

# CheckRare

Rare and Genetic Disease Network

CME/CE

## **Fabry Disease Research Highlights at *WORLDSymposium 2020***

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# Fabry Disease

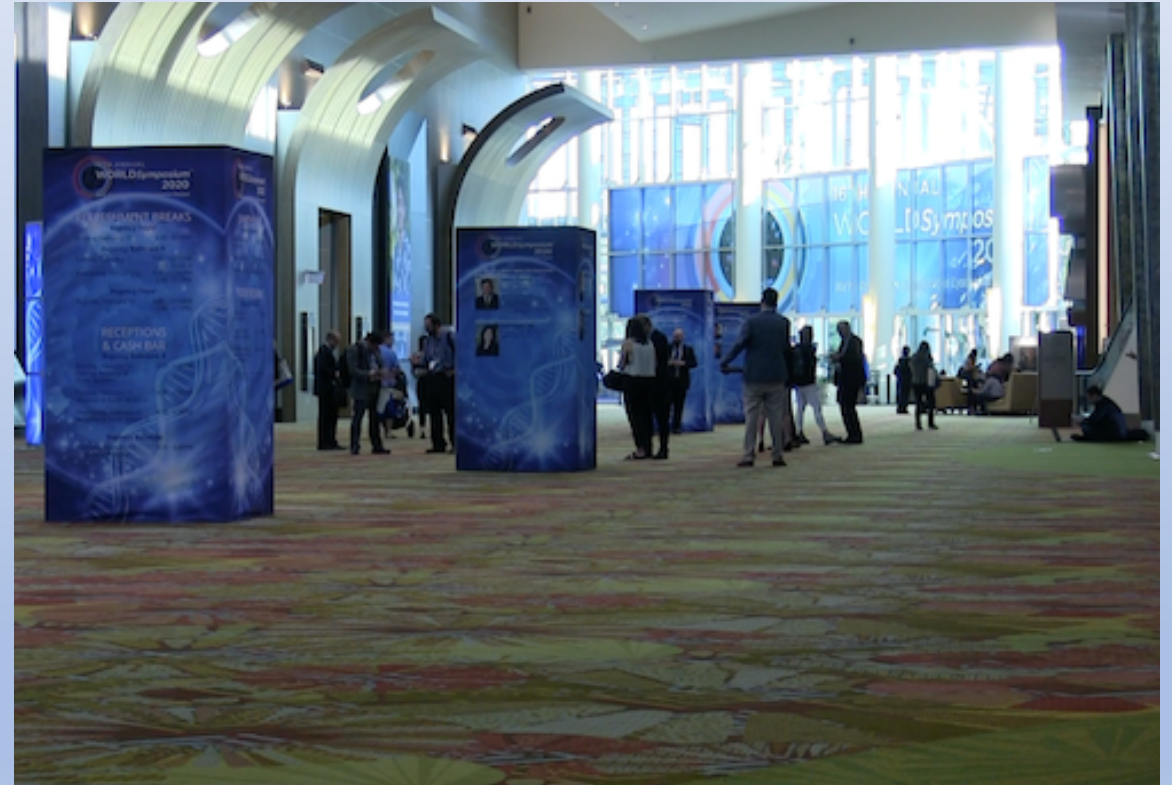
- Lysosomal storage disorder with X-linked inheritance
- Mutation in the *GLA* gene results in the deficiency of the lysosomal enzyme alpha-galactosidase A
- Low AGAL enzymatic activity leads to buildup of globotriaosylceramide in cells resulting in tissue damage
- Progressive buildup leads to complications and end organ damage in vital organs such as kidneys, heart, and CNS.

# Fabry Disease

- **Type 1: Classic Fabry Disease (<5% of normal  $\alpha$ -gal A activity)**
  - Common early symptoms include acroparesthesias, angiokeratomas, hypohidrosis, GI problems, corneal dystrophy
  - Later symptoms include serious cardiac and renal problems that can be life threatening
  - Without treatment – average life expectancy is 40 years
- **Type 2: Attenuated Fabry Disease (milder version)**
- **Treatment**
  - Enzyme replacement therapy (agalsidase alfa and agalsidase beta; only the latter is approved in USA)
  - Chaperone therapy (migalastat)
  - Numerous treatments in development

# WORLD*Symposium*

- Annual conference focused on lysosomal storage disorders
  - Fabry Disease, Gaucher disease, MPSs, etc
- 4 day event every February
  - Day 1 & 2 – Basic research
  - Day 2 & 3 – Translational research
  - Day 3 & 4 – Clinical research
- 446 poster presentation
- 84 oral presentations



# Fabry Disease: Diagnosis

- The diagnosis of Fabry Disease can be complicated
- Using the Fabry Outcomes Survey, Ramaswami et al observed the following:
- Average age of diagnosis:  $31.2 \pm 17.5$  yrs

Fabry Disease Suspected by:	
Affected family member	50%
Nephrologist	9%
Geneticists	8%
Cardiologist	8%
Pediatrician	5%

