity caused by a variant of the α -galactosidase (*GLA*) gene, with a prevalence estimated at around 1 in 40,000–170,000 births [1–3]. FD presents in both males and females; however, there is a wide spectrum of disease severity.

Two FD phenotypes have been described, the ‘classical’, with earlier onset, rapid disease progression and severe outcomes, and the ‘non-classical’ or ‘late-onset’ FD [2, 4, 5]. Although the extent of the non-classical phenotype may be initially less when compared to the classical disease presentation, the severity of individual renal or cardiac manifestations in advanced stages of patients with late-onset variants may be significant enough to require renal replacement therapy or pacemaker/cardioverter defibrillator implantation. Males with the classical phenotype typically have no residual α -Gal A activity versus males with the non-classical phenotype, where residual α -Gal A activity may be present even if below the normal range [5]. Comparatively, females with *GLA* pathogenic variants may have normal or only slightly reduced α -Gal A activity and so generally have a milder disease course [5]. However, females can also show a range of disease severity, from asymptomatic to symptomatic with severe organ involvement [2]. The differences in male and female disease phenotypes can be explained by the random inactivation of the X chromosome in heterozygous females (known as lyonization), which is dependent on the cell type and is frequently nonuniform across the silenced chromosome [6, 7].

Numerous variants of the *GLA* gene are responsible for the development of FD, with few variants presenting recurrently. Of the *GLA* variants identified through genomic screening, both pathogenic and non-pathogenic variants have been found [8]. Some of the identified variants have been classified as variants of unknown significance (VUS), indicating that, at present, the genetic changes underlying those variants have no validated association with the corresponding

phenotype or inconsistent phenotypes [8, 9]. The substantial genotypic variability of FD underlies considerable phenotypic heterogeneity, which makes FD diagnosis especially challenging, particularly in the case of a VUS [2, 8].

The pathophysiological mechanisms of FD have not yet been fully elucidated; however, the absence of α -Gal A activity determines a pathological lysosomal accumulation of globotriaosylceramide (GL-3) and/or its metabolite globotriaosylsphingosine (lyso-GL-3) within lysosome-containing tissues [2, 3, 10]. The accumulation of GL-3 and lyso-GL-3 is considered to be the main mechanism leading to cellular damage and eventually organ dysfunction. Typically, the major affected organs are the heart, kidneys, and central nervous system (CNS), and heart failure, renal failure, and stroke can result from disease progression [2, 10]. The pathology of FD is also thought to result from secondary functional and biochemical changes, particularly in the heart and kidneys [10]. Tissue lyso-GL-3 deposits may trigger chronic inflammation and accelerate rates of apoptosis in many organs, including the heart and kidneys [11, 12]. Figure 1 demonstrates the progressive nature of this damage in the heart [10].

At present, four therapies are approved for the treatment of FD in the United States (US) and/or Europe: three enzyme replacement therapies [ERTs; i.e., agalsidase beta (Fabrazyme[®], Sanofi), agalsidase alfa (Replagal[®], Takeda UK), and pegunigalsidase alfa (Elfabrio[®], Chiesi Farmaceutici)], and one pharmacological chaperone [i.e., migalastat (Galafold[™], Amicus Therapeutics)] [1, 13–16].

Both agalsidase beta (approved in Europe in 2001 and in the US in 2003) and agalsidase alfa (approved in Europe in 2001, but not approved in the US) are indicated for patients with confirmed FD and prevent the accumulation of glycosphingolipids by hydrolyzing and removing GL-3 [14, 15, 17–20]. Agalsidase beta is approved for use in individuals aged ≥ 8 years in Europe and ≥ 2 years in the US, whereas in Europe, agalsidase alfa is approved for individuals aged ≥ 7 years. Pegunigalsidase alfa (approved in both Europe and the US in 2023) is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for the

treatment of adults with confirmed FD that has a prolonged plasma half-life compared with other available ERTs [16, 21]. Migalastat (approved in Europe in 2017 for adults and adolescents aged ≥ 16 and extended to patients aged ≥ 12 years in 2021, but not reimbursed in the Netherlands, and approved in the US for use in adults, in 2018) reversibly and selectively binds with high affinity to the active sites of certain α -Gal A variants, enabling the trafficking of the variant forms to lysosomes, where migalastat disassociates and α -Gal A activity is restored, thereby allowing for catabolism of GL-3 and related substrates [1, 13, 22]. Migalastat projected therapeutic benefit in patients with FD for particular *GLA* variants is based on an in vitro assay that determines amenability, which is the basis of treatment suitability [23]. Based on this in vitro assay, it has been determined that 367 *GLA* variants are amenable to migalastat treatment and 711 are likely not [24]. Migalastat is only licensed for use in patients who have amenable variants included in a list provided by Amicus Therapeutics [1, 13, 22]. However, in vivo data from studies reassessing these variants' amenability in cells have shown conflicting results. Clinicians are advised to evaluate the pathogenic role of the variant and to monitor clinical manifestations and lyso-GL-3 levels to confirm that a variant is really amenable in vivo [24].

This narrative review focuses on the clinical evidence for the benefits of ERTs and migalastat on the three major organ systems involved in FD pathology (i.e., the renal, neurological, and cardiovascular systems) in classical and non-classical FD phenotypes, and provides a brief overview of their impact on disease manifestations and patient quality of life (QoL). The aim of this article is to help physicians across all specialties make informed decisions when prescribing therapies for FD treatment.

Data Sources and Searches

To identify relevant data, we initially conducted searches of titles and abstracts of English-language articles on the PubMed database between 24 and 28 October 2022. Search terms

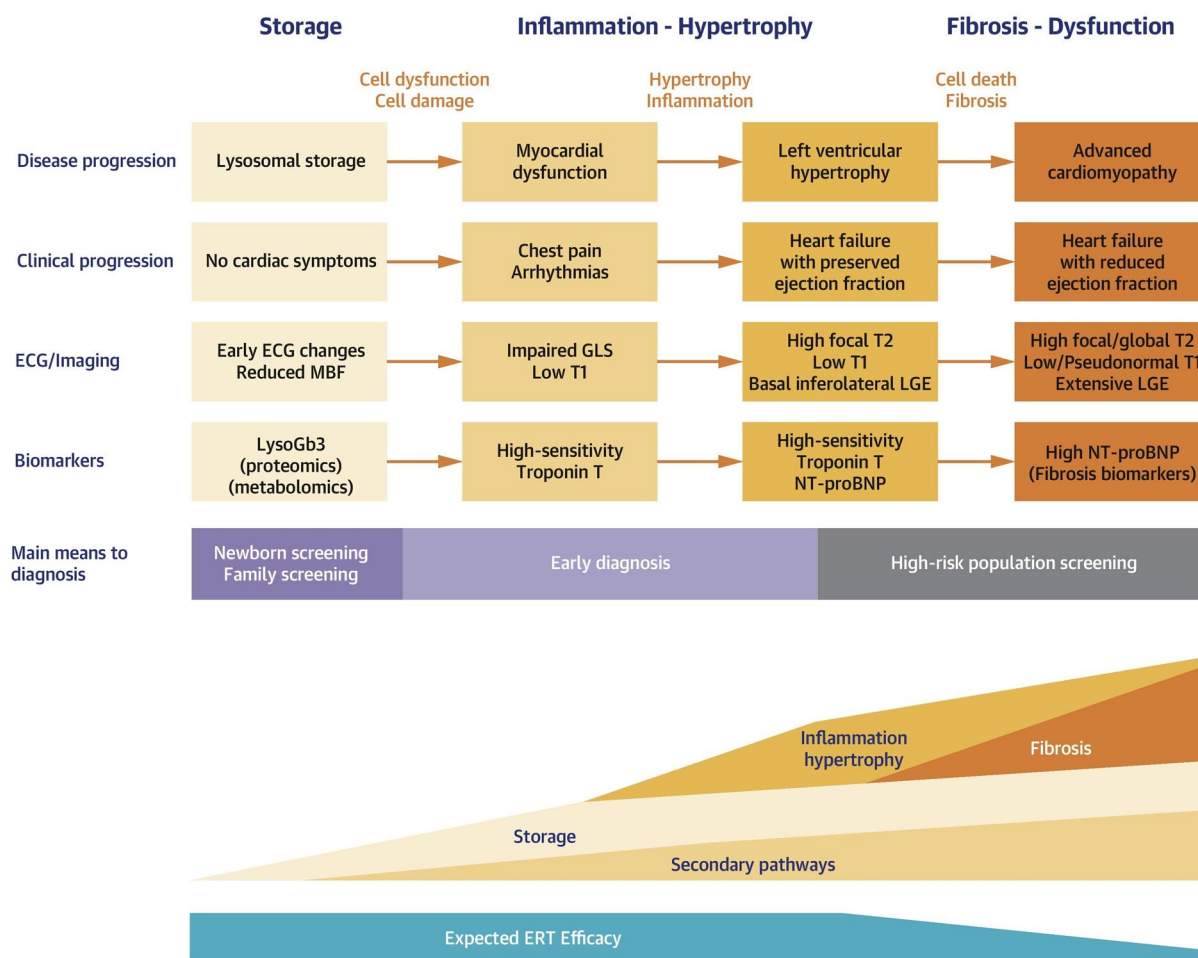


Fig. 1 Representation of the overall progressive nature of Fabry disease in the cardiac system, showing the expected clinical progression, relevant imaging biomarkers, main means to diagnosis, and in relation to expected treatment efficacy with ERT [10]. Reproduced from [10] with permission from Elsevier. *ECG* electrocardiography, *ERT*

enzyme replacement therapy, *GLS* global longitudinal strain, *LGE* late gadolinium enhancement, *LysoGb3* globotriaosylsphingosine, *MBF* myocardial blood flow, *NT-proBNP* NT-probrain natriuretic peptide, *T1* T1-weighted magnetic resonance image, *T2* T2-weighted magnetic resonance image

(along with any synonyms) included each drug name, as well as ‘enzyme replacement therapy’, in combination with the terms for FD and applicable MeSH terms relating to the effects of interest (e.g., neurological, nephrological, and cardiovascular). Other articles were subsequently identified through searches of the reference lists of articles identified in the database search, as well as from ad hoc searches for relevant literature, and from the authors’ experience in the area. Updated and newer publications after 2022 relating to pegunigalsidase alfa were also included.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RENAL INVOLVEMENT IN FD

Renal involvement is well documented in patients with FD, with substantial GL-3 accumulation seen in renal epithelial cells (podocytes) and glomerular and tubular epithelial cells [25].

