• Management of Patients with Renal Manifestations

• (including adjunctive treatments)

David G. Warnock, MD
University of Alabama at Birmingham

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

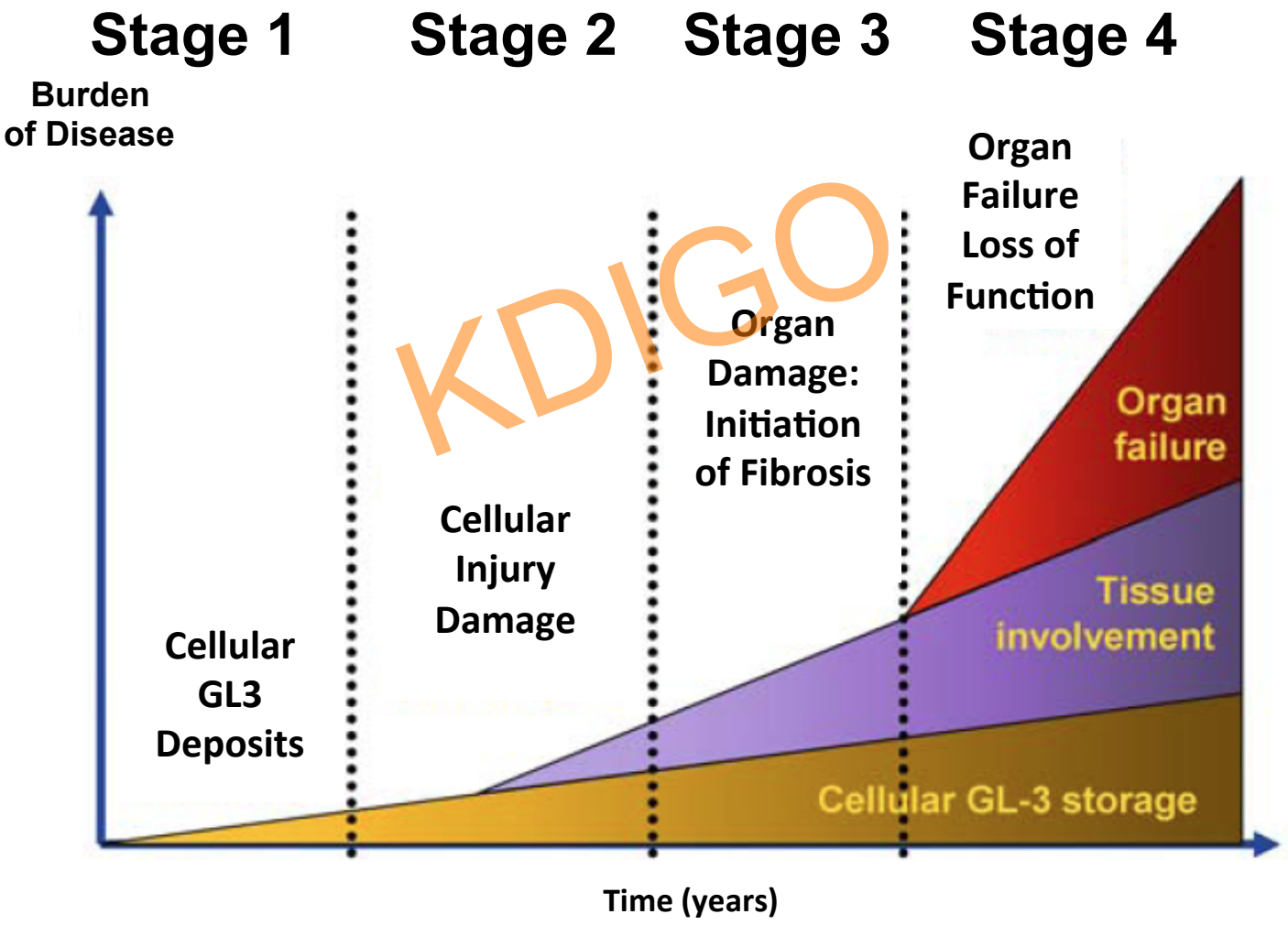
Fabry Nephropathy; Progressive Proteinuric form of Chronic Kidney Disease