- When evaluating at-risk family members, the presence of cornea verticillate, acroparesthesia and cluster angiokeratomas may have a positive predictive value for diagnosis (Simmons et al, 2020)

# Fabry Disease: Varying Presentations

- Many ubiquitous presentations including pain, recurrent fever, GI disturbance
- Up to 45% of patients with Fabry Disease may present with relapsing and/or recurring fevers without a source
- Stroke and/or progressive white matter changes, which may pose a challenge to differentiate between other neurologic disorders such as Multiple Sclerosis, may be encountered at the initial diagnosis
- Pedigree analysis may be the simplest and the most successful tool to identify the individuals with or at risk for Fabry Disease.
- Newborn screening may offer a unique opportunity to assess multiple generations and several members from the same family (Illinois experience)

# Fabry Disease: Cardiac Involvement

- Vascular stiffness was measured using applanation tonometry (Sphygmo Cor Px<sup>®</sup>) in naïve Fabry patients (n=60) and healthy volunteers (n=237). (Neto et al, San Paulo, Brazil)
- Aorta stiffening and increased carotid femoral pulse velocity were observed in patients with Fabry Disease Late Gadolinium Enhancement and high troponins are the strongest predictor of cardiac injury (Augusto et al; London, UK)
  - Both hypothesized that inflammation is a factor in cardiac involvement In FD
- Some other markers of oxidative stress such as MCT1 (monocarboxylase transporter 1) could correlate response to hypoxia in FD cardiomyopathy (Gonzalez-Lamuno et al; Santander, Spain)

# Fabry Disease: Nephropathy

- Proinflammatory and profibrotic actions of glycosphingolipids (Lyso-Gb3) suggested by upregulation of integrin, TGF-beta, cadherin and Wnt signaling in cultured human podocytes (Sanchez-Nino et al; Madrid, Spain)
- Assessing renal involvement by measuring podocyturia and Lyso-Gb3: significant correlation between podocin levels and LysoGb3 and analogues in urine measured by Mass Spectrometry (Auray-Blais et al; Sherbrooke, Canada)
- Role of fibrotic and inflammatory pathways in Fabry nephropathy: Increased TGF-Beta-1 in proximal tubular cells, myofibroblasts in peritubular interstitium, and active Caspase 3 expression in tubular epithelium in renal biopsies from untreated patients with FD (Rozenfeld et al; Buenos Aires, Argentina)



# Fabry Disease: Pain and Nervous System Involvement

- Acid sensing ion channels (ASICs) are increased in response to sphingolipids in *in vitro* models (HEK cells and neuronal cultures)
- The pathway regulating cell proliferation, differentiation and survival, apoptosis and stress (ERK) is upregulated by ASICs
- ERK activation contribution to pain (Uchitel et al)
- Neuronopathic pain scale used as an endpoint in clinical trials (Kimonis et al; Irvine, CA)

# Fabry Disease: Psychiatric Comorbidities

- Neuropsychological parameters in Fabry Disease patients (147 males / 183 females) were measured (Forshaw-Hulme et al; Salford, UK)
- 22% of males and 24% of females suffer from anxiety and depression
- All patients reported mood fluctuations prior to their diagnosis
- Better understanding of the cognitive and psychological issues facing persons with Fabry Disease is needed to properly manage these patients.

# Fabry Disease: Psychiatric Comorbidities

- Anonymous survey of neuropsychiatric symptoms sent to 31 Fabry Disease patients (Lulla DS et al; New York, NY)
- Demographics
  - 45% classic Fabry Disease; 61% female
  - 66% had been on ERT for over 5 years

Self reported measure	
Pain	97%
Pain continued after ERT	50%
Hearing loss	64%
Depression	80%
Anxiety	71%

# Fabry Disease: Other Comorbidities

- Chronic back pain in 36 persons with Fabry Disease
- VFA and DXA scans
  - 61% had imaging evidence of a vertebral fracture
  - 69% reported back pain (15% reported daily back pain)
- Authors noted that chronic back pain in persons with Fabry Disease may derive from incidental vertebral fragility fractures. Further, Fabry Disease patients should be assessed for back pain and screened for osteoporosis and vertebral fractures
- Bone strength parameters as measured by HRpQCT are found to be decreased in 16 male subjects with Fabry Disease

# Fabry Disease: Multidisciplinary Approach

- Tapia D et al; University of California Irvine
- Survey assessing patients' (n=32) perception of a multidisciplinary clinic
- Demographics
  - 32 Fabry Disease
    - 4 seen by a multidisciplinary clinic
- Results
  - All 4 person in the multidisciplinary clinic felt they were getting better care and recommended to others
  - Of 28 persons not in a multidisciplinary clinic
    - 26 thought it would be convenient
    - 16 stated it would not be a problem to see multiple specialists in one day
    - 12 stated that spending a whole day at a clinic was a concern
    - 11 stated that traveling to a clinic was a concern