While the severity of nephropathy can be variable, untreated male patients tend to progress through three clinical stages. The first stage is characterized by glomerular hyperfiltration; the second by renal dysfunctions with proteinuria, Malta crystals in the urine sediment, impaired urine concentrating and diluting ability, and lipiduria; and the third by severe renal disease [26]. The prevalence of glomerular hyperfiltration has been reported to be particularly high (50%) in younger patients with FD (≤ 40 years of age) [27]. Given that progressive nephropathy is a key feature of FD, hyperfiltration may be considered an early marker of FD, as it precedes other organ-related symptoms and signs of disease [27]. Moreover, long-term evaluation of renal function should be considered when angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are used in patients with FD because they may interfere with the evolution of renal function [27, 28]. Another early sign of FD in the kidneys is parapelvic cysts, which have been reported in 30% of patients with FD [29].

Renal Effects of Agalsidase Beta

Several studies, including phase 3 trials and those assessing both adults and children with FD, have demonstrated that renal function remains stable during agalsidase beta treatment (Table 1) [30–33], suggesting that agalsidase beta may help prevent pathological progression of kidney disease. In particular, follow-up data from one phase 3 trial at both 30 months [33] and 54 months [30] have shown sustained, long-term renal stabilization with agalsidase beta treatment in patients with FD. Various other renal benefits have also been documented with agalsidase beta (Table 1). Two studies have demonstrated significant reversal of GL-3 accumulation in renal cells with agalsidase beta [25, 30]. In a small prospective study of eight adults, proteinuria had resolved in five patients after 45 months of treatment with agalsidase beta [34].

Several studies have also suggested that agalsidase beta provides long-term renal benefits in patients with FD (Table 1). A 10-year study

reported a significant decrease in mean estimated glomerular filtration rate (eGFR) slope with agalsidase beta in patients with classical FD and high or low renal involvement at baseline [35]. Similarly, Wanner and colleagues showed that female patients (with high or low renal involvement) had stable renal function over 5 years of agalsidase beta treatment [32]. In a smaller study of 10 children with FD receiving agalsidase beta, renal stability was maintained for 8 years of follow-up; one patient with an elevated albumin-to-creatinine ratio at baseline showed normalization of renal function [36].

For patients with considerable renal function impairment at baseline, the benefits of agalsidase beta are not confirmed (Table 1). In one study of 82 adults with advanced FD, agalsidase beta treatment delayed the onset of a composite clinical outcome of renal, cardiovascular, and cerebrovascular events or death compared with placebo; larger treatment effects were observed in patients with baseline eGFR > 55 mL/min/1.73 m² compared with those with a baseline eGFR ≤ 55 mL/min/1.73 m² [37]. A single-center study in 26 patients with FD found that eGFR significantly decreased during agalsidase beta treatment in those with renal impairment at baseline [38]. Notably, in that trial, although the overall population reported stable renal function, a few patients with advanced disease (including those with glomerulosclerosis) showed kidney disease progression despite receiving agalsidase beta [38]. A pivotal phase 3 trial reported that of the six patients who had renal disease progression with agalsidase beta, all had sclerotic glomeruli and significant proteinuria at baseline [30]. Taken together, these findings suggest that the benefits of agalsidase beta are likely dependent on the extent of disease progression at the time of treatment initiation.

Renal Effects of Agalsidase Alfa

Studies have found that renal function remains stable during agalsidase alfa treatment (Table 2) [39–42]. The renal effects of agalsidase alfa also appear to be dependent on the extent of renal impairment at treatment initiation.

Table 1 Effects of agalsidase beta on the organ systems affected by Fabry disease

Citation	Study design (country)	Pts (<i>n</i>)	Treatment	Study results		
				Renal effects	CNS effects	CV effects
Thurberg et al. 2002 [25]	R, OLE (NR)	FD; ≥ 16 yrs; 97% male (58)	Agalsidase beta 1 mg/kg EOW vs. placebo for 5 mos the OL agalsidase beta 1 mg/kg EOW for 6 mos	Benefit Majority of pts achieved completed GL-3 clearance from PTC endothelial cells	–	–
Weidemann et al. 2003 [81]	OL (NR)	FD; 24–57 yrs; 13% male (16) and healthy controls (16)	Agalsidase beta 1 mg/kg EOW for 12 mos	–	–	Benefit ↑ Peak systolic strain rate in the posterior wall ($P < 0.05$) ↑ End-systolic strain in the posterior wall ($P < 0.05$) ↓ End-diastolic thickness in the posterior wall ($P < 0.05$) ↓ Myocardial mass ($P < 0.05$)

Table 1 continued

Citation	Study design (country)	Pts (<i>n</i>)	Treatment	Study results		
				Renal effects	CNS effects	CV effects
Wilcox et al. 2004 [33]	Phase 3, DB, R, PG with OLE (NR)	FD; 26–42 yrs (58)	Agalsidase beta 1 mg/kg EOW vs. placebo the OL agalsidase beta 1 mg/kg EOW	Stable Serum creatinine and eGFR remained stable over 30 mos	–	–
Banikazemi et al. 2005 [91]	Observational (US)	FD; 17–40 yrs (4)	Agalsidase beta 1 mg/kg EOW	–	–	Pain and QoL—stable Low pain scores throughout study and slight improvement in SF-36
						Pain and QoL—benefit
						GI symptoms—benefit Improved markedly
Breunig et al. 2006 [38]	OL (Germany)	Moderate-to-advanced FD; 29–57 yrs; 23% male (26)	Agalsidase beta 1 mg/kg EOW for ≤ 37 mos	Stable Stable eGFR in pts with persevered renal function but ↓ in pts with impaired renal function ($P = 0.04$)	–	Stable ↓ PWT in pts with preserved renal function ($P = 0.017$) but not in those with impaired function
Kalliokoski et al. 2006 [83]	OL (NR)	FD; 19–49 yrs; 70% male (10)	Agalsidase beta 1 mg/kg EOW for 12 mos	–	–	Stable No change in myocardial perfusion reserve

Table 1 continued

Citation	Study design (country)	Pts (n)	Treatment	Study results		
				Renal effects	CNS effects	CV effects
Banikazemi et al. 2007 [37]	DB, R, PC (North America, Europe)	FD; ≥ 16 yrs; 88% male (82)	Agalsidase beta 1 mg/kg EOW for up to 35 mos	–	–	–
				Composite clinical outcome—benefit		
				Slowed progression to the composite clinical outcome of renal, cardiac, and cerebrovascular complications and death compared with placebo		
Germain et al. 2007 [30]	Phase 3 OLE (France, Netherlands, Puerto Rico, UK, US)	FD; 17–62 yrs; 97% male (58)	Agalsidase beta 1 mg/kg EOW for 54 mos	Stable eGFR and creatinine remained stable	–	Benefit
				Pain and QoL—benefit		
				Most pts had GL-3 clearance from cardiac capillary endothelium at 6 mos		

Table 1 continued

Citation	Study design (country)	Pts (<i>n</i>)	Treatment	Study results			Other effects
				Renal effects	CNS effects	CV effects	
Wraith et al. 2008 [31]	OL (France, Poland, UK)	FD; 8–16 yrs; 88% male (16)	Agalsidase beta 1 mg/kg EOW for 48 wks	Stable	–	Stable	Pain and QoL— benefit
				eGFR and creati- nine remained stable		No change in CV outcomes	Significant improvement in post-prandial pain
Imbriaco et al. 2009 [34]	OL (Italy)	FD; 22–54 yrs; 73% male (11)	Agalsidase beta 1 mg/kg EOW for 45 mos	Benefit	–	Benefit	GI symptoms— benefit
				Proteinuria resolved in all 5/8 pts with proteinu- ria at baseline		↓ LVM (<i>P</i> < 0.001) ↓ LV wall thickness (<i>P</i> < 0.001) ↓ MT ₂ RT (<i>P</i> < 0.001)	Significant improvement in nausea and vomiting; no reports of diar- rhea
							Pain—benefit
							Improvement in neuropathic and abdominal pain

Table 1 continued

Citation	Study design (country)	Pts (n)	Treatment	Study results		
				Renal effects	CNS effects	CV effects
Warr et al. 2010 [94]	Observational (International)	FD; 0–79 yrs; 55% male (130)	Agalsidase beta 1 mg/kg EOW for 24 to 36 mos	–	–	–
Hilz et al. 2010 [82]	OL (US)	FD; 100% male (22)	Agalsidase beta 1 mg/kg EOW for 18 to 23 mos	–	–	Benefit Significant improve- ment in cardiovagal withdrawal and sympathetic cardio- vascular activation ↑ DBP (<i>P</i> = 0.002) ↑ Cardiovagal modu- lation withdrawal (<i>P</i> = 0.02)
						Pain and QoL— benefit Improvements in bodily pain scores and significant improvements in PCS and MCS scores

Table 1 continued

Citation	Study design (country)	Pts (n)	Treatment	Study results		
				Renal effects	CNS effects	CV effects
Borgwardt et al. 2013 [36]	Observational (Denmark)	FD; 60% male (10)	Agalsidase beta 1 mg/kg EOW for ≤ 8 yrs	Stable	–	Stable/Cardiac complications
				Serum creatinine and eGFR were normal at baseline and remained stable for 9, 1 with elevated serum creatinine improved		6 developed valvular involvement, 1 with mild LVH and 1 with tricuspid valve insufficiency improved. All ECG recordings were normal throughout
Fellgiebel et al. 2014 [74]	Phase 4, DB, R, PG (Canada, Czech Republic, Hungary, Poland, UK, US)	FD; 20–68 yrs; 93% male (41)	Agalsidase beta 1 mg/kg EOW for ≤ 33 mos	–	Stable	–
					Prevented WML progression	1 developed headaches, 5 had improved GI symptoms, 2 had increased symptoms and 1 was unchanged
Germain et al. 2015 [35]	Pooled analysis (France, Netherlands, UK, US)	FD; 16–62 yrs; 96% male (52)	Agalsidase beta 1 mg/kg EOW for 10 yrs	Greatest eGFR decline in the HRI cohort ^a	–	Stable
				↓ eGFR (<i>P</i> < 0.001)		No significant changes in LPVWT or IVST

Table 1 continued

Citation	Study design (country)	Pts (n)	Treatment	Study results		
				Renal effects	CNS effects	CV effects
Wilcox et al. 2016 [93]	Observational (International)	FD; 0% male (168)	Agalsidase beta 1 mg/kg EOW for ≥ 2.5 yrs	–	–	–
						GI symptoms—benefit Improvement in diarrhea (39% to 27%) and abdominal pain (45% to 31%)
Wanner et al. 2020 [32]	Observational (International)	FD; ≥ 16 yrs; 100% female (86)	Agalsidase beta 0.9–1.1 mg/kg EOW for 10 yrs	Stable eGFR stable over treatment period	–	Stable No significant changes in LPVWT or IVST
Hopkin et al. 2020 [92]	Observational (International)	FD; ≥ 18 yrs; 100% male (219); classic n = 171, later-onset n = 48	Agalsidase beta 1 mg/kg EOW	–	–	–
						GI symptoms—benefit Significant improvement in GI pain and diarrhea for classical phenotype, non-significant reductions for later-onset phenotype