Fabry disease is a podocyte disease

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

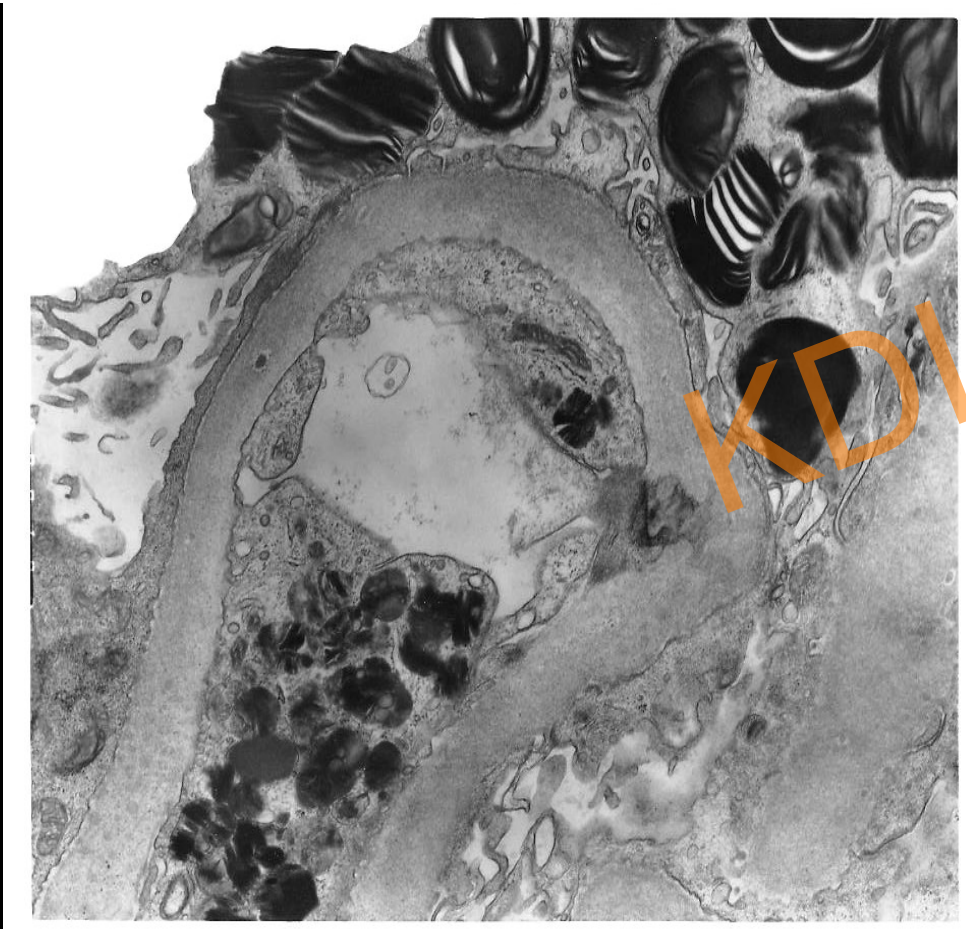
Importance of applying what Nephrologists know about CKD management to Fabry disease

