

## Enzyme Replacement Therapy and Fabry Nephropathy

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Involvement of the kidneys in Fabry disease ("nephropathy") occurs in male and female individuals. The majority of patients with progressive nephropathy will have significant proteinuria and develop progressive loss of kidney function, leading to ESRD. All too often, treating physicians may ignore "normal" serum creatinine levels or "minimal" proteinuria and fail to assess properly the severity of kidney involvement and institute appropriate management. Fabry nephropathy is treatable, even in patients with fairly advanced disease. Although the cornerstone of therapy remains enzyme replacement therapy with agalsidase, this treatment alone does not reduce urine protein excretion. Treatment with angiotensin receptor blockers or angiotensin-converting enzyme inhibitors must be added to enzyme replacement therapy to reduce urine protein excretion with the hope that this will stabilize kidney function. Kidney function, with at least estimated GFR based on serum creatinine and measurements of urinary protein, should be measured at every clinic visit, and the rate of change of the estimated GFR should be followed over time. Antiproteinuric therapy can be dosed to a prespecified urine protein target rather than a specific BP goal, with the proviso that successful therapy will usually lower the BP below the goal of 130/80 mmHg that is used for other forms of kidney disease. The overall goal for treating Fabry nephropathy is to reduce the rate of loss of GFR to  $-1$  ml/min per  $1.73$  m<sup>2</sup>/yr, which is that seen in the normal adult population. A systematic approach is presented for reaching this goal in the individual patient.

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### What Do We Know?

Nephropathy is one of the major complications of Fabry disease. Kidney biopsies show globotriaosylceramide (GL-3) accumulation in tubular epithelial cells, glomerular and endothelial cells, and vascular smooth muscle cells (1–5). With time, progressive GL-3 accumulation leads to microvascular dysfunction, occlusion, and ischemia, with subsequent development of tubular atrophy, segmental and global sclerosis, and interstitial fibrosis (6–8). Affected male individuals classically develop ESRD by the fourth decade of life (6,9,10). Cardiovascular and cerebrovascular events are also important causes of morbidity and mortality. Heterozygous female individuals may be asymptomatic or can develop overt disease.

#### Progression of Fabry Nephropathy

Branton *et al.* (6) described the course of 105 male patients with Fabry disease. By age 35 yr, 50% had overt proteinuria and 20% had reduced GFR. Fifty percent progressed to ESRD by 47 yr of age; the mean rate of change in GFR was  $-12.2$  ml/min per yr.

Schiffmann *et al.* (10) described the natural history of Fabry nephropathy with a retrospective analysis of 279 male and 168 female adults on the basis of chart reviews at 27 Fabry treatment centers. Baseline GFR was related to the progressive loss of kidney function (Table 1). Advanced Fabry nephropathy was more prevalent and occurred earlier among male than female patients, but female patients who progressed to ESRD were the same age as male patients who progressed to ESRD. Patients with proteinuria  $>1$  g/24 h had a worse prognosis, and the rate of loss of GFR was related to the baseline level of proteinuria; when stratified by proteinuria, the progression rates were similar for male and female patients (Figure 1).

Ortiz *et al.* (11) described the distribution of BP, proteinuria, and GFR in 585 male and 677 female patients from the Fabry Registry. Although a minority, approximately 200 adult patients had estimated GFR (eGFR) below the population median (81 and 88 ml/min per  $1.73$  m<sup>2</sup> in males and female patients, respectively) and also had urine protein excretion below the population median of 0.57 g/24 h for male and 0.18 g/24 h for female individuals (11). A larger proportion of female patients had significant reductions in eGFR but did not have overt proteinuria (11).

#### Enzyme Replacement Therapy and Fabry Nephropathy

**Agalsidase-Alfa Phase III Trial.** The first trial with agalsidase-alfa was carried out in 24 "classically affected" adult

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Table 1. Natural history of Fabry nephropathy: Progression rate

Stratified by Baseline eGFR			
$\geq 60$ ml/min per $1.73$ m <sup>2</sup>		$< 60$ ml/min per $1.73$ m <sup>2</sup>	
Male (n = 117)	Female (n = 42)	Male (n = 28)	Female (n = 13)
$-3.0 \pm 1.1$	$-0.9 \pm 5.8$	$-6.8 \pm 7.9$	$-2.1 \pm 5.8$

Data are means  $\pm$  SD. eGFR estimated with the Modification of Diet in Renal Disease equation (22); progression rate expressed as ml/min/ $1.73$  m<sup>2</sup>/yr (10).