Table 1 continued

^aDisease progression rates were assessed for patients with low renal involvement (LRI, $n = 32$) or high renal involvement (HRI, $n = 20$). Patients with a urine protein-to-creatinine ratio (UPCR) ≤ 0.5 g/g and $< 50\%$ sclerotic glomeruli were classified as LRI; patients with a UPCR > 0.5 g/g or $\geq 50\%$ sclerotic glomeruli at baseline were classified as HRI

CDMI color Doppler myocardial imaging, *CNS* central nervous system, *CV* cardiovascular, *DB* double blind, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *EOW* every other week, *FD* Fabry disease, *GL-3* globotriaosylceramide, *IVST* interventricular septum thickness, *LPIVWT* left posterior ventricular wall thickness, *LVI* left ventricular, *LVM* left ventricular mass, *LVMi* left ventricular mass index, *MCS* mental component summary, *mos* months, *MT₂RT* myocardial T2 relaxation time, *NR* not reported, *OL* open label, *OLE* open label extension, *PC* placebo-controlled, *PCS* physical component summary, *PG* parallel group, *PTC* proximal tubule cells, *pts* patients, *PWWT* posterior wall thickness, *QoL* quality of life, *R* randomized, *SF-36* 36-Item Short Form Survey, *UK* United Kingdom, *US* United States, *wks* weeks, *WML* white matter lesion, *yrs* years

A retrospective 10-year cross-sectional study in patients receiving agalsidase alfa reported a relatively stable eGFR in females with and without impaired renal function at baseline; however, males with baseline renal function impairment had a modest decline in eGFR [43]. In a cross-sectional analysis of an open-label extension study in 25 males with FD, eGFR showed a slight decline during 4.0–4.5 years of agalsidase alfa treatment [44]. When stratified by renal function, four patients with stage 3 chronic kidney disease (CKD) appeared to be driving the eGFR decline, with a mean decline of ~ 5.2 mL/min/1.73 m²/year [44]. While these results suggest a sex-specific response, other findings have demonstrated that both male and female patients with FD have limited benefit with agalsidase alfa if their renal function is impaired at baseline [39, 45]. The Fabry Outcome Survey has investigated sex-specific differences in treatment response among patients with FD receiving agalsidase alfa [45]. The median change in eGFR was -1.5 mL/min/1.73 m²/year for females (similar to the general decline expected due to aging) and -2.1 mL/min/1.73 m²/year for males. Among patients who had an eGFR decrease of $\geq 10\%$ according to the Modification of Diet in Renal Disease formula, there was a greater proportion of males than females with worsened renal function [45].

The importance of renal function at baseline was confirmed in a study of female patients with FD who had been receiving agalsidase alfa for 4 years [39]. Renal function remained relatively stable in the overall population; however, patients with moderate renal disease at baseline had a significant and sustained improvement over 1 year of treatment. In contrast, four patients with hyperfiltration at baseline experienced an eGFR decline [39].

Alternatively, a long-term open-label study has shown an improved slope of eGFR decline with more frequent agalsidase alfa treatment. The study examined 11 male patients who had participated in long-term agalsidase alfa clinical trials and who had a slope of eGFR decline of ≥ 5 mL/min/1.73 m²/year while receiving long-term agalsidase alfa 0.2 mg/kg every other week (EOW). Before switching to weekly dosing, the mean $\pm$ standard error of the mean

Table 2 Effects of agalsidase alfa on the organ systems affected by Fabry disease

Citation	Study design (country)	Pts (N)	Treatment	Study results			
				Renal effects	CNS effects	CV effects	Other effects
Haijioff et al. 2003 [77]	R then OLE (UK)	FD; 16–56 yrs; 100% male (25)	Agalsidase alfa 0.2 mg/kg EOW vs. placebo for 6 mos then agalsidase alfa for 36 mos	–	Benefit Improvements in hearing loss	–	–
Beck et al. 2004 [42]	Retrospective, observational (Europe)	FD; 52% male (545)	Agalsidase alfa 0.2 mg/kg EOW for ≤ 56 mos	Stable	–	Benefit	Pain and QoL—benefit
Jardim et al. 2004 [76]	Observational (Brazil)	FD; 24–47 yrs; 100% male (8)	Agalsidase alfa 0.2 mg/kg EOW for 12 mos	–	No benefit	–	Improvements in pain and EQ-5D utility scores
Schiffmann et al. 2006 [44]	OL (US)	FD; 100% male (25)	Agalsidase alfa 0.2 mg/kg EOW for 48–54 mos	Stable No significant change in eGFR was observed generally Deterioration in advanced kidney disease	–	–	–
Hoffmann et al. 2007 [89]	Observational study (International)	FD; 48% male (714)	Agalsidase alfa (dose not reported) for 24 mos	–	–	–	GI SYMPTOMS—benefit Improvements noted for all patients, significant improvements for male patients and children

Table 2 continued

Citation	Study design (country)	Pts (N)	Treatment	Study results			
				Renal effects	CNS effects	CV effects	Other effects
Hughes et al. 2008 [85]	R then OLE (UK)	FD; 100% male (15)	Agalsidase alfa 0.2 mg/kg EOW vs. placebo for 6 mos then agalsidase alfa for 2 yrs	–	–	Benefit ↓ In LVM at 6 mos ($P = 0.041$)	–
Thoféhrn et al. 2009 [40]	OL (Brazil)	FD; 79% male (9)	Agalsidase alfa 0.2 mg/kg EOW for ≤ 3 yrs	Stable No significant change in kidney function	–	–	–
Whybra et al. 2009 [39]	OL (Germany)	FD; ≥ 18 yrs; 100% female (36)	Agalsidase alfa 0.2 mg/kg EOW for 48 mos	Stable No significant change in eGFR	–	Benefit ↓ In LVM at 12 mos ($P < 0.001$)	Pain—benefit Significant improvement in BPI score ($P = 0.001$)
Hughes et al. 2011 [45]	Retrospective, observational (International)	FD; ≥ 18 yrs; 69% male (250)	Agalsidase alfa for ≥ 4 yrs	No benefit ↓ In eGFR for males	Stable	Benefit ↓ In LVM in females	Pain and QoL—stable GI symptoms—stable
Pisani et al. 2012 [50]	Retrospective, observational (Italy)	FD; mean age 44 yrs; 70% male (10)	Agalsidase alfa ≥ 1.6 yrs, post-switch from agalsidase beta	Stable No clinically significant change or eGFR change	–	Stable No change in LVEF	Pain and QoL—stable Generally, no changes across SF-36 components and no significant change in pain
Havranek et al. 2013 [79]	Retrospective, observational (UK)	FD; 2–16 yrs; 50% male (22)	Agalsidase alfa 0.2 mg/kg biweekly for 2 yrs	–	–	Stable	–

Table 2 continued

Citation	Study design (country)	Pts (N)	Treatment	Study results			
				Renal effects	CNS effects	CV effects	Other effects
Kampmann et al. 2015 [41]	Retrospective (Germany)	FD; 47% male (45)	Agalsidase alfa for 10 yrs	Stable No significant change in kidney function	-	Stable Some CV function measures improved in certain sub-groups	-
Ramaswami et al. 2019 [43]	Retrospective (International)	FD; 18–67 yrs; 52% male (221)	Agalsidase alfa 0.2 mg/kg EOW for 10 yrs	Stable No significant change in kidney function	-	Stable	-

BPI Brief Pain Inventory, CNS central nervous system, CV cardiovascular, eGFR estimated glomerular filtration rate, EOW every other week, EQ-5D European Quality of life-5 Dimensions, FD Fabry disease, GI gastrointestinal, LVM left ventricular mass, LVMi left ventricular mass index, OL open label, OLE open label extension, mos months, MWT maximum wall thickness, pts patients, QoL quality of life, R randomized, UK United Kingdom, USA United States of America, yrs years

eGFR was 53.7 ± 6.3 mL/min/1.73 m² and the mean rate of change in eGFR was -8.0 ± 0.8 mL/min/1.73 m²/year. After switching to weekly dosing, over the course of the 24-month follow-up period the mean rate of change in eGFR slowed to -3.3 ± 1.4 mL/min/1.73 m²/year ($P < 0.01$ compared with EOW), demonstrating an improved slope of decline when the same dose was given more frequently [46].

Overall, these findings suggest that the renal system is stabilized with agalsidase alfa when treatment is initiated in patients with stage 1–2 CKD; however, the benefits are less apparent in those with stage ≥ 3 CKD, for whom a minor sex-specific difference in treatment response may occur.

Comparative Effects of Agalsidase Beta Versus Agalsidase Alfa

Data directly comparing agalsidase alfa and agalsidase beta are limited; however, various non-comparative and retrospective studies have been performed and demonstrated the value of both agents in improving renal function in patients with FD, with some studies suggesting a difference in treatment effectiveness.

A systematic review compared the efficacy and safety of ERT in patients with FD using a linear regression and pooled analysis [47]. When one study assessing agalsidase beta was compared with six studies of agalsidase alfa (which had significant heterogeneity), there were no significant differences between the treatments with regards to renal complications. However, a significant difference in renal impairment was seen between patients treated with agalsidase beta and untreated patients (in 11 studies), emphasizing the importance of initiating ERT to prevent renal disease [47]. Similarly, a retrospective study that directly compared agalsidase alfa and agalsidase beta reported no significant differences in eGFR slope, regardless of whether eGFR was < 60 or ≥ 60 mL/min/1.73 m² [48].

A head-to-head study by Vedder and colleagues comparing the same dose of agalsidase alfa and agalsidase beta (0.2 mg/kg EOW; i.e., an unlicensed dose of agalsidase beta) reported no differences in renal function [49]. This study

also assessed treatment failure, defined as renal disease progression (either a 33% increase in serum creatinine or requirement for dialysis or transplantation), cardiac disease progression (heart failure requiring hospitalization, a new infarction, or the need for cardioversion or anti-arrhythmic drugs), or a neurologist-diagnosed new cerebrovascular accident or new lacunar infarctions identified on magnetic resonance imaging by an experienced neuroradiologist. Of note, treatment failure due to renal insufficiency (> 33% increase in serum creatinine) was only reported in patients receiving agalsidase alfa (Table 3) [49].