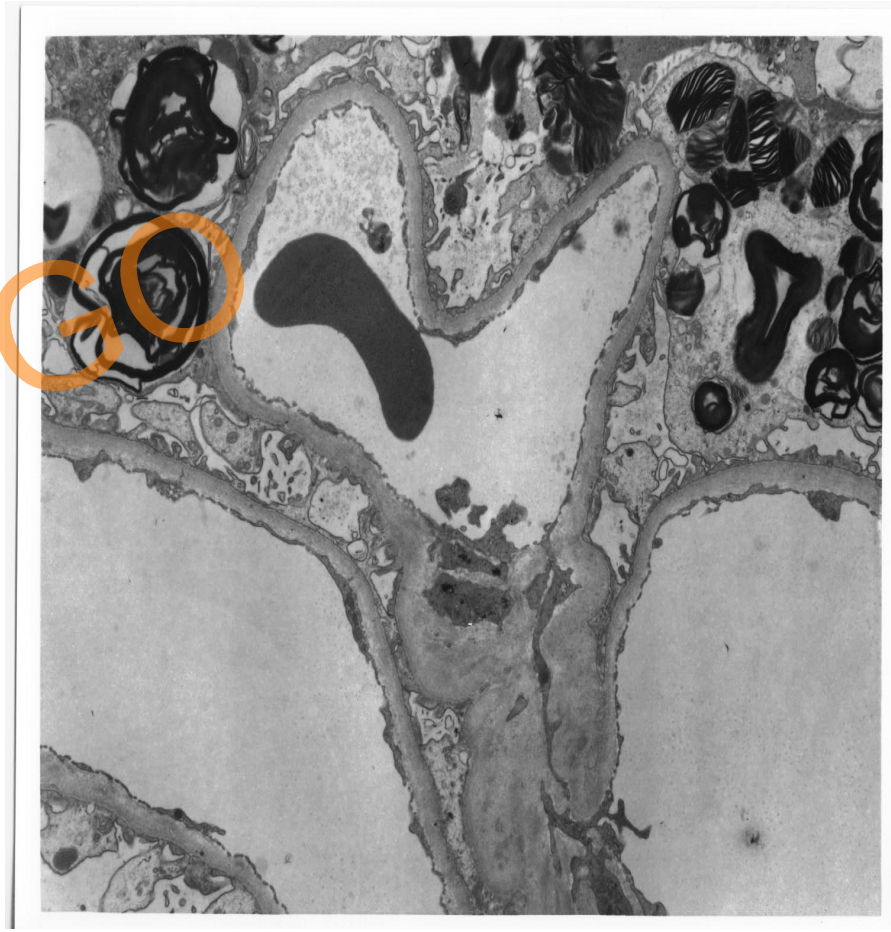
Fabry Disease: Accumulation, Cellular Injury, Compromised Function, Organ Failure



