Poster #EE64

Impact of baseline characteristics on indirect treatment comparisons (ITCs) in Fabry disease: A systematic literature review (SLR)

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Introduction

- Patients with Fabry disease (FD), a rare metabolic disorder, present with high heterogeneity in disease characteristics[1]
- Symptoms of FD include episodes of excruciating pain, fever, and burning sensations usually in the hands and feet. Over time, patients develop renal dysfunction, cardiac disease, cerebrovascular complications, respiratory abnormalities, and nervous system manifestations[1]
- With no published interventional studies directly comparing all enzyme replacement therapies (ERTs) and treatments, it is important for indirect treatment comparisons to consider potential treatment effect modifiers (TEMs)

Objective

- **We conducted a systematic literature review (SLR) of real-world evidence (RWE) in FD to identify patient characteristics that may impact clinical outcomes**

Methods

- **The SLR followed established guidance and methods described by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), National Institute for Health and Care Excellence, and Centre for Reviews and Dissemination (Figure 1)**

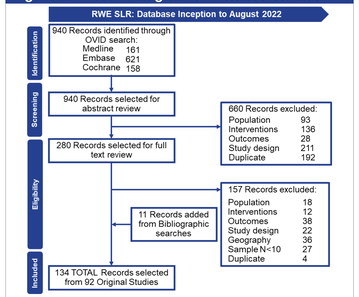
Figure 1. SLR in Fabry disease methods summary

Population	• Adult patients (≥18 years) diagnosed with FD
Interventions	• Agalsidase alfa • Agalsidase beta • Ibiglustat • Lucerastat • Migalastat • Pegylated alfa galactosidase • Pegunigalsidase alfa • Venglustat
Outcomes	• Effectiveness (including eGFR, lysoGb3, LMVI, CV events, renal events, UP/Cr, survival) • Safety
Study design	• Prospective observational studies • Retrospective studies • Registry analyses • Database analyses • Non-interventional studies • Systematic reviews, meta-analyses, indirect comparisons, pooled analysis, based on RWE data
Databases searched	• Ovid MEDLINE ALL, Embase, Econlit, and Cochrane (from inception to 2022) • Search date: 1st August 2022 • English language studies • No restrictions on geography or comparator
Data collection	• Data extracted by one reviewer and independently checked by a second, senior reviewer • Any discrepancies resolved by a third reviewer

Results

- **A total of 940 publications were identified. Of these, 92 original studies fulfilled the PICOS criteria (Figure 2)**
- **Within the included studies, several potential TEMs in FD were identified (Figure 3)[2-17]: early/delayed ERT, sex, phenotype, baseline left ventricular hypertrophy (LVH), reduced estimated glomerular filtration rate (eGFR), prior ERT and migalastat treatment, presence of anti-drug antibodies (ADAs), and baseline proteinuria**

Figure 2. PRISMA diagram of included studies



Prompt vs delayed ERT initiation

- Males initiating ERT before 25 years of age (Early) were 7 times more likely to reach a lysoGb3 level <20 nmol/L than males initiating treatment ≥25 years of age (Late) (adjusted odds ratios [OR] of 7.38; 95% confidence interval [CI] 1.91 to 34.04, p=0.006)[2]
- The adjusted lysoGb3 levels one year after ERT initiation in male patients were 12.9 nmol/L lower in the Early-treatment compared with the Late-treatment group (95% CI -20.1 to -5.8, p<0.001)[2]
- Prompt (<24 months) ERT initiation after symptom onset was associated with a significantly lower risk of cardiovascular (CV) (hazard ratio [HR]=0.62, p<0.001) and renal event (HR=0.57, p<0.001) compared to delayed (≥24 months) ERT initiation[5]
- Prompt (<24 months) vs delayed (≥24 months) ERT initiation from diagnosis was also associated with a significantly lower risk of CV events (HR=0.83; p=0.003) but not renal events (HR=0.96, p=0.563)[5]

Sex

- Sex impacted the rate of eGFR change over 10 years in patients treated with agalsidase alfa who had a baseline eGFR ≥60 mL/min/1.73m^2; the mean eGFR slope (95% CI) remained relatively stable in females (n=52) at −0.55 ml/min/1.73m^2/year (−1.12 to 0.01) and slightly declined in males (n=79) at −1.99 ml/min/1.73m^2/year (−2.45 to −1.54)[6]
- A linear disease progression model based on 98 patients treated with ERT estimated a decline in eGFR for males and not females (eGFR slopes of -3.07 ml/min/1.73m^2/year vs -0.07 ml/min/1.73m^2 per year, respectively)[7]

Phenotype

- An analysis of treated males with classic phenotype vs non-classic phenotype showed classic phenotype was associated with eGFR regression (p=0.008), increased risk of renal transplantation (HR=7.9, p=0.005), and higher lysoGb3 levels (median 21.1 ng/mL vs 4.5 ng/mL, p=0.0005)[8]