During a global shortage of agalsidase beta in 2009, many patients switched to agalsidase alfa, which allowed for the real-world assessment of differences in treatment response over time [28, 50–53]. A systematic review and meta-analysis of seven studies determined that, in general, there was no change in renal function during the course of this switch [54]. Although one study showed a benefit with agalsidase alfa when assessing cystatin C-based eGFR and creatinine/cystatin C-based eGFR [52], other studies have reported some cases of worsening renal function after switching to agalsidase alfa [28, 53, 54]. A Latin American study assessing the effects of switching from agalsidase beta to agalsidase alfa (which was not included in this meta-analysis) also showed no change in mean eGFR over a 24-month follow-up period [55].

In a subsequent meta-analysis and systematic review of patients who switched from agalsidase beta to agalsidase alfa, a significant loss of renal function after switching was observed in 4 of the 15 studies; this was not reversed despite agalsidase alfa dose increases [56]. Lyso-GL-3 levels decreased after patients switched back to agalsidase beta, which suggests that there was a dose-dependent effect and/or that agalsidase beta was more advantageous in these patients. In one of the included studies, eGFR improved following the switch back to agalsidase beta [56]. Three studies have demonstrated a continuous decline in eGFR in patients with FD switched from agalsidase beta to agalsidase alfa [28, 52, 53]; in one of the studies, this decline was attenuated in patients who had switched back to agalsidase beta [53]. Therefore, it has been suggested

that, rather than eGFR, plasma lyso-GL-3 levels may be a more sensitive indicator of treatment response after switching back to agalsidase beta [57].

Taken together, these data highlight the importance of initiating ERT prior to the development of renal disease. Moreover, data on switching to higher doses of agalsidase alfa indicated that loss of renal function was not prevented. As such, long-term post-switch data suggest a benefit with agalsidase beta over agalsidase alfa.

Renal Effects of Migalastat

In patients with FD, eGFR generally remains stable over the course of treatment with migalastat, with most studies reporting non-significant eGFR decline (Table 4) [4, 58–61]. To our knowledge, however, two studies have reported a significant eGFR decline with migalastat [62–64]; in one study, renal function decreased after 1 year of migalastat therapy, and, in some cases, plasma lyso-GL-3 levels increased after switching to migalastat therapy [62], while, in the other study, eGFR decreased by $-5.0 \text{ mL/min/1.73 m}^2$ in females and by $-4.6 \text{ mL/min/1.73 m}^2$ in males after 12 months of migalastat treatment [64]. The yearly loss in eGFR was more moderate after 24 months of migalastat treatment ($-2.6 \text{ mL/min/1.73 m}^2/\text{year}$ in females and $-4.4 \text{ mL/min/1.73 m}^2/\text{year}$ in males) [64]. A post hoc analysis of a combined phase 3 and extension study reported that renal function was relatively stable regardless of sex, phenotype, or treatment status [65]. Another post hoc analysis of phase 3 studies determined that migalastat-treated patients with amenable *GLA* variants had fewer clinical events (including renal events) than ERT-treated patients over 18 months [66]. Interestingly, this analysis found that a higher baseline eGFR was a predictor for experiencing a clinical event [66].

Two studies support the renal benefits of migalastat, with treatment providing a reduction in GL-3 levels in renal endothelial cells [4, 23]. When migalastat was compared with other ERTs in a phase 3 migalastat trial, there was no significant difference between treatment groups in the

Table 3 Studies comparing the effects of agalsidase beta and agalsidase alfa treatment on the organ systems affected by Fabry disease

Citation	Study design (country)	Pts (N)	Treatment	Study results		
				Renal effects	CV effects	Other effects
Vedder et al. 2007 [49]	Prospective, OL (Netherlands)	FD; 19–76 yrs; 50% male (36)	Agalsidase beta or agalsidase alfa 0.2mg/kg EOW for ≥ 12 mos	Stable No difference in eGFR or urinary protein data	Benefit w/ ERT No significant change in cardiac mass at 12 mos w/ either ERT (median change – 11% with agalsidase alfa vs. – 15% with agalsidase beta)	Pain and QoL—stable No difference
Tsuboi et al. 2012 [51]	Observational (Japan)	Mild-to-moderate FD; 31–68 yrs; 36% male (11)	Agalsidase beta 1 mg/kg EOW (24 mos) then agalsidase alfa 0.2 mg/kg EOW (12 mos)	Stable No significant change in eGFR	Stable w/ agalsidase alfa ↓ LVMI ($P = 0.0137$)	Pain and QoL—stable
Pisani et al. 2013 [50]	Observational (Italy)	FD; mean age 44 yrs; 70% male (10)	Pre-ERT to agalsidase beta 1 mg/kg EOW for ≥ 48 mos, then agalsidase alfa 0.2mg/kg EOW for ≥ 20 mos	Stable w/ ERT Renal function remained stable	Benefit w/ ERT Significant decrease in cardiac mass w/ agalsidase beta that was maintained post-switch to agalsidase alfa	–
Ripeau et al. 2017 [55]	Observational (Argentina, Venezuela)	FD; 10–56 yrs; 70% male (33)	Agalsidase beta 1 mg/kg EOW (12 mos) then agalsidase alfa 0.2 mg/kg EOW (12 mos)	Stable No significant change in eGFR	Stable No significant changes in LVMI, IVST or LPVWT	Pain and QoL—stable

Table 3 continued

Citation	Study design (country)	Pts (N)	Treatment	Study results		
				Renal effects	CV effects	Other effects
Krämer et al. 2018 [53]	Observational (Germany)	FD; ≥ 18 yrs; 62% male (112)	Continued agalsidase beta 1 mg/kg EOW for ≥ 12 mos (regular dose); agalsidase beta 0.5 mg/kg EOW, then agalsidase alfa 0.2 mg/kg EOW (≥ 12 mos) or directly switched to agalsidase alfa (switch); switched to agalsidase beta after receiving agalsidase alfa for ≥ 12 mos (re-switch)	Stable	Stable	–
				No significant change in eGFR w/ regular dose group; annual ↓ eGFR w/ switch group and re-switch groups	No significant changes in cardiac parameters	
Lenders et al. 2018 [107]	Open cohort (Germany, Austria, Switzerland)	FD; 100% male (26)	Agalsidase alfa 0.2 mg/kg or agalsidase beta 1 mg/kg (7–204 mos)	No benefit	Stable	–
				Mild ↓ eGFR loss in ADA-saturated pts (more pronounced in non-ADA-saturated pts)	Stable intraventricular septum thickness in ADA-saturated pts (↑ in the non-ADA-saturated pts)	
Arends et al. 2018 [48]	Observational (Canada, Germany, Netherlands, UK)	FD; 73% male (387)	Agalsidase beta 1 mg/kg EOW vs. agalsidase alfa 0.2 mg/kg EOW for ≥ 9 mos	Stable	Stable	–
				No significant change in eGFR	No significant change in LVMI	

ADA antidrug antibodies, CV cardiovascular, eGFR estimated glomerular filtration rate, EOW every other week, ERT enzyme replacement therapy, FD Fabry disease, IVST interventricular septal thickness, LVMI left ventricular mass index, LVPWT left ventricular posterior wall thickness, mos months, OL open label, Pts patients, QoL quality of life, UK United Kingdom, w/ with, w/o without, yrs years

reduction of renal function over time (Table 4) [60]. However, further research is warranted to determine whether the effect of migalastat on renal outcomes is due to migalastat or instead due to a continuation of treatment following 12 months of prior ERT. Real-world data from an analysis of the Fabry Registry emphasize the importance of careful monitoring after switching patients from agalsidase beta to migalastat [67]. This analysis described within-patient clinical outcomes for patients with FD treated with agalsidase beta for ≥ 1 year as first primary therapy, followed by ≥ 6 months of migalastat as second primary therapy; the study inclusion cut-off date was 7 April 2023. The assessments of eGFR and plasma GL-3 suggested that disease progression occurred after switching (both for the comparison of before and after switching and in linear mixed models) [67].

As mentioned above, migalastat is only indicated in patients who have an amenable *GLA* variant [1, 13, 22]. Consequently, while migalastat may have favorable effects on renal function, these benefits do not apply to all patients with FD.

NEUROLOGICAL INVOLVEMENT IN FD

Patients with FD can present with CNS complications, such as cerebral small vessel disease (SVD), characterized by white matter hyperintensities, cerebral microbleeds, and cerebral infarcts [68–70]. In one study, 45% of patients with FD presented with white matter lesions (WMLs) at their first visit to the clinic, with the likelihood of WMLs significantly increasing with age [71]. Phenotypic differences were reported for both sexes; those with classical FD were significantly more likely to have WMLs than those with non-classical FD, and males were more likely to have WMLs than females [71]. There is a strong correlation between WML severity and the speed of cognitive deterioration, and clinical disease severity in patients with FD [72]. Of the neurological effects, cerebrovascular events are the most common and can be the most clinically

disabling affliction, with a poorly understood pathogenesis [68–70, 73].

Age is an important factor with regard to the neurological effects of FD. It is a predictor of SVD, with older patients having a higher risk of stroke than younger patients; of note, patients with FD tend to develop SVD at a younger age than the general population [70]. However, in general, the cerebrovascular effects in younger patients with FD is not well studied [68–70, 73].

Neurological Effects of Agalsidase Beta

In a study of the effects of agalsidase beta on WML progression, the proportion of patients with stable WML burden was significantly greater among patients receiving ERT than in those receiving placebo (Table 1) [74]. Notably, there was a clinically and statistically significant reduction or stabilization of WML load in patients aged ≤ 50 years up to 33 months after treatment initiation [74]. In addition, this study highlighted the importance of initiating treatment prior to serious organ involvement, with a correlation found between left ventricular hypertrophy (LVH) and WML burden [74]. Finally, a meta-analysis of seven cohort studies and two randomized controlled trials found that ERT for FD had a beneficial effect on stroke prevention [75].

Neurological Effects of Agalsidase Alfa

Few studies have investigated the effect agalsidase alfa has on the CNS as a primary aim (Table 2). In a small study investigating CNS involvement following 1 year of agalsidase alfa treatment in four patients who had WMLs at baseline, two patients remained stable and two experienced worsening of WMLs [76].