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



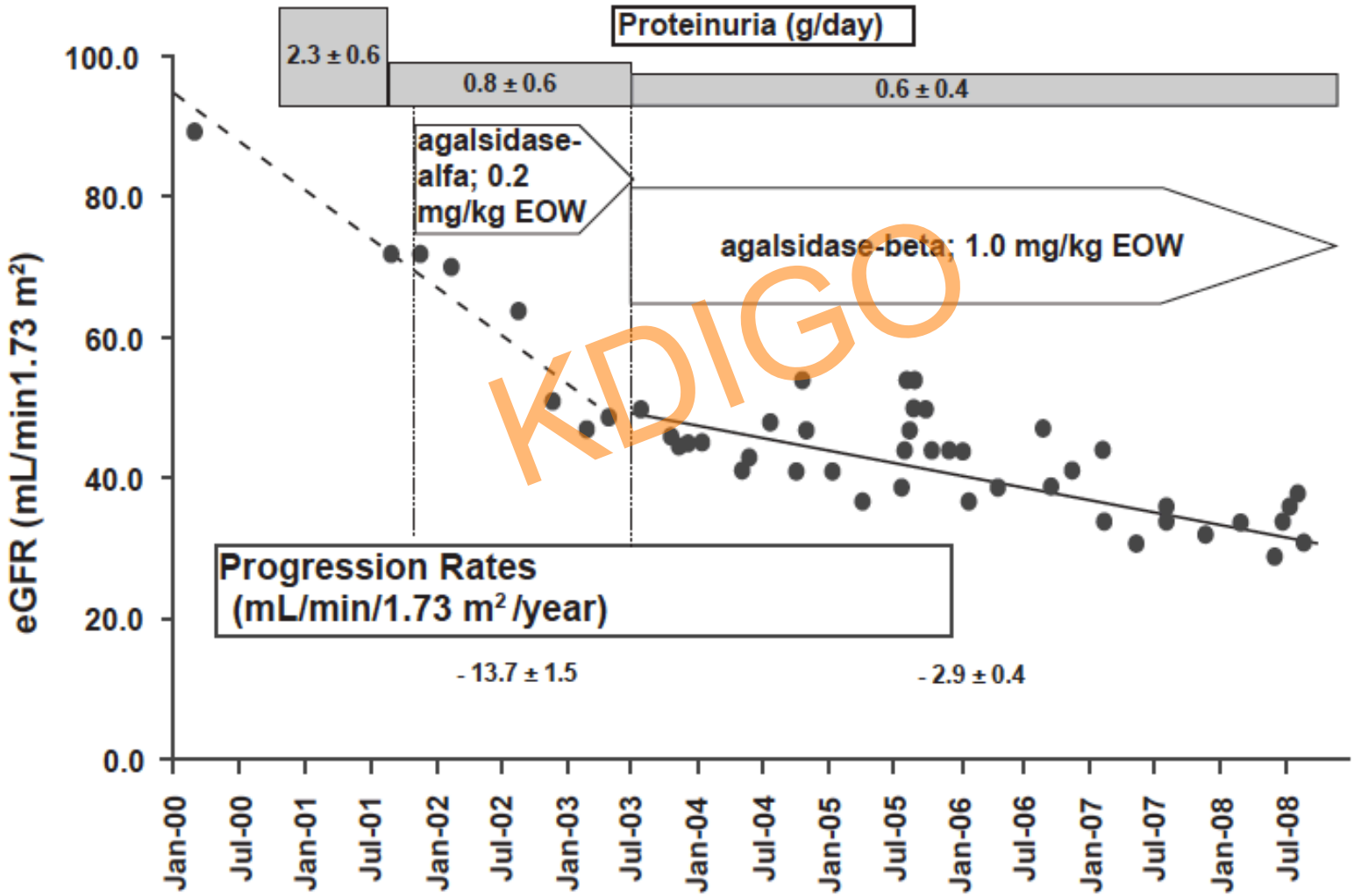


Nov 2004 (3.4 g/d)

Jan 2006 (0.5 g/d)

Fervenza et al. Biologics: Targets and Therapy 2008; 2:1-22

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



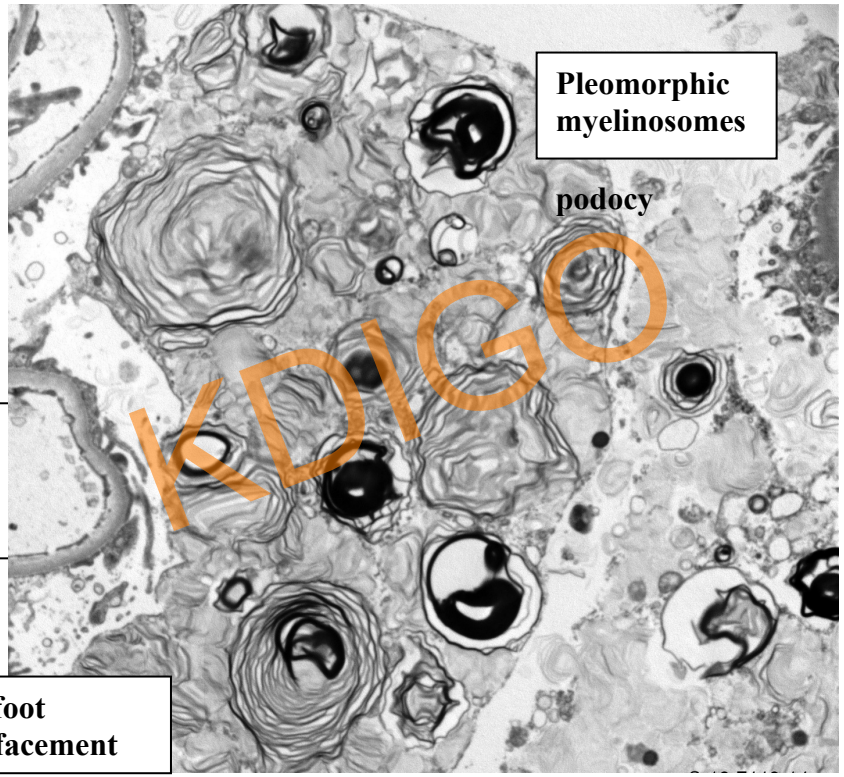
Fervenza et al. Biologics: Targets and Therapy 2008; 2:1-22

