Fabry Disease Research Highlights: WORLDSymposium 2021

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Learning Objective

Describe the latest research related to Fabry disease to better understand the condition and manage people with Fabry disease
WORLDSymposium 2021

- Annual meeting focused on lysosomal storage diseases
- Usually, a 5-day live event in February
- 2021 – virtual
  - Plenty of great data but the meeting lacked its normal urgency
- Considered to be “the conference” for new information about lysosomal storage disorders, including Fabry disease
- Since Fabry disease requires a team approach (cardiology, nephrology, neurology, gastroenterology, ophthalmology, dermatology, etc.), not all health care professionals involved in Fabry disease have access to WORLDSymposium information
New Insights into Natural History


- FOS is now 20 years old with a total of 4402 people with Fabry disease from 144 centers in 22 countries.
  - Treatment with agalsidase alfa (n=2407), agalsidase-beta (n=190), and migalastat (n=225)
- Small decline in eGRF slope (-1.6 ml/min/1.732/yr) in 20 yrs of ERT
- Small increase in LVMI slope (+0.4 g/m2.7/yr) in 20 yrs of ERT
- Mean age of symptom onset vs age of diagnosis still very high
  - Symptom onset: Males, 19.8 yrs; Females, 25.3 yrs
  - Diagnosis: Males, 32.6 yrs; Females, 37.1 yrs
- Conclusions:
  - FOS provides more insight into treatment efficacy. Still need more education about early symptoms.
ERT and the Impact of Starting Late


Multidisciplinary clinic at UCLA examined physical health and QoL in 26 Fabry disease patients on ERT.

- Most had classic FD including peripheral neuropathic pain, some form of cardiac involvement, angiokeratomas, corneal verticillata, hypohidrosis, tinnitus, gastrointestinal symptoms, renal involvement.
- Other common findings included pulmonary involvement, lymphedema, hearing loss, and significantly, three patients had strokes.
- ERT improved plasma GL-3
- In patients who started ERT later, renal dysfunction and health-related QoL decline continued.
Possible Earlier Diagnosis?

• Earlier onset Fabry disease
  • Fairly easy to diagnose with symptoms (angioeratomoas, hypohidrisis, corneal opacity)

• Later-onset Fabry disease
  • More difficult to diagnose and may not suspect until substantial kidney and/or cardiac damage occurred
  • Need to reduce time to diagnosis
Possible Earlier Diagnosis?


• Several algorithms being studied to filter through 2 million people in Trust in England hospital system.

• Looking for early patterns in diagnostic coding to determine patients with Fabry disease before they develop cardiovascular or renal problems.


• Looking for patterns of pain as an early symptom of Fabry disease in German Pain Registry (N = 260,103)

• Step 1 of a 3-Step plan


• Developed AI model comparing medical data from 4978 patients with Fabry disease vs 1,000,000 without Fabry disease

• AI model achieved 0.82 area under the curve

• 10-fold to 180-fold enrichment in identifying patients at risk of having Fabry disease
Switching to New ERT

Linhart A et al. Switching from agalsidase alfa to pegunigalsidase alfa to treat patients with Fabry disease: 1 year of treatment data from BRIDGE, a phase 3 open-label study. *Mol Genet Metab. 2021; 132 (suppl): S65.*

- 22 adults with Fabry disease, stable with agalsidase alfa. Switched to pegunigalsidase alfa. 20 completed the 1 year study. Baseline characteristics below

<table>
<thead>
<tr>
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<th>Overall (N=20)</th>
<th>Female (N=7)</th>
<th>Male (N=13)</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>45.8 (± 2.2)</td>
<td>46.7 (± 4.7)</td>
<td>45.2 (± 2.5)</td>
</tr>
<tr>
<td>Classic vs non classic Fabry</td>
<td>12 vs 8</td>
<td>0 vs 7</td>
<td>12 vs 1</td>
</tr>
<tr>
<td>eGRF (ml/min/1.73m²)</td>
<td>79.5 (± 4.9)</td>
<td>86.1 (± 6.7)</td>
<td>75.9 (± 6.6)</td>
</tr>
<tr>
<td>eGRF annualized slope (ml/min/1.73m²/yr)</td>
<td>-5.9 (± 1.3)</td>
<td>-5.0 (± 1.7)</td>
<td>-6.4 (± 1.9)</td>
</tr>
<tr>
<td>Plasma lyso-Gb3 (nmol/L) (Normal &lt; 2.4)</td>
<td>38.5 (± 9.7)</td>
<td>13.8 (± 2.3)</td>
<td>51.8 (± 13.6)</td>
</tr>
</tbody>
</table>
Switching Treatment