# FDA-approved Treatment Options

## Agalsidase beta

- FDA approved enzyme replacement therapy
- New data show the therapy stabilizes cardiac outcomes [1], slows the progression of renal decline [2], and reduces gastrointestinal problems [3] in Fabry Disease patients.
- Dosing
  - Standard dosing for agalsidase beta is 1 mg/kg every two weeks
  - Henderson et al at the Children's Hospital in Pittsburg [4] found a subset of children (9 -12 yrs) who had a pattern of increased symptoms (pain, GI symptoms, brain foggy) during the last few days of the two week cycle
  - Changing the dosing schedule to every 10 days resulted in reduced symptoms and better quality of life

1. DasMahapatra et al. *Mol Gen Metab.* 2020; 129: S45-46. 2. Fan et al. *Mol Gen Metab.* 2020; 129: S55.

3. Hopkin et al. *Mol Gen Metab.* 2020; 129: S74. 4. Henderson et al. *Mol Gen Metab.* 2020; 129: S71.

# FDA-approved Treatment Options

## Migalastat

- FDA approved chaperone therapy
- Osborne and colleagues at Salford Royal Foundation Trust presented several posters on Fabry Disease, including two focused on the experience using migalastat in their clinic treatment. They observed:
  - Migalastat was effective in both treatment naïve Fabry patients and in those previously taking ERT.[1]
  - In a group of 78 Fabry patients given migalastat, over a one year treatment period, mean eGFR was 81 to 79 ml/min and lysoGb3 reduced from 7.2 to 7.0 ng/ml. Three of the patients switched back to ERT due to GI symptoms or perceived deterioration in cardiac function.[2]
  - No significant difference for incidence of stroke among patients switching from ERT to Migalastat
  - FD biomarkers (Lyso Gb3) may not reflect therapeutic efficacy optimally.[3]

# Preclinical Studies to Deliver AGAL to Tissues

- Using extracellular vesicles to deliver highly active GLA to the lysosomes that may enable better biodistribution and brain delivery (Abasolo et al; Barcelona, Spain)
- Engineered  $\alpha$ -GAL A variants with improved stability, efficacy and predicted immunogenicity (CDX-6311) (Hallows et al; Redwood City, CA)



# Treatment Options in Development

## Pegunigalsidase-alfa

- Plant derived ERT being developed
- Results of phase I/II dose ranging study (Hughes D et al)
  - Measured BLISS (Barisoni Lipid Inclusion Scoring System) to assess renal biopsies
  - Baseline BLISS was 4.23 and after 6 months of treatment, BLISS dropped to 0.83
- Interim results of a phase III switching (BRIDGE) study (Linhart A et al; Praha, Czech Republic)
  - Data from 16 (of 22) adults with Fabry Disease were presented. All patients were being treated with agalsidase alfa (approved outside the US) for at least two years and switched to pegunigalsidase-alfa
  - After one year of treatment, the study saw clinically significant improvements in renal function

## Lucerastat Oral Monotherapy

- Design of Phase 3 Study using PRO regarding pain with ediary as the primary measure, secondary measures GI symptoms, plasma Gb3 levels (Wanner et al; Wurzburg, Germany)

# Treatment Options in Development

## Gene Therapy: Liver-directed gene therapy using AAV and Ex Vivo (stem cell therapy)

- **FLT190**
  - A liver-directed AAV (AAVS3) gene therapy
  - A phase I/II study ECLIPSE is in development (Hughes D et al; London, UK)
- **ST920 201**
  - A liver-directed AAV2/6 gene therapy
  - A phase I/II STARR study is underway in the U.S. (Hughes, Goker-Alpan, et al; London, UK)
- **FAB201**
  - Integrating Lentiviral vectors transduce CD34<sup>+</sup>
  - 8 patients were dosed in Phase ½ trials in Canada and Australia. Primary efficacy end point is a decrease in Gb3 inclusions per peritubular capillary
  - Patient 1- 87% reduction in kidney biopsy at 48 weeks with stable kidney and cardiac functions, and sustained AGAL activity (WBC and plasma). Discontinued ERT 18 months after dosing. AEs related to myeloablative conditioning, underlying disease, and other preexisting conditions (Volck et al; Cambridge, MA)

# Summary

- Fabry Disease can present initially with nonspecific symptoms (back pain, fever, etc) and diagnostic journey usually involves multiple specialists
- Individualized monitoring and multidisciplinary care involving patient and the extended family
- Other comorbidities including psychiatric and social problems that may be related to disease burden are common in patients with Fabry Disease
- Early diagnosis with Newborn Screening is underway but the simple exploration of the family history using a three generational pedigree has the most yield to identify at risk individuals
- Multiple organs exhibit evidence of involvement of inflammatory and fibrotic pathways leading to the late complications of Fabry Disease
- The current standard of care using ERT improves renal and cardiac outcomes in FD
- Improved novel Enzyme Replacement Therapies show promising results in Phase 3 trials
- Limited real life clinical experience with pharmacologic chaperone therapy. Migalastat has been used in both naïve and switch patients with Fabry Disease
- Substrate Reduction therapy trial aims reduction of Fabry Disease related pain as the primary outcome measure
- Gene therapy using AAV (liver directed) and ex vivo stem cell therapy are underway