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)

Fervenza et al. Biologics: Targets and Therapy 2008; 2:1-22

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

Krishna et al. 4th Update on Fabry Nephropathy Nephron Clin Pract. 2015; in press

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)

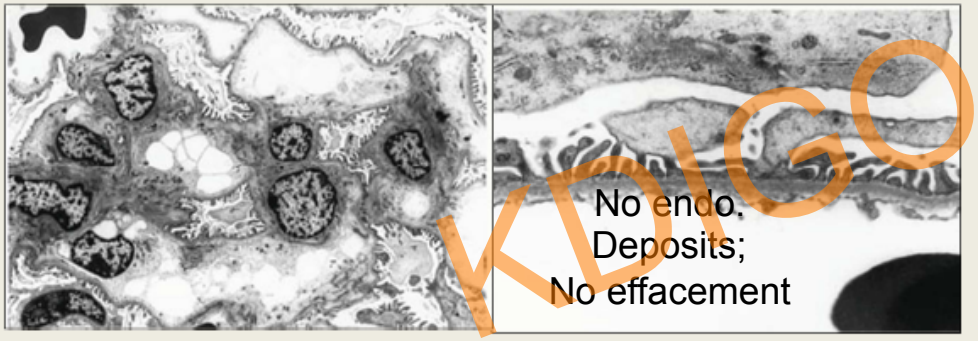


Figure 1 Normal podocytes, non-Fabry-patient, EM

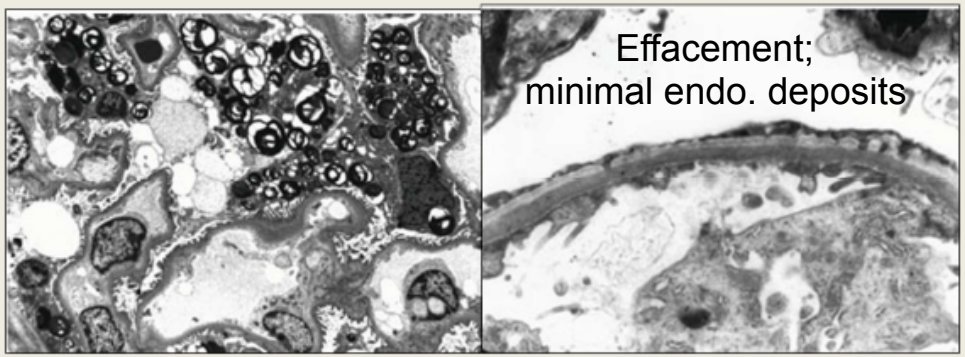


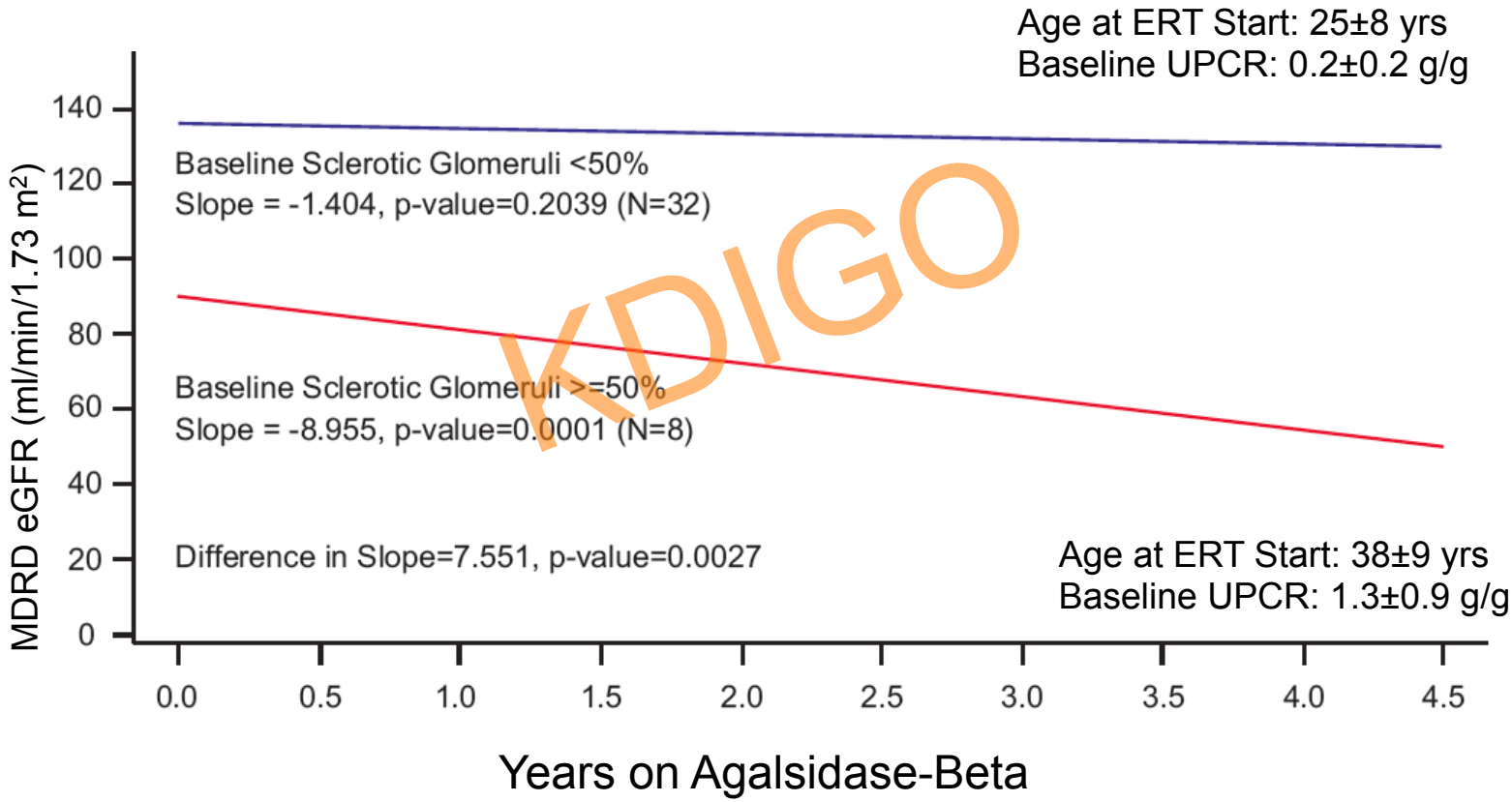
Figure 2 GL3-accumulation and podocyte effacement in a Fabry boy, 13 years old[2], EM

