Clinical evidence for the treatment of patients with Fabry disease: a systematic literature review

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Background

• Fabry disease (FD) is a rare, X-linked, lysosomal storage disorder caused by a deletion or mutation in the GLA gene, resulting in the absence or deficiency of α-galactosidase A.1

• ‘Classic’ FD is characterized by low or no α-galactosidase A activity, resulting in the classic set of signs and symptoms that predominantly affects males. ‘Variant’ FD reflects more variable α-galactosidase A activity and a more attenuated and variable presentation.2

• The clinical presentation of FD is heterogenous, and patients with FD may vary in age of symptom onset, disease severity and timing of progression.6 Cardiovascular disease is the main cause of death in patients with FD.1

• The standard of care for clinically evident FD is enzyme replacement therapy (ERT) with agalsidase alfa or agalsidase beta, or oral chaperone therapy with migalastat for those with an amenable mutation.

• Accurate identification of patients most likely to benefit from treatment and the appropriate time to begin treatment remains an unmet clinical need.

Objective

• This systematic literature review (SLR) was conducted to identify and analyse published evidence on the clinical efficacy and real-world effectiveness of current treatments in patients with FD.
Methods

- The SLR was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.³
- MEDLINE®, Embase® and the Cochrane Library were searched, as well as relevant congresses indexed in Embase® from each database inception to December 2019.
- Abstracts published from 2017 to 2019 were manually searched from the following congresses: Fabry Family Education Conference, Lysosomal Diseases Conference, The European Conference on Recent Advances in Lysosomal Diseases, ISPOR, SSIEM and World Symposium on Lysosomal Diseases.
- Search was limited to articles or abstracts in English language.
- Outcomes evaluated included:
  - Cardiac outcomes/endpoints, including left ventricular mass (LVM)/left ventricular mass index (LVMI); left ventricular posterior wall thickness; intraventricular septal wall thickness; and cardiac events including myocardial infarction, cardiac surgery, arrhythmia, angina and heart failure.
  - Renal outcomes, including estimated/measured glomerular filtration rate (eGFR/mGFR), and renal events including dialysis and transplantation.
- Studies were grouped on the basis of type of treatment evaluated for each specific outcome and within each treatment group on the level of evidence, with randomized clinical trials (RCTs) providing a higher level of evidence than single-arm and observational studies. LVMI and eGFR values are reported for the longest studies available, irrespective of study design, in this poster.

Results

- 153 studies were assessed, including a subset of RCTs and observational studies containing outcomes on LVMI and/or eGFR discussed here (Figure 1).

Figure 1. PRISMA flow diagram for the studies in the SLR

Records identified through database searching (n=2847)
  Embase (n=1211)
  Cochrane (n=350)
  PubMed (n=81)
  ProQuest* (n=1442)

Records screened (title and abstract) (n=1675)

Hand searching (n=18)

Full-text studies screened (n=808)

Studies included (n=153 from 390 publications)

Duplicates removed (n=1172)

Records excluded (n=867)

Full-text articles excluded (n=436)

15 RCTs (104 publications)
3 non-RCTs (3 publications)
19 single-arm trials (24 publications)
116 observational studies (259 publications)
Cardiovascular outcomes

- LVMI was stabilized or reduced by agalsidase alfa (n=11 studies; total follow-up ≤10 years) and agalsidase beta (n=8; ≤2 years): agalsidase alfa –13.55 g/m².7 from baseline; agalsidase beta slope vs baseline, 0.98 vs 0.46 g/m².7. Migalastat (n=3, 6- to 30-month studies) also reduced LVMI (–6.6 g/m².7 from baseline).12
- In the only RCT identified that measured LVMI, patients who received agalsidase alfa 0.2 mg/kg every other week (EOW) vs 0.2 mg/kg weekly had minimal progression of LVMI over the 53-week study period (baseline to week 53 EOW: 76.1 to 79.8 g/m².7; weekly: 82.6 to 79.3 g/m².7).4
  - The least squares mean (LSM) difference in LVMI change from baseline between the 0.2 mg/kg EOW and 0.2 mg/kg weekly doses was not statistically significant (–2.2 g/m².7; P=0.658; Figure 2).
  - LVMI decreased from baseline in both men (–1.0 g/m².7) and women (–2.4 g/m².7) that were given the 0.2 mg/kg weekly dose. However, in the 0.2 mg/kg EOW group, LVMI increased from baseline in males (7.2 g/m².7) and decreased in females (–4.8 g/m².7).

