THE FOS registry: How can we improve?

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Disclosure of Interests

Shire HGT: Consultancy, honoraria, sponsored education, research grant, educational grant. Chair FOS Executive 2005-9

Sanofi Genzyme: Consultancy, honoraria, sponsored education, research grant, educational grant.

Protalix/Pfizer: Consultancy, honoraria, sponsored education, research grant, educational grant.

Amicus: research Grant
Overview

• FOS statistics and overview
• Key papers illustrating strengths of FOS
• Key papers illustrating weaknesses of FOS
• How can the industry databases be improved?
• Issues for the workshops – the key contributors to the Registries are all here....
FOS countries and sites
(as of August 2015)

# Active Countries: 20 over 5 continents
• New coming on board in 2015: Denmark, Korea, Mexico, Russia

# Sites:
• 168 with enrolled patients
• 97 sites active (recruiting)

New countries and sites in feasibility / submission phase:
• Austria, Brazil, Denmark, France, S. Korea, Mexico, Russia, Taiwan, UK

<table>
<thead>
<tr>
<th>Country</th>
<th># Sites</th>
<th>Country</th>
<th># Sites</th>
</tr>
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<tbody>
<tr>
<td>Argentina</td>
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<td>Israel</td>
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<td>Taiwan</td>
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<tr>
<td>Germany</td>
<td>9</td>
<td>UK</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TOTAL</td>
<td>97</td>
</tr>
</tbody>
</table>
All patients (with/without ICF)

- 3225 patients (1763 females and 1462 males)
- 434 children at FOS entry (215 girls and 219 boys)

Patients with ICF: 2725 patients (1505 females and 1220 males)

- Of these, there were 336 children at FOS entry (168 girls and 168 boys)
1773 Replagal-treated patients (763 females and 1010 males)

Of these, there were 179 children at start of Replagal (53 girls and 126 boys)
Percentage of patients (with ICF) by country

Data extract: 3 August 2015

- United Kingdom, 350, 12.8%
- United States, 14, 0.5%
- Argentina, 80, 2.9%
- Canada, 282, 10.3%
- Germany, 492, 18.1%
- Japan, 421, 15.4%
- Brazil, 42, 1.5%
- Austria, 47, 1.7%
- Australia, 120, 4.4%
- Belgium, 14, 0.5%
- Switzerland, 64, 2.3%
- Czech Republic, 53, 1.9%
- France, 125, 4.6%
- Spain, 117, 4.3%
- Finland, 12, 0.4%
- Slovenia, 30, 1.1%
- Sweden, 23, 0.8%
- Portugal, 17, 0.6%
- Taiwan, 104, 3.8%
- Norway, 0, 0.0%
- Hungary, 18, 0.7%
- Japan, 421, 15.4%
- Germany, 492, 18.1%
- Italy, 169, 6.2%
- Spain, 117, 4.3%
- Finland, 12, 0.4%
- Slovenia, 30, 1.1%
- Sweden, 23, 0.8%
- Portugal, 17, 0.6%
- Taiwan, 104, 3.8%
- Norway, 0, 0.0%
- Hungary, 18, 0.7%
- France, 125, 4.6%

Data extract: 3 August 2015
PUBLICATIONS UPDATE AND FUTURE PUBLICATIONS
FOS strengths

• Has raised awareness of Fabry disease among physicians
• Depth of data allows disease modelling and generation of hypotheses on pathogenesis; eg stroke, genotype/phenotype associations
• Motivates physicians to design new tools eg questionnaires
Key papers:

**Allows generation of a useful model:**
Age adjusting severity scores for Anderson-Fabry disease.
Hughes DA1, Ramaswami U, Barba Romero MÁ, Deegan P; FOS Investigators.

**Development of a new tool:**
Measuring patient experiences in Fabry disease: validation of the Fabry-specific Pediatric Health and Pain Questionnaire (FPHPQ).
Genotype phenotype correlation based on large numbers of patients

Susanne Pitz, Gisela Kalkum, Laila Arash, Nesrin Karabul, Andrea Sodi, Sylvain Larroque, Michael Beck, Andreas Gal

PLOS One March 17 2015

Ocular signs correlate well with disease severity and genotype in Fabry disease; Data from FOS
Natural History/Outcome of ERT

Main strength is that it is an observational database

- The effectiveness of long-term agalsidase alfa therapy in the treatment of Fabry nephropathy.
- Feriozzi S, Torras J, Cybulla M, Nicholls K, West M; FOS Investigators.

- Cardiac manifestations of Anderson–Fabry disease: results from the international Fabry outcome survey
  - Alesˇ Linhart*, Christoph Kampmann, Jose´ L. Zamorano, Gere Sunder-Plassmann,
  - Michael Beck, Atul Mehta, Perry M. Elliott on behalf of European FOS Investigators
  - European Heart Journal May 2007
Limitations of FOS - 1

- Limited independence from industry
- Incomplete data
- Investigations done at different centres; issues of comparability
- No data on agalsidase beta treated patients
- Consent issues; restrictions on use of genotype data
- Retrospective, observational design
- Treatment criteria across centres are inconsistent
- To what extent is it a marketing tool?
FOS analysis - 2015

• Comparison of renal and cardiac outcomes in FOS patients with expected outcomes in untreated cohorts

• Evidence that ERT with Agalsidase alpha alters the natural history of Fabry disease and may improve life expectancy
Treated and Untreated Cohorts for Comparison\(^1,2\)