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

Note: Minimal glomerular capillary endothelial deposits

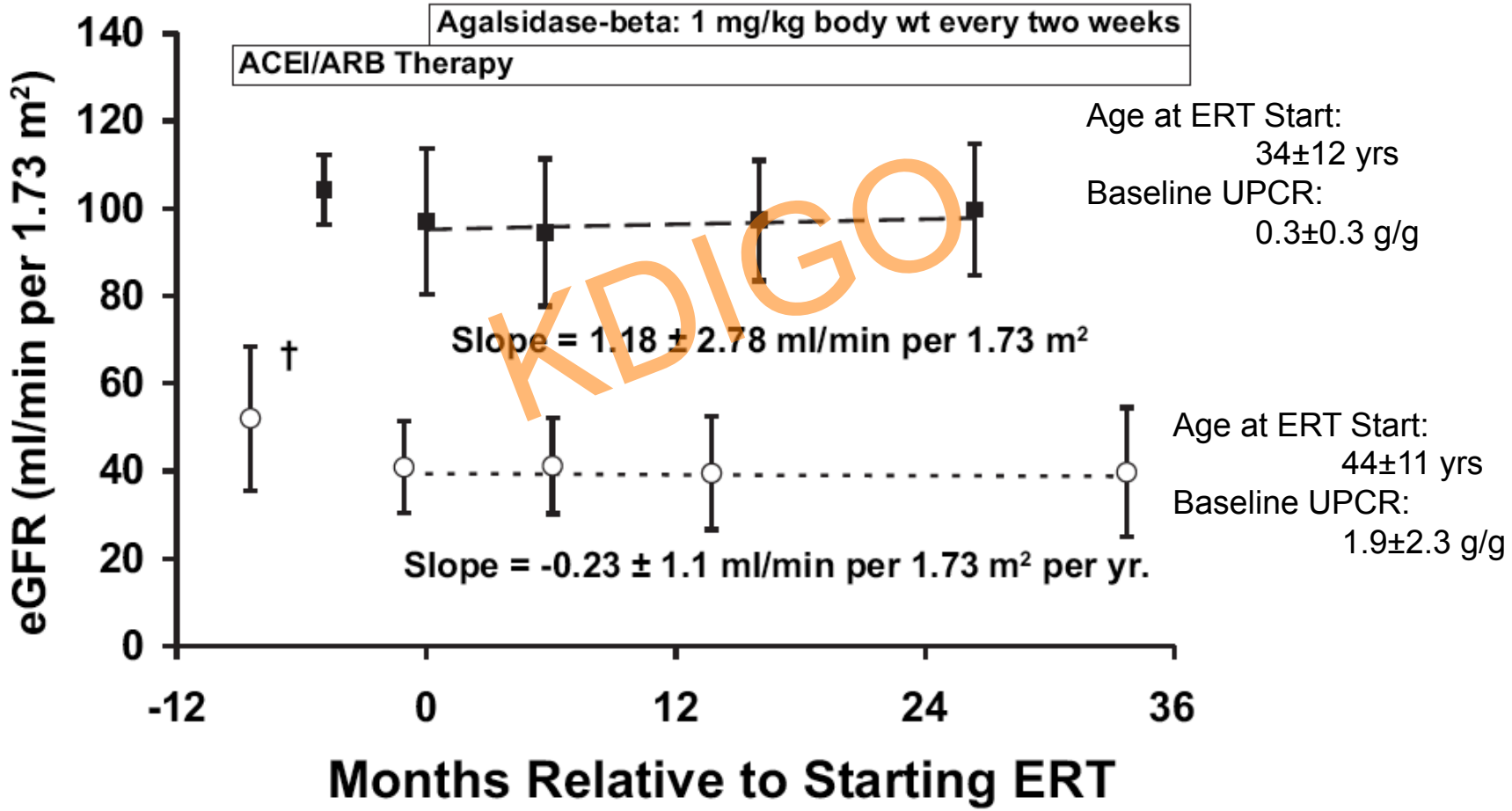
Kanai et al JMD Reports 2010; 1:39

Baseline Glomerulosclerosis and Decline of eGFR on ERT (Phase 3 ext)