Figure 2. Effect of agalsidase alfa on LVMI in patients with FD from an RCT evaluating 0.2 mg/kg EOW and 0.2 mg/kg weekly doses
Cardiovascular outcomes, cont’d

- In a large observational study that stratified patients by phenotype (i.e., male classic; male non-typical; female variants), LVMI remained stable following 5 years of agalsidase alfa treatment in males with classic FD (P>0.112 vs baseline).
  - A significant improvement in mean LVMI (mean [SD] change from baseline of −5.3 [9.9] g/m²; P=0.031) was observed after one year of treatment with agalsidase alfa in males with non-typical variant FD, which remained stable through 5 years (P>0.05 for years 2 to 5 versus baseline).
- In the analysis of data from the Fabry Outcome Survey (FOS) registry, agalsidase alfa treatment led to significantly reduced LVMI in females (mean change from baseline −22.9 g/m²; P=0.001) over a period of 1 to 4 years.
- In a head-to-head RCT comparing agalsidase alfa (0.2 mg/kg EOW; n=18) with agalsidase beta (0.2 mg/kg EOW; n=16), there were no significant differences in the decrease in LVMI between treatment groups after 12 and 24 months of treatment (P=0.5).
- Four studies evaluated LVMI in patients who switched from agalsidase beta to agalsidase alfa. In one study, switching from agalsidase beta to agalsidase alfa significantly improved LVMI from 58.1 g/m² to 51.5 g/m² (P=0.0137) at 1 year following the switch. In the other three studies, LVMI remained stable at 1–2 years following the switch to agalsidase alfa.
- Oral migalastat therapy was assessed in two RCTs and an observational study, all of which reported significant reductions in LVMI.
  - In the multicentre, randomized, controlled FACETS study modified intention-to-treat population, there was a significant decrease in LVMI from baseline to 24 months (mean value, −7.7 g/m²; 95% CI, −15.4 to −0.01).
  - In the randomized, controlled ATTRACT study, LVMI decreased significantly from baseline to month 18 in patients treated with migalastat (−6.6 g/m²; 95% CI, −11.0 to −2.2), whereas a smaller, non-significant change was observed in patients remaining on ERT (−2.0 g/m²; 95% CI, −11.0 to 7.0).

Renal outcomes

- eGFR was improved or stabilized by agalsidase alfa (n=15 studies, follow-up ≤10 years) and agalsidase beta (n=8 studies; ≤8 years): agalsidase alfa vs untreated, mean annual change −2.86 vs −6.8 mL/min/1.73 m²; agalsidase beta baseline vs follow-up, 77.3 vs 79.0 mL/min/1.73 m². Migalastat (n=5, 6- to 18-month studies) also stabilized eGFR (−0.4 mL/min/1.73 m² from baseline).
- In the placebo-controlled RCT of agalsidase alfa, there was a significant decline in eGFR in the placebo group (−16.1 mL/min/1.73 m²) compared with a small increase in the agalsidase alfa group (2.1 mL/min/1.73 m²) over a 6-month period (P=0.02).
Renal outcomes, cont’d

- One observational study reported that mean eGFR levels remained stable from 1 to 5 years following initiation of agalsidase alfa, with a change from a mean of 83.5 mL/min/1.73 m² at baseline to a mean of 82.6 mL/min/1.73 m² at year 5.7
- Six long-term studies, which included five observational studies and one open-label study, showed overall stabilization of eGFR from 1 to 4 years following initiation of agalsidase alfa after switching from agalsidase beta.8-10,15-17
- In three retrospective analyses of data from the FOS registry, the mean annualized decline in eGFR ranged from −3.17 to −1.42 mL/min/1.73 m² per year in male patients following 5–10 years of agalsidase alfa treatment (Figure 3).18-20

Figure 3. Mean eGFR slopes in patients with FD following a 5- or 10-year duration of agalsidase alfa treatment from 3 FOS registry studies

Conclusions

- On the basis of published clinical evidence on outcomes in patients with FD, all FD treatments significantly improved or stabilized LVMI and eGFR.
- More studies with longer follow-up were available for agalsidase alfa (≤10 years for LVMI/eGFR) than for agalsidase beta (≤2 years for LVMI; ≤8 years for eGFR) or migalastat (≤30 months for LVMI; ≤24 months for eGFR).
- Limited data, particularly from RCTs, highlights the need for continued research to determine which treatment approaches provide optimum benefits for patients with FD.

References

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