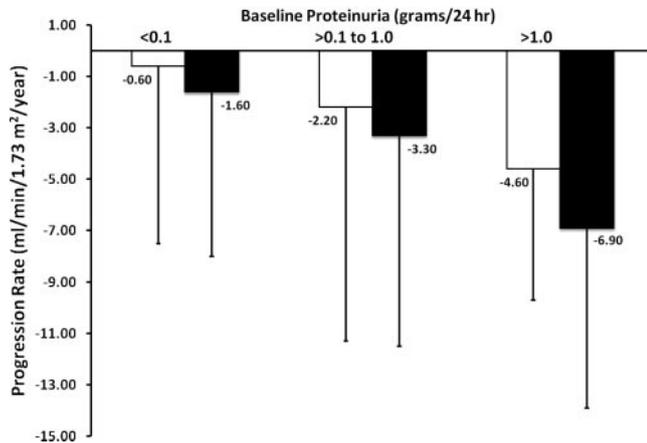


Figure 1. Natural history of Fabry nephropathy. The rate of loss of GFR (ml/min per  $1.73$  m<sup>2</sup>/yr) is shown stratified by gender and baseline 24-hour protein excretion (g). □, female; ■, male. Data replotted from reference (10).

male patients with Fabry disease (12), with the outcome measure being reduction in neuropathic pain. GFR was stabilized in the treated group but decreased 18% in the placebo group. There were significant increases in the segmental sclerosis scores for the active treatment group after 24 weeks, which may have reflected the presence of proteinuria in these patients. Baseline proteinuria exceeded 1 g/d in five patients who were on enzyme replacement therapy (ERT) treatment and three who were on placebo, without any effect of ERT on proteinuria.

**Agalsidase-Beta Phase III Trial.** Fifty-eight patients (56 male) were randomly assigned to agalsidase-beta or placebo (13). Clearing GL-3 accumulation in renal interstitial capillaries was the primary outcome measure. Twenty (69%) of 29 patients in the treatment group and none of the placebo group achieved complete GL-3 clearance ( $P < 0.001$ ). The baseline GFR was 83 ml/min in the treatment group and 96.6 ml/min in the placebo group. Kidney function did not change in either group at the end of the 24-week double-blind study or after 6 mo of open-label treatment.

**Agalsidase-Beta Phase IV Trial.** Eight-two adult patients (72 male) with baseline GFR  $< 80$  ml/min per  $1.73$  m<sup>2</sup> were randomly assigned to agalsidase-beta or placebo (14). The primary end point was the first clinical event: Kidney events (33% increase in creatinine or reaching ESRD), cardiac events, central nervous system (CNS) events, or death. The study reported 27 primary outcome events, 17 (63%) of which were sustained

increases in serum creatinine. Thirteen (41.9%) of 31 patients in the placebo group had primary outcome events (seven renal events, four cardiac, two CNS, zero deaths), and 14 (27.4%) of the 51 agalsidase-beta-treated patients had primary outcome events (10 renal events, three cardiac, zero CNS, one death from pulmonary embolus). After adjustment for baseline proteinuria, agalsidase-beta was associated with a 53% risk reduction in the primary event rate ( $P = 0.058$ ). Secondary analysis showed that the benefit of ERT was greater in patients with GFR values  $> 55$  ml/min per  $1.73$  m<sup>2</sup>, whereas patients with GFR values  $< 55$  ml/min per  $1.73$  m<sup>2</sup> did not seem to benefit from ERT (14).

