Fabry Outcome Survey (FOS): demographics and survival analysis from a 20-year patient registry of Fabry disease

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Background

• The Fabry Outcome Survey (FOS; NCT03289065) is an observational, prospective, multicentre registry for patients with a confirmed diagnosis of Fabry disease.

• FOS was established on April 1, 2001 as a drug registry and transitioned to a disease registry in 2016, after which time any patient with Fabry disease, regardless of treatment status or treatment type, could be enrolled.

• Patients with Fabry disease often experience renal decline and cardiac progression, increasing the risk of complications, which include end-stage renal disease, cardiomyopathy and stroke.1

• Enzyme replacement therapy has been shown to result in the stabilization or slowing of renal decline and cardiac progression in patients with Fabry disease,2,3 particularly when initiated promptly, before the development of irreversible organ damage.4,5

• Here, we present the baseline patient characteristics, renal (estimated glomerular filtration rate [eGFR]) and cardiac (left ventricular mass index [LVMI]) progression and Kaplan-Meier survival estimates for patients with Fabry disease enrolled in FOS.

Methods

• Patients are enrolled in FOS on a voluntary basis and are managed under the direction of their physician in accordance with routine clinical practice.

• FOS has been approved by the ethics committees/institutional review boards of participating centres, and all participants have given written informed consent.

• Data on patient demographics, eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI; patients ≥16 years of age)6 or the Schwartz formula (patients <16 years),7 LVMI and survival time were collected via the FOS registry's web-based electronic case report form for the period from database inception in 2001 to January 7, 2021.

• Kaplan-Meier curves and log rank tests were used to compare event-free probabilities and survival time.

• Baseline was defined as the date closest to treatment initiation, within a window of –6 to +3 months, for treated patients, and as date of FOS entry for untreated patients.

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Results

**Patient characteristics**
- A total of 4297 patients with confirmed informed consent were enrolled in FOS from 144 centres in 26 countries up to January 7, 2021. Of these, 4080 had not received dialysis prior to treatment start: 2251 had received agalsidase alfa at any time (treated cohort) and 1829 remained untreated throughout the follow-up period.
- Compared with treated patients, untreated patients were younger at the time of data extraction, predominantly female and had higher eGFR* and lower LVMI at baseline, suggestive of milder disease (Table 1). As a result, no further comparisons were made between treated and untreated cohorts.
- Within the treated cohort, there were 1998 adult patients age ≥18 years (49.9% male) and 253 children age <18 years (68.8% male).
- The treated cohort included a similar proportion of males and females (52.0% vs 48.0%).
- Females were older at symptom onset, diagnosis and treatment start than males (Table 1).
- Median baseline eGFR was higher for males than females*, whereas median baseline LVMI was similar for males and females (Table 1).

**Annual rate of renal and cardiac change in agalsidase alfa-treated patients**
- For patients treated with ≥3 eGFR measurements (age ≥16 years, CKD-EPI formula), median (Q1, Q3) eGFR at baseline was 98.0 (77.9, 115.1) mL/min/1.73m² (n=1254).
  - Annual rate of change of eGFR was −1.55 mL/min/1.73m² for agalsidase alfa-treated patients (n=1254).
  - Annual rate of decline in eGFR was greater for males than females (−1.95 vs −1.11 mL/min/1.73m²; Figure 1A).
- For treated patients with ≥3 LVMI measurements, median (Q1, Q3) LVMI at baseline was 49.2 (38.0, 56.4) g/m²⁻² (n=591).
  - Annual rate of change of LVMI was 0.42 g/m²⁻² for agalsidase alfa-treated patients (n=591).
  - Annual rate of increase in LVMI was greater for males than females (0.49 vs 0.34 g/m²⁻²; Figure 1B).

**Survival in agalsidase alfa-treated patients**
- A total of 157 (7.0%) treated patients died during the study period. The median (Q1, Q3) survival time from baseline (treatment start in the treated cohort) was 6.30 (3.62, 10.13) years; n=2251.
  - Overall, Kaplan-Meier probability estimates for survival to 10, 15 and 19 years were 0.917, 0.840 and 0.700, respectively.
  - Survival rates were significantly higher for females vs males at 15 years (log rank P=0.0147 and overall (log rank P=0.0213; Figure 2).
  - Patient numbers at later time-points were low.

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**Table 1. Baseline characteristics: agalsidase alfa-treated patients with no dialysis before treatment start (n=2251)**

<table>
<thead>
<tr>
<th></th>
<th>Male (n=1080)</th>
<th>Female (n=611)</th>
<th>Treated (n=2251)</th>
<th>Untreated (n=1829)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%):</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>1171 (100)</td>
<td>0</td>
<td>1171 (52.0)</td>
<td>437 (23.9)</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>1080 (48.0)</td>
<td>1080 (48.0)</td>
<td>1392 (76.1)</td>
</tr>
<tr>
<td><strong>Age at symptom onset, years:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (missing)</td>
<td>758 (413)</td>
<td>609 (472)</td>
<td>1366 (885)</td>
<td>610 (1219)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>18.6 (17.3)</td>
<td>21.6 (18.1)</td>
<td>22.3 (18.10)</td>
<td>22.0 (18.38)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>11.0 (7.26,0)</td>
<td>21.0 (10.0,43.0)</td>
<td>14.0 (8.0,36.0)</td>
<td>14.0 (8.0,35.00)</td>
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<tr>
<td><strong>Age at diagnosis, years:</strong></td>
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</tr>
<tr>
<td>N (missing)</td>
<td>1115 (56)</td>
<td>1023 (57)</td>
<td>2138 (113)</td>
<td>1626 (203)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.4 (18.2)</td>
<td>21.2 (16.9)</td>
<td>21.3 (18.2)</td>
<td>21.0 (18.4)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>28.0 (15.0,45.0)</td>
<td>42.0 (28.0,51.0)</td>
<td>36.0 (19.0,50.0)</td>
<td>33.0 (20.0,47.0)</td>
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<tr>
<td><strong>Age at treatment start, years:</strong></td>
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<td>N (missing)</td>
<td>1115 (56)</td>
<td>1023 (57)</td>
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<td>21.3 (18.2)</td>
<td>21.0 (18.4)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>35.0 (22.5,51.0)</td>
<td>41.5 (30.0,61.5)</td>
<td>41.2 (27.1,54.2)</td>
<td>–</td>
</tr>
</tbody>
</table>

* eGFR assessed using Schwartz formula for patients <16 years and the Chronic Kidney Disease Epidemiology (CKD-EPI) formula for patients ≥16 years of age.

Male: BL, baseline; Q, quartile. **eGFR assessed using Schwartz formula for patients <16 years and the Chronic Kidney Disease Epidemiology (CKD-EPI) formula for patients ≥16 years of age.**
Discussion

• The FOS registry has provided valuable longitudinal insights on Fabry disease over 20 years, with over 4000 patients from 26 countries enrolled since its inception in 2001.

• Greater rates of eGFR decline and increases in LVMI were observed for males vs females.
  – However, males had higher eGFR at baseline compared with females; likely as a result of bias owing to age differences between these subpopulations.

• The annual rate of decline in eGFR for female patients treated with agalsidase alfa was close to values reported for a normal healthy population (∼1.1 vs ∼1.0 mL/min/1.73 m² per year).  

• The higher survival rates for females vs males observed in this analysis correspond with higher life expectancies reported for females vs males with Fabry disease.

References

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