Hearing impairment is substantially more prevalent in patients with FD compared with a healthy population of equivalent age [77]. In a study of male patients with FD, there was a significant long-term benefit of agalsidase alfa for high-frequency hearing, although no benefit was observed for low-frequency hearing, while, overall, hearing deteriorated during the

Table 4 Effects of migalastat on the organ systems affected by Fabry disease

Citation	Study design (Country)	Pts (N)	Treatment	Study results		
				Renal effects	CV effects	Other effects
Germain et al. 2016 [23]	Phase 3, R, DB, PG w/ OLE (International)	FD w/ or w/o amenable vts; 16–74 yrs; 36% male (67)	Migalastat 150 mg EOD vs. placebo for 6 mos then migalastat 150 mg EOD	Stable	Benefit	GI symptoms—benefit
				All pts: No difference in GL-3 response at 6 mos (41% vs. 28%; $P = 0.30$) ↓ Annualized eGFR at 24 mos in all pts or in pts w/ amenable vts	↓ LVMI in pts w/ amenable vts	Improvements in 3/5 domains in the GSRs: diarrhea, reflux, and indigestion
Müntze et al. 2018 [62]	OL (Germany)	FD; 20–74 yrs; 62% male (21)	Migalastat (123 mg/kg) EOW for 12 mos	No benefit	Benefit	α-Gal A activity—benefit
				↓ eGFR ($P = 0.012$) ↑ Creatinine	↓ LVMI ($P = 0.012$)	↑ α-Gal A activity ($P = 0.001$)
Germain et al. 2019 [4] FACETS study	Phase 3, R, MC, DB w/ OLE (International)	FD (classic and non-classic phenotype); 16–74 yrs; 100% male (50)	Migalastat 150 mg EOD vs. placebo for 6 mos then migalastat 150 mg EOD	Stable	Benefit	GI symptoms—benefit
				Slight ↓ in eGFR _{CKD-EPI}	↓ LVMI	Improvement in GSRs diarrhea domain scores

Table 4 continued

Citation	Study design (Country)	Pts (N)	Treatment	Study results		
				Renal effects	CV effects	Other effects
Hughes et al. 2017 [60] ATTRACT study	Phase 3, R, OL then OLE (International)	FD; 18–72 yrs; 44% male (57)	Migalastat 150 mg EOD vs. ERT (agalsidase alfa, [0.2 mg/kg] or agalsidase beta [1.0 mg/kg] biweekly) for 18 mos then migalastat for 12 mos	Stable ↓ eGFR _{create} and mGFR _{iohexol} in both treatment groups	Benefit ↓ LVMI vs. ERT	Pain and QoL—benefit
Schiffmann et al. 2018 [95] Sub-analysis of the FACETS study	Phase 3, R, MC, DB w/ OLE (International)	FD; 16–74 yrs; 100% male (50)	Migalastat	–	–	GI symptoms—benefit Improvement in GSRS scores
Lenders et al. 2020 [63] FAMOUS study	MC observational (Germany)	FD; ≥ 16–yrs; 53% male (59)	Migalastat 123 mg/kg EOD	No benefit ↓ eGFR _{create} in men ($P = 0.0020$) and women ($P = 0.0004$)	Benefit ↓ LVMI overall ($P = 0.001$) and in men ($P = 0.0061$) and women ($P = 0.0050$)	Pain—stable
Feldt-Rasmussen et al. 2020 [59] OLE of ATTRACT study	Phase 3, R, OL then OLE (International)	FD; 16–74 yrs; 44% male (48)	Migalastat 150 mg EOD vs. ERT (agalsidase alfa, [0.2 mg/kg] or agalsidase beta [1.0 mg/kg] biweekly) for 18 mos then migalastat for 12 mos	Stable ↓ eGFR _{CKD-EPI} at 30 mos	Benefit ↓ LVMI at 30 mos	–

Table 4 continued

Citation	Study design (Country)	Pts (N)	Treatment	Study results		
				Renal effects	CV effects	Other effects
Narita et al. 2020 [58] ATTRACT subgroup analysis in Japanese pts	Phase 3, R, OL then OLE (International)	FD; Japanese; 16–74 yrs; 43% male (7)	Migalastat 150 mg EOD vs. ERT (agalsidase alfa, [0.2 mg/kg] or agalsidase beta [1.0 mg/kg] biweekly) for 18 mos then migalastat for 12 mos	Stable ↓ eGFR _{create} and mGFR _{iohexol}	Benefit ↓ LVMI (2D/M-mode)	–
Riccio et al. 2020 [87]	Observational (Italy)	FD; 18–66 yrs; 100% male (7)	Agalsidase alfa (0.2 mg/kg) or agalsidase beta (1.0 mg/kg) EOW for 12 mos then migalastat 123 mg EOD for 12 mos	Stable	Benefit ↓ LVMI ($P = 0.016$)	Pain and QoL— benefit Only w/ ERT
Bichet et al. 2021 [65] Pooled analysis of the FACETS and ATTRACT studies and their OLE	Pooled analysis of two phase 3, R w/ OLE (International)	FD; ERT-naïve or ERT-experienced	Migalastat 123mg vs. placebo for 24 mos (FACETS) then OL migalastat 123mg Migalastat 123mg vs. ERT for 30 mos (ATTRACT) then OL migalastat 123mg	Stable	–	–

Table 4 continued

Citation	Study design (Country)	Pts (N)	Treatment	Study results		
				Renal effects	CV effects	Other effects
Camporeale et al. 2023 [61]	Observational (Italy)	Fabry disease; 45.4 ± 15.7 yrs; 55% male (33)	Migalastat 123mg/kg EOD	Stable	Stable No change in LV mass ($P = 0.55$) and an increase in septal T1 ($P = 0.056$)	– Improvement in exercise tolerance

α -Gal A α -galactosidase A, DB double blind, CV cardiovascular, $eGFR$ estimated glomerular filtration rate, $eGFR_{CKD-EPI}$ Chronic Kidney Disease Epidemiology Collaboration equation for estimated glomerular filtration rate, $eGFR_{crea}$ creatinine as a measure of estimated glomerular filtration rate, EOD every other day, EOW every other week, ERT enzyme replacement therapy, FD Fabry disease, GI gastrointestinal, GL-3 globotriaosylceramide, GSKS Gastrointestinal Symptom Rating Scale, LV left ventricular, LVMI left ventricular mass index, MC multicenter, $mGFR_{iohexol}$ measured glomerular filtration rate by iohexol clearance, mos months, OL open label, OLE open-label extension, PG parallel group, pts patients, QoL quality of life, R randomized, vts variants, w/o without, yrs years

first 6 months of treatment [77]. A subsequent retrospective study showed similar findings, with improvements seen in some male patients with FD, although none of the female patients with hearing loss regained any hearing [45]. These findings suggest that agalsidase alfa may improve some of the neurological effects of FD, but more data are needed to provide clarity.

Comparative Effects of Agalsidase Alfa Versus Agalsidase Beta

The head-to-head comparison study of agalsidase alfa versus agalsidase beta at the same dose (0.2 mg/kg EOW; i.e., an unlicensed dose of agalsidase beta) by Vedder and colleagues did not assess neurological benefits over time; however, five of the six patients with treatment failure over 24 months had progression of brain magnetic resonance imaging (MRI) abnormalities (three receiving agalsidase beta and two receiving agalsidase alfa) [49]. One patient receiving agalsidase alfa died of cerebral infarction after 20 months of treatment (Table 3) [49].

In the systematic review and meta-analysis assessing the switch from agalsidase beta to agalsidase alfa, only one study investigated neurological effects, with no significant differences observed over the study period [54]. In a comparative systematic review of ERT in seven cohort studies assessing agalsidase beta and five investigating agalsidase alfa, linear regression showed that agalsidase beta was associated with a significantly lower incidence of cerebrovascular complications than agalsidase alfa or no treatment [47].

Neurological Effects of Migalastat

Despite the expectation that migalastat should cross the blood–brain barrier, to date, there are no studies available investigating its CNS effects, most likely due to the more recent approval of this agent compared with agalsidase alfa and agalsidase beta.

CARDIOVASCULAR INVOLVEMENT IN FD

According to the Fabry Outcome Survey, cardiac disease is the main cause of death among patients with FD, regardless of whether or not they receive ERT [78]. Cardiac complications may be subtle in children and adolescents with FD, and progressively worsen as the patient ages [79].

A sex-specific difference in cardiovascular complications was observed in a study of 182 patients with FD who underwent cardiovascular MRI [80]. LVH was significantly more prevalent in males than females, the prevalence increased with age in both sexes. A similar pattern of male- and age-prevalence was observed with late gadolinium enhancement (Fig. 2) [80].

Cardiovascular Effects of Agalsidase Beta

Several studies have shown cardiac benefits following agalsidase beta treatment [30, 34, 35, 81, 82], as well as a stabilizing effect in other studies (Table 1) [31, 32, 38, 48, 83].

Of note, the majority of studies used echocardiography to assess cardiovascular effects, which has inferior precision to cardiac MRI [84]. Two studies used cardiac MRI to evaluate the cardiovascular effects, both of which demonstrated benefits with agalsidase beta [34, 81]. The first of these studies showed significant improvements in cardiovascular measures and an amelioration of clinical cardiological symptoms in all patients receiving agalsidase beta for 2 years [34]. In the second study, agalsidase beta provided significant improvements in peak systolic strain and end-diastolic strain of the posterior wall over 1 year, as determined by color Doppler myocardial imaging, while echocardiography showed a reduction in end-diastolic posterior wall thickness [81]. In addition to these benefits, MRI showed a reduction in myocardial mass [81]. These results indicate that agalsidase beta may improve regional myocardial function and reduce LVH in patients with FD [81]. An early phase 3 trial of agalsidase beta reported clearance of GL-3 in cardiac capillary endothelial cells for most

patients after only 6 months of treatment, indicating a positive impact on cardiac tissue [30]. However, previous studies have indicated that capillary endothelium clearance does not necessarily reflect myocyte clearance [25].

The benefits of agalsidase beta treatment may be dependent on the extent of underlying cardiac disease at the time of treatment initiation (Table 1). In a small study in children who had no cardiac abnormalities at baseline, there were no changes in cardiac parameters after 48 months of agalsidase beta treatment [31]. In another small study, six out of ten pediatric patients developed valvular involvement during the 8-year follow up period (at 6–21 years of age), as measured by echocardiography; however, none had subjective symptoms [36]. Two patients, one with mild LVH at baseline and one with mild tricuspid valve insufficiency, had normal echocardiography findings after 1 year of receiving agalsidase beta. No electrocardiography abnormalities were reported during the study [36].

In a detailed investigation of the cardiac effects of agalsidase beta, a significant proportion of patients with FD without signs or symptoms of cardiac involvement at baseline had more subtle indications of reduced cardiac health compared with healthy controls [82]. In this study, agalsidase beta significantly improved orthostatic regulation and baroreflex sensitivity, with improvements in heart rate, blood pressure and sympathetic activation over 18 or 23 months [82].