Baseline LVH

- The risk for a CV event was higher in the subgroup with LVH versus normal left ventricular mass index (LVMI) at baseline (HR=1.57; 95% CI 1.21 to 2.05; p<0.001)(**Figure 5**), but the risk for a renal event was similar between the 2 subgroups (HR=1.90; 95% CI 0.94 to 3.85; p=0.074)[9]

Figure 5. Risk of CV events with LVH[9]

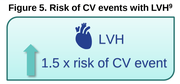


Figure 3. Impact of potential TEM in FD

Positive potential TEM

Prompt ERT treatment	• Younger patients (<25 years) present better biomarker responses to ERT than older (≥25 years) patients[2] • Prompt initiation of ERT (within 2 years of symptom onset or diagnosis) results in more favorable renal, cardiac and biomarker outcomes[2-5]

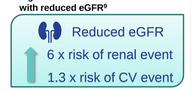
Negative potential TEM

Male sex	• Males presented worse renal outcomes than females in ERT-treated patients[6,7]
Classic phenotype	• Classic phenotype was associated with eGFR regression, increased risk of renal transplantation, and higher lysoGb3 levels than non-classic phenotype[8]
Baseline LVH	• Baseline LVH increased the risk of CV events in patients on ERT[9,10]
Reduced eGFR	• Impaired baseline renal function was associated with an increased risk of CV, renal and neurological events and a faster annual decline in eGFR when on ERT[9-13]
Baseline proteinuria	• Urinary protein to creatinine ratio (UP/Cr) is the most significant indicator of renal disease progression (eGFR) in adult FD[14,15]
Prior ERT and migalastat	• The clinical benefits of migalastat were more pronounced in ERT-naïve patients than in those with prior ERT experience[16]
Presence of ADAs	• Patients with ADAs reported smaller reductions in both plasma lysoGb3 and urinal Gb3 levels than patients without ADAs[8,17]

Reduced eGFR

- The subgroup with low eGFR (<90 mL/min/1.73m^2) at baseline had a significantly higher risk for a CV event (HR=1.33; 95% CI 1.04 to 1.70; p=0.021) or a renal event (HR=5.88; 95% CI 2.73 to 12.68; p<0.001) compared with patients with a normal eGFR (≥90 mL/min/1.73m^2) at baseline (**Figure 6**)[9]
- An eGFR<60 mL/min/1.73m^2 was associated with a 3- to 7-fold increase the risk of clinical events in different Cox regression models[12]
- In ERT-naïve patients, a baseline eGFR of <75 mL/min/1.73m^2 increased risk of CV events by more than 3-fold (HR=3.59, p=0.0273) and combined CV, renal, and neurological events by nearly 5-fold (HR=4.77, p=0.0007), whilst receiving ERT[13]

Figure 6. Risk of CV and renal events with reduced eGFR[9]



Proteinuria

- Patients with rapid renal disease progression (decline in eGFR) had significantly higher mean average baseline UP/Cr than patients with slower progression (1.5 versus 0.2 for men; 1.4 versus 0.5 for women; p<0.0001)[14]
- A baseline UP/Cr of >1 g/g was strongly associated with rapid renal disease progression compared to a baseline UP/Cr of <0.3 g/g (OR=112; 95% CI 4 to 3109; p=0.0054)[15]

Prior ERT and migalastat treatment

- Over a 12-month follow-up period of patients on migalastat treatment, eGFR in the ERT-naïve group (n=33) remained stable (mean eGFR at initiation was 82 ml/min and at 12 months was 81.2 ml/min) but was slightly declined in the prior-ERT group (n=44) (mean eGFR at initiation was 81 ml/min and at 12 months was 77.2 ml/min)[16]
- Left ventricular mass in the ERT-naïve group fell from 128.9 g/m^2 at treatment initiation to 117.2 g/m^2 at 12 months and appeared stable in the prior-ERT group (113.6 g/m^2 at initiation and 115.9 g/m^2 at 12 months)[16]
- Note: These changes are small and represent RWE for a small number of patients on migalastat treatment; patients selected in this study may not reflect the overall FD population

ADAs

- Over a six-year ERT treatment follow-up period, the reduction in plasma lysoGb3 was significantly less in males with ADAs (n=12) than in males without ADAs (n=11) (compared to baseline) (p<0.043)[17]
- In male patients without ADAs, urinary Gb3 levels decreased markedly in the first year of ERT treatment and remained decreased through to year 6 compared to baseline (range 19 to 387 nmol/24 hour; p=0.028). In male patients with ADAs, urinary Gb3 levels remained comparable to baseline in the first year of treatment (p=0.79) and remained elevated for up to 8 years of treatment (range 216 to 4547 nmol/24 hour)[17]
- ADA-positive, compared to -negative patients, presented with a significantly higher frequency for dialysis and renal transplantation (n=6/18 [33.3%] vs n=1/27 [3.7%]; p=0.012)[8]