**Change in Kidney Disease Progression**

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
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<tbody>
<tr>
<td>eGRF Slope (ml/min/1.732/yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preswitch</td>
<td>-6.5</td>
<td>-7.0</td>
</tr>
<tr>
<td>Postswitch</td>
<td>-6.6</td>
<td>-7.0</td>
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</table>

- 18/20 continued in long-term extension study following 1 yr study
- Most treatment emergent adverse events were mild to moderate
- Two patients withdrew due to hypersensitivity reaction
Gene Therapy

• Current treatment for Fabry disease
  • ERT and chaperone therapy
  • Both delay progression but do not stop progression
• Fabry, like all lysosomal storage disorders, is a genetic condition. Fabry due to mutations in GLA gene
• Much like first ERT to treat Gaucher disease, lysosomal storage diseases are leading the way for gene therapies
• Many gene therapies in development, two were presented at WORLDSymposium
Gene Therapy


- ST-920: liver-tropic recombinant AAV2/6 vector encoding the cDNA for human α-Gal A


- AVR-RD-01: lentiviral gene therapy involving autologous stem cells
- Data from Phase 1 and Phase 2 studies are promising
Comorbidities: Cardiomyopathy


- 114 adults with Fabry disease:
  - 72 with left ventricular hypertrophy (LVH)
  - 76 without LVH
- People with LVH had significantly lower
  - Myocardial blood flow (MBF)
  - Global longitudinal strain (GLS)
  - Longitudinal relaxation time (TI)
  - Transverse relaxation time (T2)
Comorbidities: Cardiomyopathy

• Low T1 patients (32/72) had
  • Higher LV mass index (67 ± 14 vs 59 ± 10 g/m²; \( P = 0.011 \))
  • Higher Sokolow-Lyon index (22[16–28] vs 17[13–23]mm, \( P = 0.031 \))
  • More fractionated QRS complexes (44 vs 18%, \( P = 0.020 \)).

• Normal T1 patients (40/72) had
  • Reduced GLS (−18 ± 2 vs −20 ± 2%, \( P < 0.001 \))
  • Microvascular impairment (lower MBF 2.5 ± 0.7 vs 3.0 ± 0.8 mL/g/min, \( P = 0.028 \))
  • Subtle T2 elevation (50 ± 4 vs 48±2ms, \( P = 0.027 \))
  • Limited LGE (%LGE 0.3±1.1 vs 0%, \( P= 0.004 \))
  • Shorter P wave duration (88±12 vs 94±15ms, \( P = 0.010 \))
  • More symmetric T wave with lower T wave time ratio (Tonset-Tpeak)/(Tpeak-Tend) (1.5 ± 0.4 vs 1.8 ± 0.4, \( P < 0.001 \))
### Comorbidities: Cardiomyopathy

#### Stages of Fabry cardiomyopathy

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<tbody>
<tr>
<td>I</td>
<td>Pre-LVH pre-detectable storage stage</td>
<td>microvascular dysfunction, impaired GLS and altered atrial depolarization and ventricular repolarization intervals</td>
</tr>
<tr>
<td>II</td>
<td>Storage stage</td>
<td>low T1 mapping pre-LVH</td>
</tr>
<tr>
<td>III</td>
<td>LVH and myocardial inflammation</td>
<td>High T2</td>
</tr>
<tr>
<td>IV</td>
<td>LV fibrosis and impairment</td>
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Covid and Fabry Disease


- Real world experience of 22 patients with Fabry disease who had Covid-19 infection
  - 2 patients died. Both had serious cardiac and renal problems associated with Fabry disease prior to infection
- International experts recommend that patients with Fabry disease in the higher risk group strictly comply with Covid-19 safety precautions and that they be considered for early access to vaccines against the virus
Covid and Clinical Trials


- Lucerastat – oral substrate reduction therapy in development
- Pivotal, placebo-controlled, randomized, double blind phase 3 clinical trial was underway
- March 2020: Covid-19 = protocol addendum
- Switched to remote visits
  - Primary and secondary endpoints (neuropathic pain, GI systems) can be collected remotely (eDiary)
  - Oral treatment can be shipped to home
- Safety: Data analysis did not reveal any interactions of lucerastat with frequently used Covid-19 medications
- Steps taken may also improve patient experience, compliance, and engagement
Clinical Pearls

• 20 years of ERT and data collection
• Improvements in diagnosis observed in recent years
  • Still need for improvement
  • New diagnostic tools in development
• ERT and chaperone therapies are effective but ...
  • Newer ERT in development
  • Newer SRT in development
  • Gene therapies in development
• Comorbidities
• Covid
  • New clinical trials are a challenge
  • Treatment is a challenge
• TEAM APPROACH