- **Morbidity outcomes**
  - FOS evaluable treated morbidity cohort (eGFR <80 mL/min) (n=79; 31 M, 41 F)
    - Untreated: Banikazemi et al.\(^4\), placebo group (n=31; 27 M, 4 F)

- **Renal outcomes**
  - FOS evaluable treated renal cohort (≥3 GFR values) (n=268; 135 M, 133 F)
    - Untreated: Schiffmann et al.\(^3\) (n=395; 243 M, 152 F)

- **Cardiac outcomes**
  - FOS evaluable treated cardiac cohort (≥3 LVMI values) (n=164; 71 M, 93 F)
    - Untreated: Kampmann et al.\(^5\) (n=166; 66 M, 100 F; longitudinal study n=76; 38 M, 38 F)

- The three cohorts were compared with untreated patients from three published studies

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- ERT, enzyme replacement therapy; eGFR, estimated glomerular filtration rate; F, female; FOS, Fabry Outcome Survey; LVMI, left ventricular mass index; M, male

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Ag alpha Increases Time to First Event

Time to first composite event (cardiac, renal, cerebrovascular event or death) as defined in Banikazemi et al.

FOS evaluable treated morbidity cohort\(^1,2\)
(n=79, 48% males)

- After 24 months, the probability of a composite morbidity event was approximately 16% in the FOS ERT cohort overall and approximately 26% for males only, compared with approximately 45% overall for the Banikazemi et al. placebo group, which comprised 87% male patients.

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\(^{a}\)Cumulative probability function of these events
\(^{b}\)Time to first composite event on or after start of agalsidase alfa ERT; \(^{c}\)Time on study to first composite event
CI, confidence interval; FOS, Fabry Outcome Survey

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1. BECK, M. et al. 2015
2. BECK M, et al. SSIEM 2014, Innsbruck, Austria, 2–5 September, P-452 ;
Ag alpha increases Age at First Event

**Age at first composite event (cardiac, renal, cerebrovascular event or death) as defined in Schiffmann, et al**

- **FOS evaluable treated cohort**
  - Male (n=360)
    - 50 percentile point estimate: 48.0
    - 95% CI: 44.2–50.4
  - Female (n=317)
    - 50 percentile point estimate: 56.9
    - 95% CI: 54.1–59.9

- **Schiffmann population (untreated)**
  - Male (n=279)
  - Female (n=168)

**Mean age at first event**
- **M: 48 / F: 57 years**
- **M: 41 / F: 53 years**

- Median age at first event was 48 years for treated men compared with 41 years for untreated men
- Median age at first event was 56.9 years for treated women vs 53 years for untreated women

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- **a** Age at first composite event on or after start of agalsidase alfa ERT
- **b** Age at first composite event
- CI, confidence interval; ERT, enzyme replacement therapy; F, female; FOS, Fabry Outcome Survey; M, male
- 1. BECK, M. et al. 2014; submitted;

Date of Preparation: April 2015 - KWT/C-APROM/REP/15/0003
Agalsidase Alfa increases Estimated Median Survival Time

Estimated median age for 50% survival in male patients: **77.5 years**

- **FOS evaluable treated cohort**: 1
  - (n=677)
  - Male (n=360)

- **Schiffmann untreated population**: 2
  - (n=279, all males)

**Estimated median age for 50% survival**:

- **77.5 years**
- **60 years**

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1. BECK, M. et al. 2014; submitted;
How can FOS be improved?

- Improve data completeness – focus on fewer centres?
- Increase independence from industry
- Include data on agalsidase beta
- Gather and publish more data on safety of agalsidase alfa – eg antibody formation; and impact of agalsidase alfa treatment on putative bio markers of Fabry disease
Royal Free LSD Unit

Range of LSDs in patients at the Royal Free Hospital

Total n = 454

Patients

Lysosomal storage disorder

Fabry

Gaucher

MPS

POMPE

Neimann Pick

Others

Male (185)

Female (269)
# Fabry disease mutations in the RFH cohort

<table>
<thead>
<tr>
<th>Total number of mutations in cohort</th>
<th>59</th>
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<tbody>
<tr>
<td>‘Null’ mutations</td>
<td>19</td>
</tr>
<tr>
<td>Nonsense</td>
<td>8</td>
</tr>
<tr>
<td>Frameshift</td>
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</tr>
<tr>
<td>Deletion</td>
<td>3</td>
</tr>
<tr>
<td>‘Classic’ (early onset) (R227X, n=20)</td>
<td>18</td>
</tr>
<tr>
<td>Missense</td>
<td>18</td>
</tr>
<tr>
<td>Late onset (including N215S [n=60] and A143T [n=10])</td>
<td>4</td>
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How can both registries be improved?

- Simplify data entry
- Increase physician input
- Generate a combined database of natural history and a combined prediction of treatment effect adjusted for age/gender/severity/product to give a complete model of the disease
Conclusions

• The FOS registry has made a major contribution toward improving understanding of Fabry disease and its treatment
• It could be improved with greater physician and patient influence
• An important challenge is to capture the diversity of the natural history and response to treatment; gender, mutation, comorbidities, genetic modifiers, disease status at treatment initiation, supportive treatments…..
ACKNOWLEDGEMENTS

• Very many
• Patients
• Colleagues locally and internationally
• Industry sponsors