Table 1. Study overview

Study	Design	N	M/F, n	Interventions	Potential TEM Comparison
Arends et al. 2017[2]	Retrospective, multicenter study	85	M=85	Agalsidase alfa, agalsidase beta	ERT treatment initiated <25 years old (Early; n=21) vs ≥25 years old (Late; n=64)
Hughes et al. 2017[3]	Post-hoc analyses of the Fabry Outcome Survey	1836	NR	Agalsidase alfa	ERT treatment initiated <24 months of diagnosis (Early; n=934) vs >24 months after diagnosis (Delayed; n=1002)
Linhart et al. 2017[4]	Post-hoc analyses of the Fabry Outcome Survey	1275	M=804 F=471	Agalsidase alfa	ERT initiated <24 months of symptom onset (Early; n=147) vs >24 months after symptom onset (Delayed, n=1128)
Hughes et al. 2021[5]	Post-hoc analyses of the Fabry Outcome Survey	2051	M=1130 F=921	Agalsidase alfa	ERT initiated <24 months of symptom onset (Early; n=172) vs ≥24 months after symptom onset (Delayed, n=1202) ERT treatment initiated <24 months of diagnosis (Early; n=1006) vs ≥24 months after diagnosis (Delayed; n=1045)
Ramaswami et al. 2019[6]	International, prospective, multicenter study	181	M=90 F=62	Agalsidase alfa	Male vs female
Nowak et al. 2017[7]	Prospective, multicenter study	98	M=37 F=61	Agalsidase alfa, agalsidase beta	Male vs female
Mauhin et al. 2018[8]	Prospective, multicenter study	103	M=53 F=50	Agalsidase alfa, agalsidase beta	Classic phenotype males (n=29) vs non-classic phenotype males (n=16) Patients with ADAs (n=18) vs patients without ADAs (n=27)
Feriozzi et al. 2020[9]	Retrospective analysis of the Fabry Outcome Survey	1093	M=551 F=542	Agalsidase alfa	Baseline LVH (n=306) vs normal LVMI (n=254) and reduced eGFR (n=433) vs normal eGFR (n=660)
Feriozzi et al. 2017[10]	Retrospective analysis of the Fabry Outcome Survey	1147	NR	Agalsidase alfa	Baseline LVH (n=NR) vs normal LVMI (n=NR) and reduced eGFR (n=NR) vs normal eGFR (n=NR)
Arends et al. 2017[11]	Retrospective, multicenter cohort study	293	M=163 F=130	Agalsidase alfa, agalsidase beta	Baseline eGFR <60mL/min/1.73m^2 (n=NR) vs baseline eGFR ≥60mL/min/1.73m^2 (n=NR)
Goicoechea et al. 2021[12]	Retrospective, multicenter analysis	69	M=42 F=27	Agalsidase alfa	Baseline eGFR <60mL/min/1.73m^2 (n=NR) vs baseline eGFR ≥60mL/min/1.73m^2 (n=NR)
Lenders et al. 2017[13]	Retrospective analysis	54	M=26 F=28	Agalsidase alfa, agalsidase beta	Baseline eGFR ≤75mL/min/1.73m2 (n=18) vs baseline eGFR >75mL/min/1.73m2 (n=36)
Wanner et al. 2010[14]	Retrospective data registry analysis	462	M=121 F=341	ERT	High (n=219) vs low (n=243) averaged UP/Cr ratio
Warnock et al. 2012[15]	Retrospective data registry analysis	213	M=151 F=62	Agalsidase beta	Baseline UP/Cr ratio >1g/g (n=NR) vs <0.3 g/g (n=NR)
Orsborne C and Jovanovic A 2020[16]	Retrospective outcome analysis	77	M=38 F=53	Migalastat	Prior ERT (n=44) vs ERT-naïve (n=33)
Rombach et al. 2012[17]	Prospective, observational study	59	M=29 F=30	Agalsidase alfa, agalsidase beta	Patients with ADAs (n=12) vs patients without ADAs (n=11). No females developed ADAs

Limitations

- This is an SLR of RWE for a rare disease. As such, the identified studies generally included small patient numbers and may not represent the overall FD population due to missing data
- In most of the studies, patients were not selected at random and in the case of registry analyses, relied on patient enrollment in the registry, resulting in potential selection bias

Conclusions

- **This SLR identified several patient characteristics that may impact the effectiveness of treatments in FD**
- **Adjustments for these characteristics should be considered during indirect treatment comparisons to ensure unbiased outcomes**

Funding: This study was funded by Chiesi USA Inc. Medical writing services were provided by Leah Wiltshire of Cytel, Inc.

Abbreviations: ADA, anti-drug antibody; CI, confidence interval; CV, cardiovascular; ERT, enzyme replacement therapy; eGFR, estimated glomerular filtration rate; F, female; FD, Fabry disease; Gb3, globotriaosylceramide; HR, hazard ratio; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; lysoGb3, globotriaosylsphingosine; M, male; NR, not reported; OR, odds ratio; PICOS, Population, Intervention, Comparator, Outcomes, Study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RWE, real-world evidence; SLR, systematic literature review; TEM, treatment effect modifier; UP/Cr, urinary protein to creatinine ratio; vs, versus.

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