A long-term study showed that cardiac hypertrophy progressed during the pre-treatment period, as assessed by left ventricular posterior wall thickness (LVPWT) and interventricular septal thickness (IVST), but appeared to stabilize after agalsidase beta treatment [32]. In another long-term study of patients treated for > 10 years with agalsidase beta, LVPWT and IVST remained within normal ranges in patients aged < 40 years (with no LVH at baseline) [35]. However, patients aged > 40 years (with LVH at baseline), had a significant increase in LVH despite receiving agalsidase beta [35]. Of note, another study demonstrated a link between the effects of agalsidase beta on cardiac function and renal function [38]. Although a non-significant reduction

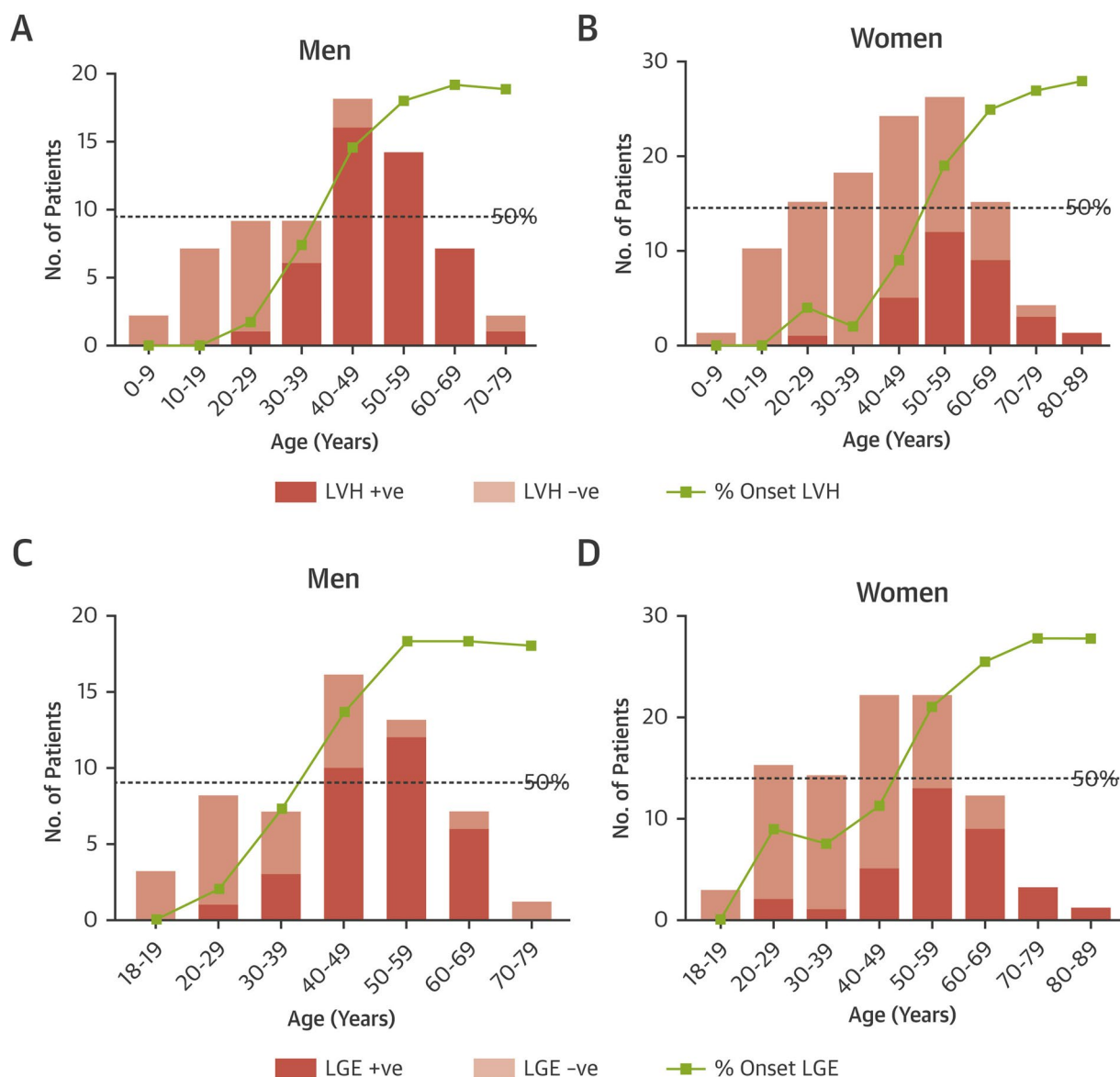


Fig. 2 Respective cumulative onset of cardiac conditions, including left ventricular hypertrophy (LVH) in **a** men and **b** women, and late-gadolinium enhancement (LGE) in **c** men and **d** women with Fabry disease, separated by

age group. The *green line* indicates cumulative penetrance [80]. Reproduced from [80] with permission from Elsevier. *No.* number, *NT-proBNP* N-terminal pro-brain natriuretic peptide

in posterior wall thickness (PWT) was observed overall, the reduction in PWT was found to be significant among patients with preserved renal function [38]. This highlights the importance of monitoring the effects of treatment on all major organ systems affected by FD.

These studies demonstrate that agalsidase beta may provide cardiovascular benefits in patients with FD, although the extent of cardiac disease, which tends to progress with increasing age, may affect the degree of measurable treatment effectiveness.

Cardiovascular Effects of Agalsidase Alfa

Several studies investigating agalsidase alfa therapy in patients with FD have demonstrated cardiovascular benefits [39, 42, 85], and a stabilizing effect (Table 2) [41, 43, 45].

All studies investigating agalsidase alfa used either echocardiology or cardiac MRI to measure cardiac parameters; in cases where echocardiology alone was used, the accuracy of the results may be somewhat limited [84]. Compared with placebo, 6 months' agalsidase alfa treatment was associated with a non-significant reduction ($P = 0.47$) in myocardial GL-3 levels, with a significant reduction of left ventricular mass (LVM) only in the first 6 months of treatment, followed by no change over 2 years [85]. Of note, quantification of myocardial GL-3 was performed by high-performance liquid chromatography using whole myocardial samples, thus not providing any data on effective myocyte clearance, with the measured reduction likely sustained by endothelial cell clearance.

A few long-term studies have examined differences in treatment response based on sex and underlying disease state; however, the results were contradictory (Table 2). A retrospective study showed that the LVM index (LVMI) remained relatively stable with agalsidase alfa over 10 years, but patients who had LVH at baseline had a slight increase in LVMI, which was observed in both male and female patients [43]. Similarly, in another retrospective study, LVMI significantly improved with 1 year of treatment, although the only significant improvement observed after 10 years was in males with a baseline LVMI of $\geq 50 \text{ g/m}^{2.7}$ [41]. Improvements in other cardiac structural parameters were also observed in male patients, including a significant reduction in mean wall thickness. Most changes in cardiac functional parameters during agalsidase alfa treatment were similar between the sexes [41]. In contrast, in a retrospective study, only female patients with baseline LVH experienced a significant decrease in LVMI after 4 years of agalsidase alfa treatment [45]. Likewise, in a female-only study with baseline LVH in 69% of patients, agalsidase alfa was associated with a significant decrease in LVM,

and many patients with New York Heart Association class II–III heart failure showed improvement over 4 years [39].

Only one study has examined the effects of agalsidase alfa in pediatric patients with FD [79]. The majority of patients had no change in cardiac function over 2 years, although 7 of 22 patients developed T-wave abnormalities and 3 developed LVH [79].

These findings suggest that agalsidase alfa may improve cardiac parameters, although further research is required to determine possible long-term clinical cardiovascular benefits or whether there are sex-specific differences in treatment response.

Comparative Effects of Agalsidase Beta Versus Agalsidase Alfa

The majority of studies comparing the cardiovascular effects of agalsidase alfa and agalsidase beta report a switch from one agent to another (Table 3). In the systematic review and meta-analysis of the agalsidase beta to agalsidase alfa switch, two studies reported cardiac improvements post-switch to agalsidase alfa, and one study reported worsening of IVST [54]. Another study in this review demonstrated that, although left ventricular ejection fraction was unchanged in ERT-naïve patients who initiated agalsidase beta, and remained unchanged post-switch to agalsidase alfa, there were significant decreases in LVMI and LV wall thickness that were maintained post-switch to agalsidase alfa [50]. Another study of Japanese patients reported a significant improvement in LVMI from baseline (where patients had been receiving agalsidase beta) to 12 months post-switch to agalsidase alfa [51]. In another switching study (which was not included in the meta-analysis), there was no change in LVMI, IVS, or LVPWT after switching from agalsidase beta to agalsidase alfa [55]. A subsequent meta-analysis and systematic review of switching ERTs showed that cardiac parameters remained generally stable post-switch to agalsidase alfa, with one patient across the studies reporting a significant worsening of LVH [56].

A comparative systematic review that included four studies of agalsidase alfa and three of agalsidase beta versus untreated patients, found that agalsidase beta was associated with significantly fewer cardiovascular complications than untreated patients [47]. However, no significant differences in cardiovascular events were seen between agalsidase alfa and agalsidase beta or no ERT [47].

In a 1-year retrospective study of both agalsidase beta and agalsidase alfa by Arends and colleagues in 2018, combined treatment data showed a decrease in LVMI only in patients who had baseline LVH, irrespective of treatment received; however, a higher proportion of patients treated with agalsidase beta had a LVMI decrease when adjusted for baseline levels [48]. Although all of these studies demonstrated cardiovascular benefits with ERT (Table 3), the study suggests that agalsidase beta may provide better cardiac outcomes than agalsidase alfa. More head-to-head comparative studies of ERTs in patients with FD are warranted.

In the head-to-head ERT study of agalsidase alfa or agalsidase beta at a dose of 0.2 mg/kg EOW (i.e., an unlicensed dose of agalsidase beta) by Vedder and colleagues, no LVM reduction was observed with either treatment after 12 or 24 months of follow-up [49]. Treatment failure due to atrial fibrillation (i.e. cardiac disease progression) occurred in three patients: one male patient and one female patient after 42 and 36 months of agalsidase beta treatment, respectively, and in one male patient treated with agalsidase alfa for 30 months [49].

Sex-specific differences in cardiovascular outcomes have been reported with the ERTs in patients with FD [86]. A study that used cardiac MRI to assess the impact of ERT on cardiovascular parameters assessed 100 patients (37 on agalsidase alfa, 13 on agalsidase beta, and 50 untreated) over a median of 37 months [86]. There were no sex-specific differences observed in cardiac parameters (including ischemic heart disease or hypertension); however, males had more baseline cardiac involvement than females and tended to have higher rates of disease progression, despite the use of an ERT [86]. These data support the cardiovascular benefits of

ERTs and reinforce the need for early treatment initiation.

