• Management of Patients with Renal Manifestations
  • (including adjunctive treatments)

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Disclosure of Interests

DG Warnock has active research support and consulting arrangements with Genzyme Corporation, Shire LLC, Protalix Biotherapeutics and Amicus Biopharmaceuticals. These activities have been fully disclosed and are managed under a Memorandum of Understanding with the Conflict of Interest Resolution Board of the University of Alabama at Birmingham.

For US patients, agalsidase-beta at 1 mg/kg IV every other week is what is currently available as specific therapy for Fabry Disease.
Overview: Fabry Nephropathy

Fabry Nephropathy; Progressive Proteinuric form of Chronic Kidney Disease

Fabry disease is a podocyte disease

Optimizing management of Fabry disease: Importance and Utility of Renal Biopsy

Importance of applying what Nephrologists know about CKD management to Fabry disease
Fabry Disease: Accumulation, Cellular Injury, Compromised Function, Organ Failure

Time (years)

Stage 1  Stage 2  Stage 3  Stage 4

Burden of Disease

Organ Failure Loss of Function

Organ Damage: Initiation of Fibrosis

Cellular GL3 Deposits

Cellular Injury Damage

Tissue involvement

Cellular GL-3 storage

Stage 1
Stage 2  Stage 3  Stage 4

Tondel Nephron Clinical Practice 2015; 129:16-21
36 yr old male (W236X), GFR = 23 ml/min, 0.5 gm proteinuria on ARB, ERT dose: 33 mg/kg

Nov 2004 (3.4 g/d)    Jan 2006 (0.5 g/d)

ERT at 0.2 mg/kg versus 1.0 mg/kg (36 year old male; R227X)

41 yr old male, GFR = 40 ml/min, 0.6 g/day proteinuria: ERT dose, 9 mg/kg

GL3 deposits in podocytes, mesangial and capillary endothelium, persisting effacement despite control of proteinuria and agalsidase-alpha (1.8 yrs; 0.2 mg/kg)

17 yr old female (R227X); Lisinopril but no ERT

Proteinuria (200 mg/day) detected at age 12. Proteinuria treated with lisinopril but not with ERT. Despite repeated requests, the kidney biopsy was not done until age 17.
Foot Process Effacement with Normal Urinalysis in Classical Fabry Disease

13 year boy with neuropathic pain, C328Y mutation, and ACR 0.7 mg/mmol (6.5 mg/mg) (normal <2.5 mg/mmol)

*Figure 1* Normal podocytes, non-Fabry patient, EM

*Figure 2* GL3-accumulation and podocyte effacement in a Fabry boy, 13 years old², EM

GL3 deposits in Podocyte and other cells, foot process effacement BUT no Albuminuria!

Note: Minimal glomerular capillary endothelial deposits

Kanai et al JMD Reports 2010; 1:39
Baseline Glomerulosclerosis and Decline of eGFR on ERT (Phase 3 ext)

Age at ERT Start: 25±8 yrs
Baseline UPCR: 0.2±0.2 g/g

Baseline Sclerotic Glomeruli <50%
Slope = -1.404, p-value=0.2039 (N=32)

Baseline Sclerotic Glomeruli >=50%
Slope = -8.955, p-value=0.0001 (N=8)

Difference in Slope=7.551, p-value=0.0027

Age at ERT Start: 38±9 yrs
Baseline UPCR: 1.3±0.9 g/g

MDRD eGFR (ml/min/1.73 m²)

Years on Agalsidase-Beta

Stabilization of eGFR with Agalsidase-beta (1 mg/kg) and control of UPCR <0.5 g/day

Agalsidase-beta: 1 mg/kg body wt every two weeks

ACEI/ARB Therapy

Age at ERT Start: 34±12 yrs
Baseline UPCR: 0.3±0.3 g/g

Slope = 1.18 ± 2.78 ml/min per 1.73 m²

Age at ERT Start: 44±11 yrs
Baseline UPCR: 1.9±2.3 g/g

Slope = -0.23 ± 1.1 ml/min per 1.73 m² per yr.

Months Relative to Starting ERT
FAACET STUDY: Control of Proteinuria with ERT at 1 mg/kg every two weeks

- 24 “classic” patients (15 males; age 43 years)
- 3 monthly baseline visits with titration of RAAS agents to achieve goal of UPCR <0.5 g/g
- Patients then followed every 3 months for 21 months
- Outcome measure: eGFR slope over 21 months
- 18 reached UPCR goal but only 6 stabilized eGFR; age at which they started ERT was the critical factor
  - Do they have Fabry nephropathy? (no biopsies)
  - Other agents besides RAAS: statins, Vitamin D, amiloride?
  - Did they developed neutralizing antibodies?

Warnock et al. FAACET J Medical Genetics 2015: in press
FAACET: eGFR on Agalsidase-beta (1 mg/kg) and control of UPCR <0.5 g/day

Goal

<table>
<thead>
<tr>
<th>Slope (ml/min/1.73 m²/year)</th>
<th>Met Goal Above Goal</th>
<th>Met Goal</th>
<th>Above Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>18</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>B.</td>
<td>41y</td>
<td>47y</td>
<td>42 years</td>
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Warnock et al. FAACET J Medical Genetics 2015: in press
Serum-Mediated Inhibition of ERT in Fabry Disease

Table 1. Differences between Males

<table>
<thead>
<tr>
<th>Measures</th>
<th>ERT-inhib – (23)</th>
<th>ERT-inhib + (18)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>ERT inhibition</td>
<td>30%</td>
<td>81%</td>
<td>&lt;0.001</td>
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<tr>
<td>Age, years</td>
<td>41</td>
<td>44</td>
<td>0.46</td>
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<tr>
<td>Months on ERT</td>
<td>59</td>
<td>86</td>
<td>0.05</td>
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<tr>
<td>Lyso-GB3, ng/ml</td>
<td>27</td>
<td>49</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonsense mutation, n</td>
<td>6 (26%)</td>
<td>13 (72%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MSSI score</td>
<td>13</td>
<td>21</td>
<td>0.03</td>
</tr>
<tr>
<td>DS3 score</td>
<td>18</td>
<td>25</td>
<td>0.04</td>
</tr>
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Fabry Nephropathy: Summary

- Fabry Nephropathy involves podocytes, epithelial cells (podocytes and tubular cells), and vascular cells.
- Podocytes and vascular smooth muscle cells don’t have optimal access to available ERT.
- Early involvement with cellular injury (effacement) precedes signs of organ damage (e.g., proteinuria, reduced eGFR).
- The optimal ERT dose for stopping progression of nephropathy has to be defined in every patient.
- Waiting for organ damage before starting specific therapy does not lead to optimal patient outcomes in CKD; this is the rationale for starting ERT earlier than is currently recommended by various guidelines.
Fabry Nephropathy: Conclusions

- Progression in CKD is optimally managed with a common approach: define burden of disease and chronicity; control proteinuria, diet, smoking
- Regular follow up with monitoring of renal status is an important part of CKD care
- Patients who progress despite control of proteinuria?
  - What is the optimal target for controlling UPCR?
  - Do they have Fabry nephropathy? (biopsy)
  - Has the pathology changed? Adequate response to therapy? (Re-biopsy)
  - Other agents: statins, Vitamin D, amiloride
  - Have they developed neutralizing antibodies?