Germain et al. J Amer Soc Neph 2007; 18:1547-1557

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



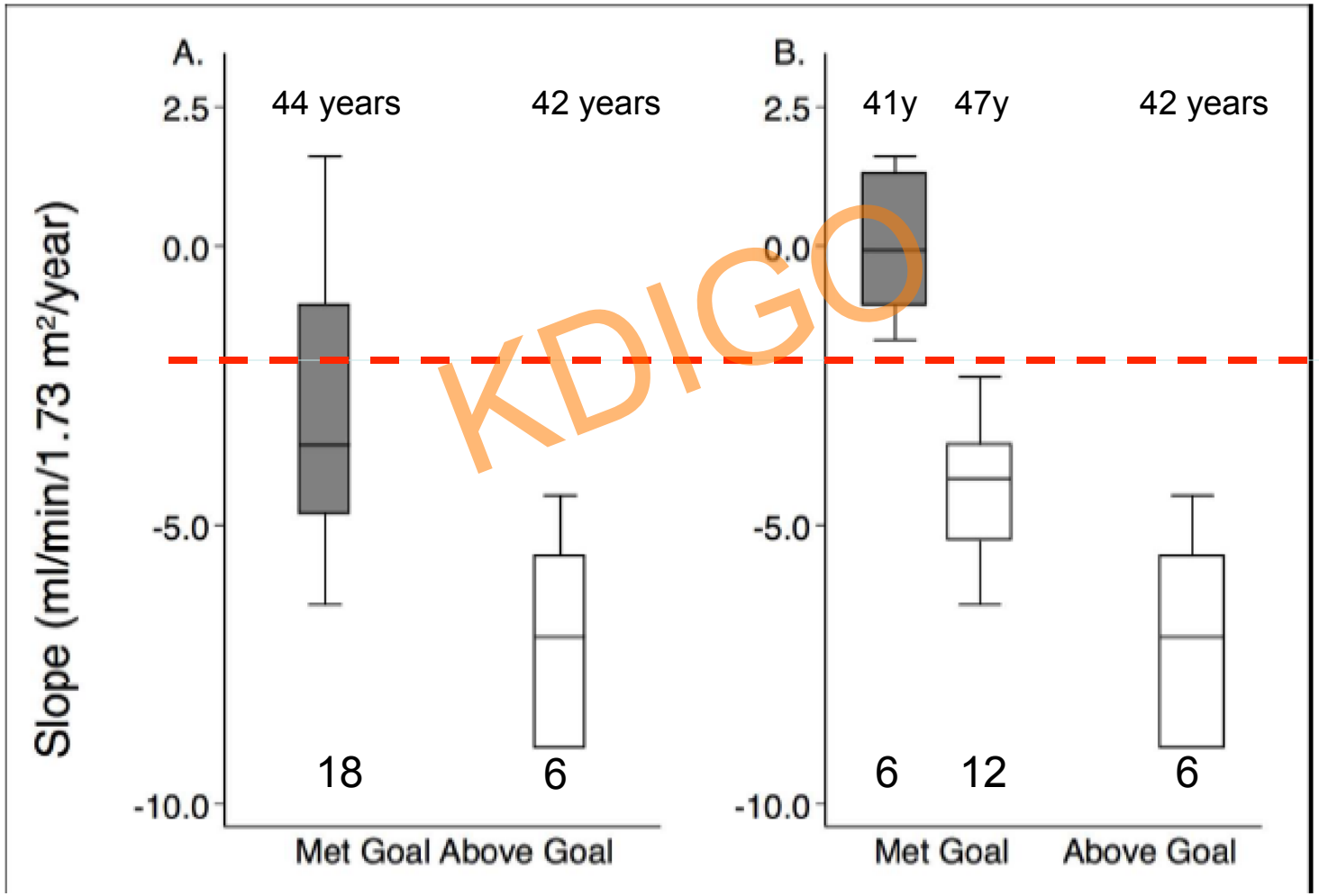
Tahir et al J Amer Soc Nephrol 2007; 18:2609-2617

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



Warnock et al. FAACET J Medical Genetics 2015: in press

Serum-Mediated Inhibition of ERT in Fabry Disease

Table 1. Differences between Males			
Measures	ERT-inhib – (23)	ERT-inhib + (18)	P value
ERT inhibition	30%	81%	<0.001
Age, years	41	44	0.46
Months on ERT	59	86	0.05
Lyso-GB3, ng/ml	27	49	0.02
Nonsense mutation, n	6 (26%)	13 (72%)	<0.01
MSSI score	13	21	0.03
DS3 score	18	25	0.04

Lenders et al. JASN 2015: in press

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 patients
- 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?