Cardiovascular Effects of Migalastat

Multiple studies have demonstrated the cardiovascular benefits of migalastat, with significant reductions in LVMI seen with echocardiographic evaluations over the course of treatment; in all these studies, the effect of migalastat on LVMI was evaluated by echocardiography not by MRI (Table 4) [23, 58, 59, 61–63]. Of note, the benefits of migalastat do not appear to be sex-specific, with significant LVMI reductions observed in both male and female patients with FD [63]. Importantly, within many studies, a significant LVMI reduction was observed in patients with baseline LVH [23, 59, 62].

Significant improvements in LVMI from baseline were observed in a study of male patients with FD after switching from agalsidase alfa or agalsidase beta to migalastat, although patients with abnormal cardiac parameters had no improvement with either treatment [87]. In a comparative trial, migalastat treatment for 18 months led to a small, but statistically significant, reduction in LVMI; in contrast, the reduction in LVMI with agalsidase alfa or agalsidase beta did not reach statistical significance [60]. This evidence suggests that migalastat ameliorates selected cardiac parameters.

Although these data provide evidence for the cardiovascular benefits of migalastat, these studies all measured cardiac parameters using echocardiography. However, a more recent study, which used cardiac MRI, showed stabilization of LVM and an increase in T1 over 18 months of treatment with migalastat in a small group of treatment-naïve patients with baseline cardiac involvement [61]. Notably, the majority of patients (81.3%) had a late-onset phenotype of FD. At 18 months' follow-up, a tendency to increasing troponin T values in the entire study population was noted, from a baseline median of 8.0 (range 4.0–21.0) ng/L to 14.5 (3.5–26.0) ng/L, which was above the normal value and approaching statistical significance ($P = 0.06$) [61].

OTHER DISEASE MANIFESTATIONS AND QUALITY OF LIFE

While the abovementioned organ systems are the primary focus of FD treatment to prevent disease progression and preserve life, patients also experience other disease manifestations, such as diarrhea, constipation, and abdominal pain, that affect their QoL [88]. The pathophysiological mechanisms of gastrointestinal complications in FD are still not clear, with the symptomatology presenting similarly to diarrhea-predominant inflammatory bowel syndrome [89]. Pain, particularly neuropathic pain, is often one of the earliest symptoms of FD in most patients and a significant contributor to reduced QoL [5, 90]. Therefore, it is important to determine the impact of available treatments on these factors.

Effects of Agalsidase Beta

A few studies have shown the benefits of agalsidase beta on the gastrointestinal system (Table 1). Agalsidase beta was associated with marked improvements in gastrointestinal symptoms in a prospective study of 25 patients with FD [38]. In another study, patients with severe gastrointestinal symptoms had a marked improvement after 8 months of agalsidase beta treatment [91]. This finding was supported by data from the Fabry Registry, in which male patients with classic or later-onset FD had a general reduction in gastrointestinal symptoms with agalsidase beta [92]. At treatment initiation, a higher proportion of patients with the classical phenotype had abdominal pain and diarrhea than those with the later-onset phenotype; following treatment, significant reductions in these symptoms were only observed in patients with the classical phenotype [92]. Data from the Fabry Registry on female patients receiving agalsidase beta showed an improvement in the proportion of patients with abdominal pain (from 45 to 31%) and diarrhea (from 39 to 27%) over a mean follow-up of 5.7 years [93].

Across a few studies, patients reported improvements in pain and QoL with agalsidase

beta (Table 1) [30, 34, 83]. A study of ten children with FD found variation in the symptomatology over 8 years of treatment with agalsidase beta, with all patients reporting having more energy and nine engaging in more physical activity [36]. Five patients had improvements in gastrointestinal symptoms, and most of those with headaches at baseline reported improvements [36]. Another pediatric study reported encouraging results with regard to improvements in QoL, including a significant increase in the number of school days [31]. Another Fabry Registry study reported significant improvements with agalsidase beta across all Short-Form 36 (SF-36) Health Survey physical and mental component summary scores among male patients [94]. There is evidence to support the benefits of agalsidase beta on reducing gastrointestinal and pain symptoms and improving patient QoL.

Effects of Agalsidase Alfa

Although data relating to the effects of agalsidase alfa on pain and QoL are limited, this ERT also appears to provide some benefits. The Fabry Outcome Survey study reported significant improvements in the EuroQoL-Five Dimensions utility score and Brief Pain Inventory (BPI) score among 304 patients receiving agalsidase alfa (Table 2) [42]. Similarly, a study of female patients with FD reported a significant reduction in the ‘worst pain’ BPI score with 1 year of agalsidase alfa treatment [39]. A 4-year Fabry Outcome Survey study of agalsidase alfa treatment in female versus male patients with FD reported no change in the prevalence of pain attacks or abdominal pain in females; however, in comparison to symptoms at baseline, there was a reduction in diarrhea (from 32 to 26%) and body pain (from 28 to 21%) [45]. For males, there was almost no change in abdominal pain or diarrhea from baseline, and a slight increase in body pain, while pain attacks were reduced (from 73 to 68%) [45].

In one study of 342 patients with FD, which investigated the effects of agalsidase alfa on gastrointestinal symptoms and QoL, there was

a reduction in the proportion of patients with gastrointestinal symptoms after 24 months' treatment [89]. Children and male patients had significant symptomatic improvements during treatment, with no children experiencing gastrointestinal symptoms after treatment initiation [89].

These findings indicate that further investigations into sex-specific differences underlying the effects of agalsidase alfa on pain and QoL are warranted.

Comparative Effects of Agalsidase Beta Versus Agalsidase Alfa

As discussed above, only one study has directly compared agalsidase beta and agalsidase alfa. Within this head-to-head study, there was no significant reduction in BPI score with either ERT after 12 or 24 months of treatment at the same 0.2-mg/kg EOW dose (i.e., an unlicensed dose of agalsidase beta) [49]. In the systematic review and meta-analysis of the switch from agalsidase beta to agalsidase alfa, three studies investigating pain showed no difference in severity post-switch, whereas one study reported fewer pain attacks; however, the latter study also reported worsening of gastrointestinal symptoms post-switch [54]. Three studies investigated changes in QoL, with no changes observed post-switch [54]. The other switching study reported that SF-36 physical functioning and BPI scores had improved following the switch to agalsidase alfa [55].

The most recent meta-analysis and systematic review of switching found that most symptoms were stable post-switch; however, two studies reported a worsening of Mainz Severity Score Index (MSSI) in patients who switched to agalsidase alfa and in those who switched back to agalsidase beta [56]. Interestingly, the recent studies in this meta-analysis showed an increase in pain symptoms in patients on agalsidase alfa that improved after switching back to agalsidase beta [56].

Overall, there are mixed results regarding the potential benefits of one agalsidase over the other; however, more recent long-term follow-up data showing improvements in pain after the

switch back to agalsidase beta warrants further investigation.

Effects of Migalastat

In the phase 3 FACETS study, 6 months of treatment with migalastat was associated with significant reductions in diarrhea compared with placebo (Table 4) [95], as well as a small improvement in the Gastrointestinal Symptoms Rating Scale subscale score [4]. Although no major improvements were seen in a 2-year observational study during migalastat treatment, pain, MSSI, and Depression and Somatic Symptoms Scale scores remained stable (Table 4) [63].

When compared with ERTs, one study reported migalastat was associated with similar SF-36 and BPI scores [60]; in a separate study, BPI scores only improved with ERT and remained stable with migalastat [87]. These data suggest that migalastat has a beneficial effect on improving diarrhea in patients with FD and may reduce pain symptoms and prevent the deterioration of QoL.

PRELIMINARY DATA ON THE EFFECTS OF PEGUNIGALSIDASE ALFA IN FD

Pegunigalsidase alfa has been recently approved for the treatment of FD in Europe and the US. Two phase 3 clinical trials (BRIDGE and BALANCE) have been published to date [96, 97]; data from a third phase 3 clinical trial (BRIGHT) are currently available as a congress abstract [98] and in a European Medicines Agency Assessment Report (EMA EPAR) [99]. The first clinical study (BRIDGE) evaluated the open-label use of pegunigalsidase alfa (1 mg/kg every 2 weeks) in adults with FD who had previously received agalsidase alfa in a 3-month dose-ranging study, followed by a 9-month extension [96]. Switching to pegunigalsidase alfa was well tolerated and provided additional clinical benefit, particularly with respect to the kidney function trajectory and the FD biomarker

plasma lyso-globotriaosylceramide (Gb3) in most patients [96]. The BALANCE study was conducted in adults with FD and an annualized eGFR slope of lower than $-2 \text{ mL/min/1.73 m}^2/\text{year}$ and who had been treated with agalsidase beta for ≥ 1 year, to assess the non-inferiority of pegunigalsidase alfa versus agalsidase beta [97]. Patients were randomly assigned 2:1 to receive pegunigalsidase alfa 1 mg/kg or agalsidase beta every 2 weeks for 2 years. Although pegunigalsidase alfa was non-inferior to agalsidase beta after 24 months of treatment for annualized eGFR slope (final analysis) [97], non-inferiority could not be demonstrated at the 12-month interim analysis (results available in the EMA EPAR [99]). Indeed, interim analysis results indicated a difference in annualized eGFR slope in favor of agalsidase beta [difference of $-0.749 \text{ mL/min/1.73 m}^2$, 95% confidence interval (CI) 3.03–1.51] [99]. The open-label BRIGHT study investigated an alternative dosing regimen for pegunigalsidase alfa, of 2 mg/kg once every 4 weeks, in patients who had switched from either agalsidase alfa or agalsidase beta [98]. Study results were inconclusive [99], and, indeed, 2 mg/kg once every 4 weeks is not an approved dose of pegunigalsidase alfa [100].

UNMET CLINICAL NEEDS IN PATIENTS WITH FD

As FD is highly heterogenous, it can be challenging to diagnose and manage [31]. The Fabry Registry data showed that patients with FD tend to experience their first symptoms at a young age; however, ERT tends to only be initiated decades later [101]. Bridging the gap between symptom onset and diagnosis remains a critical clinical need. Although guidelines addressing the management of FD are available, they are complex and divided by sex and/or clinical phenotype [102–104]. This may be due (in part) to the influence of sex and clinical phenotype on the clinical complexity of FD.

In a study by El Sayed and colleagues, in which 213 patients with FD (median age 50 years) were evaluated from birth to last visit, the rate of major cardiovascular events

(including death, cardiovascular death, heart failure hospitalization, sustained ventricular arrhythmias, myocardial infarction, conduction abnormality, and atrial fibrillation) was 11.0 per 1000 patient-years (95% CI 6.6–17.3) in males with classical FD, 4.4 per 1000 patient-years (95% CI 2.5–7.1) in females with classical FD and 5.9 per 1000 patient-years (95% CI 2.6–11.6) in males with non-classical FD [105]. None of the females with non-classical FD had major cardiovascular events. Sex and phenotype significantly influenced the risk of major cardiovascular events, indicating the need for patient-specific follow-up and treatment [105].

Recommendations from an international panel of FD specialists specify that males with classical FD should receive treatment regardless of symptoms, whereas females with classical FD should only receive treatment following the appearance of major organ injury [104]. Unfortunately, while female patients are less adversely affected by FD, they can experience varied symptomatology and there is some evidence that they are undertreated. In one study, female patients were treated with ERTs substantially less frequently than males (34% vs. 82%, respectively), and some untreated female patients had major organ involvement, including LVH [101].

Despite the benefits of available treatment options, none can substantially reverse the major organ damage caused by FD progression. Of these treatments, ERT does not provide dramatic improvements in outcomes for all organ systems. This is probably due to the pathophysiological pathway at the origin of the disease where different mechanisms (storage, inflammation, apoptosis, etc.) lead to chronic and non-reversible tissue damage, such as sclerosis and fibrosis. To date, no therapeutic options have offered substantial amelioration of organ dysfunction; instead, they provide various grades of stabilization in progressive end-organ damage and the related functioning slope.

Various studies have shown correlations between major organ systems and disease progression [35, 76, 77]. While children and adolescents may not show obvious signs of cardiac complications, careful screening has highlighted subtle abnormalities that are understood to be LVH precursors [79]. Therefore, all three

treatments should be initiated prior to disease progression and the development of irreversible pathological organs changes [30, 38, 65, 83], which may help to address the abovementioned unmet clinical needs.

AN OPTIMAL AND PRACTICAL THERAPEUTIC APPROACH: AUTHORS' PERSPECTIVE

The developments in FD treatment over the past 20 years has significantly changed the natural history of the disease and has improved patient survival, morbidity, and QoL. However, in some cases, the introduction of FD therapy is unable to reverse symptoms or arrest/slow disease progression. There can be several reasons for therapeutical failure, including a delayed diagnosis, delayed treatment initiation, or variable drug efficacy. Alternatively, in some cases, therapy is administered in the presence of polymorphisms or benign mutations (e.g., the D313Y variant), diverting resources from patients who may be severely affected. In these cases, eventual symptoms (often neurological, and similar to those documented in FD), are not due to the disease but are only concomitant and cannot be resolved by/cannot benefit from FD therapies.

Since FD is a progressive disease that can lead to organ failure, an optimal therapeutic approach relies on more than just an early diagnosis. Minimizing the time between the onset of symptoms and diagnosis, as well as the time between diagnosis and initiation of treatment, is likely to improve the effect of therapy on signs and symptoms. However, an early diagnosis should not take precedence over the correct diagnosis. Indeed, before the choice of a specific treatment is made, it is crucial to achieve the correct FD diagnosis. The increasing number of new variants and VUS can make it difficult to determine the real pathogenic role of the variant, which in turn makes it challenging to accurately determine when to start therapy or which drug to administer to a specific patient.

The definition of a real phenotype should start from a familial evaluation of disease burden, also considering possible intrafamilial variability. Thereafter, a complete patient investigation (clinical, biochemical, and histopathological examination) is required to confirm or exclude the pathogenic role of a *GLA* variant. At present, it is generally thought that elevated levels of lyso-GL-3 and the ultrastructural presence of zebra-bodies in tissue biopsies are the most relevant elements to distinguish pathogenic variants from benign variants, especially if they are new or a VUS. Therefore, a multidisciplinary approach that can aid in making the correct diagnosis is recommended before the initiation of a particular therapy. Geneticists and clinicians should seek advice/collaboration with other physicians involved in the diagnosis and management of FD.

Once the correct phenotype and disease burden has been established, it is necessary to identify the therapeutic goals of each patient. Improvement of signs/symptoms such as pain and albuminuria is possible if treatment starts very early in childhood or adolescence. However, if diagnosis is delayed and treatment begins in adulthood, in the presence of proteinuria, or initial LVH, therapeutic goals should be adjusted to aim for at least the stabilization of signs and symptoms and the reduction of disease progression. Finally, in the advanced phases of the disease, the presence of chronic renal failure or advanced cardiac involvement may limit the achievement of therapeutic goals.

The choice of the best treatment strategy should not be based only on therapeutic goals but also on other factors. Genotype, phenotype, age of onset, onset symptom, and disease burden are the main factors that a multidisciplinary team should consider in the choice of treatment strategy. Personalizing or individualizing the choice of treatment should be based on the decision-making of an expert team and physicians should not be influenced entirely by the desires of the patient. For example, patients may prefer oral therapy to intravenous therapy, but there may be no clinical indication towards

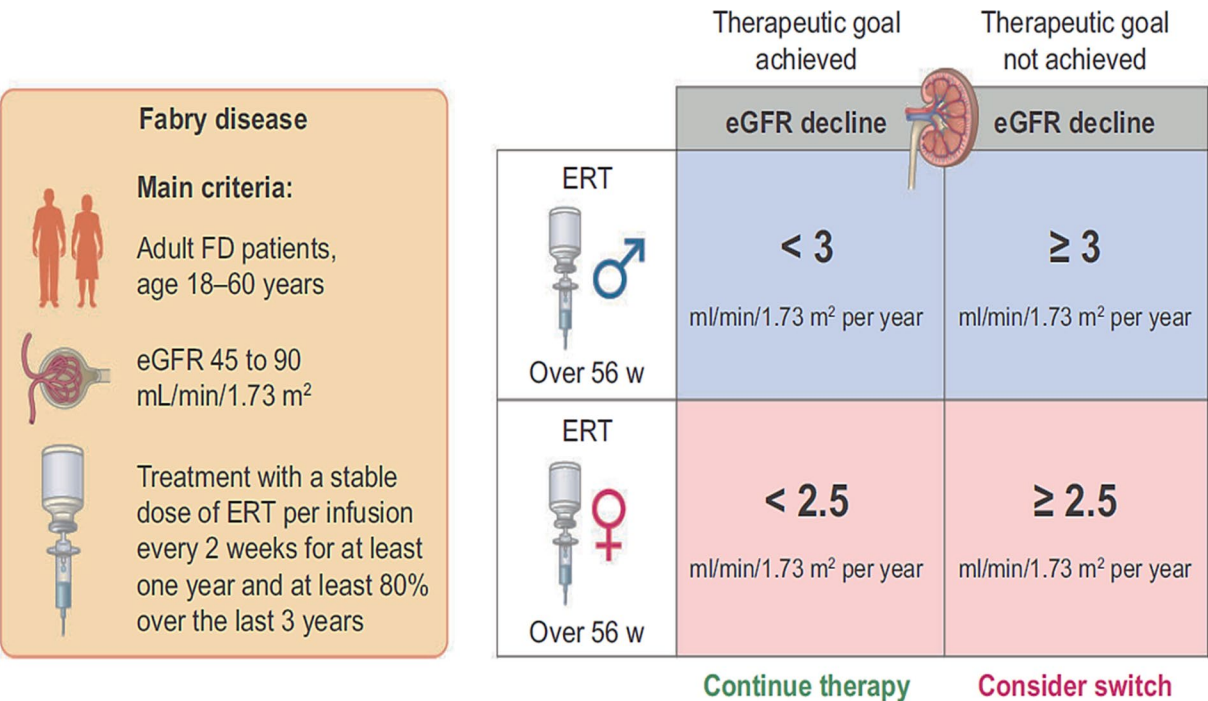


Fig. 3 Estimated glomerular filtration rate (eGFR) and response to treatment in adult patients with Fabry disease [106]. Reproduced from [106] with permission from

Oxford University Press and the European Renal Association. *ERT* enzyme replacement therapy, *FD* Fabry disease

this treatment. Similarly, a home treatment setting may not always represent the best choice for a patient who shows limited treatment compliance.

In relation to the progression of nephropathy in patients with FD, a recent expert opinion paper has pointed out the role of an elevated eGFR slope as a possible factor that may be able to modify and adjust the therapeutic strategy in patients with FD [106]. Based on data of the effects of ERTs on eGFR decline and of the evidence supporting the role of eGFR slopes as a surrogate endpoint for CKD progression, the authors suggest that a treatment should be deemed effective when the eGFR decline is < 1 mL/min/1.73 m²/year and not effective when eGFR loss remains ≥ 3 mL/min/1.73 m²/year in males or ≥ 2.5 mL/min/1.73 m²/year in females (Fig. 3). This leads to practical clinical recommendations and guidance for patients with FD, and suggests that a change in treatment may be appropriate if individualized therapeutic goals are not achieved [106].

There is limited consensus on the timing of treatment initiation in FD. Initiating treatment at diagnosis in male children with classic severe variants and at diagnosis in adult male patients is less controversial, but there is more difficulty around the decision of treatment initiation in females. In our opinion, adult females with a classic variant who are symptomatic for at least one sign or have symptoms of organ involvement should initiate treatment very soon after the diagnosis. Young females with late-onset variants and a benign course of disease in family members do not require immediate initiation, but should be monitored closely until the onset of signs or symptoms. In all cases, concomitant adjunctive treatment should be considered if specific therapies do not completely remove signs or symptoms (such as pain or proteinuria).

If therapeutic goals are not achieved, then a change in treatment should be considered to arrest disease progression. Several reports have documented a positive effect on disease progression when using an increased dose of infused

agalsidase. Furthermore, the switch from agalsidase alfa to agalsidase beta has been shown to attenuate the steepness of eGFR slope decline in patients with normal or mild chronic renal failure [56].

The above treatment and strategy considerations aim to improve the management of patients in clinical practice to provide better outcomes and an improved QoL.

CONCLUSIONS

FD is a debilitating disease that negatively impacts the renal, neurological, and cardiovascular systems, in addition to QoL. Patients often present with substantial, irreversible organ damage, and management of this heterogeneous population is challenging. While all four available treatment options offer benefits, migalastat is only appropriate for patients with amenable GLA variants. Agalsidase beta shows beneficial effects across the renal, neurological, and cardiovascular systems, as well as compelling QoL improvements, and may help prevent renal disease progression. Moreover, agalsidase beta has demonstrated a stabilizing effect in patients previously treated with agalsidase alfa. Limited data are available on the efficacy of pegunigalsidase alfa at present. Mounting evidence suggests that relative disease progression often occurs across organ systems and that subtle pathological changes may develop without overt signs or symptoms, even in pediatric patients. This suggests that treatment effectiveness depends on early treatment initiation and the dose delivered to maximize benefits, improve QoL, and prolong life.

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Declarations

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