#### Open-Label Studies of ERT Dosage and Frequency of Dosing

The effect of dosing interval with agalsidase-alfa has been examined (15) in adult male patients with progressive decline in eGFR despite 2 to 4 years of ERT at 0.2 mg/kg agalsidase-alfa every other week. Before switching to weekly dosing, the mean decline in eGFR was  $-8.0 \pm 2.8$  ml/min per  $1.73$  m<sup>2</sup>/yr. Four patients with low baseline proteinuria (average  $223 \pm 60$  mg/d) progressed on agalsidase-alfa given every other week at a rate of  $-6.6 \pm 2.1$  ml/min per  $1.73$  m<sup>2</sup>/yr. After switching to weekly dosing, they had an improvement in kidney function ( $4.2 \pm 5.4$  ml/min per  $1.73$  m<sup>2</sup>/yr). A previous report of a single patient also described rapid loss of kidney function despite control of proteinuria with apparent stabilization of kidney function when ERT dosing was increased (16,17). The remaining patients described by Schiffmann *et al.* (15) had higher baseline proteinuria levels and with agalsidase-alfa given at 0.2 mg/kg on a weekly basis had some improvement but still progressed at a rate of  $-5.5 \pm 4.2$  ml/min per  $1.73$  m<sup>2</sup>/yr.

Information is available from the Fabry Outcome Survey about the course over 3 years of 165 adult patients who were treated with agalsidase-alfa (18). The overall change in eGFR was  $-1.68$  ml/min per  $1.73$  m<sup>2</sup>/yr for those with baseline proteinuria  $< 0.50$  g/24 h and  $-3.98$  ml/min per  $1.73$  m<sup>2</sup>/yr for those with baseline proteinuria  $> 0.50$  g/24 h.

West *et al.* (19) published a review of Fabry nephropathy in men who were treated with agalsidase-alfa. The mean baseline GFR among 54 patients (excluding those with measured GFR  $> 135$  ml/min per  $1.73$  m<sup>2</sup>) was  $85 \pm 30$  ml/min per  $1.73$  m<sup>2</sup>. After 6 mo of placebo therapy, the annualized rate of change of GFR was  $-7.0 \pm 33$  ml/min per  $1.73$  m<sup>2</sup>. Among 85 men who were treated with agalsidase-alfa, the annualized rate of change

was  $-3.0 \pm 9$  ml/min per  $1.73 \text{ m}^2/\text{yr}$ . These data suggest that agalsidase-alfa may have slowed the rate of decline of GFR. Although the progression rate was greater than expected for age-matched normal control subjects (19,20), the majority of these patients did not receive angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).

An open-label extension study of the phase III study of agalsidase-beta has been published (21). After 54 mo of treatment, eight patients had protocol kidney biopsies, which showed complete maintenance of GL-3 clearance of renal capillary endothelial cells. eGFR remained stable in 41 patients, but six patients with significant baseline proteinuria ( $>1.0$  g/d) or segmental and global sclerosis in more than half of their glomeruli had rapid loss of GFR.

#### *eGFR Progression Rates in Fabry Nephropathy*

Table 2 summarizes the progression rates that have been reported for a number of prospective studies, trials, and case reports. Very few of these studies achieved slowing of progression to the optimal rate of  $-1.0$  ml/min per  $1.73 \text{ m}^2/\text{yr}$  (19,22). The patients reported by Schwarting *et al.* (23) and Breunig *et al.* (24) also warrant comment; even though urine protein was  $<0.50$  g/24 h, the progression rates were  $-5.0$  and  $-4.7$  ml/min per  $1.73 \text{ m}^2/\text{yr}$ , respectively, on the basis of two measurements of eGFR, which may not accurately reflect the rate of progression or averaged urine protein excretion. Variability in the rates of change of GFR could reflect differences in baseline characteristics of the different patient populations, treatment duration, the prevalence of ACEI/ARB use, achieved urine proteinuria reduction, and techniques of GFR measurement that complicate the comparison of different treatment groups.

#### *Use of ACEIs and ARBs in Fabry Nephropathy*

Studies of chronic kidney disease (CKD) show that renoprotective treatments effectively limit the progressive decline in GFR to the extent that proteinuria is reduced (25,26). The rate of eGFR decline largely depends on the level of proteinuria achieved during antiproteinuric therapy (27). With this approach, the goal is to achieve a rate of GFR decline equal to that observed in the general population (28).

ERT does not reduce proteinuria, and pediatric patients have developed overt proteinuria despite ongoing ERT (4), emphasizing the need to monitor and treat proteinuria in patients who are already receiving ERT.

Treatment with ACEIs and/or ARBs was undertaken in an open-label study of 10 patients, most of whom had control of their proteinuria before initiation of ERT (29). When urine protein excretion was controlled to  $\leq 0.50$  g/d in patients who were treated with agalsidase-beta at  $1.0$  mg/kg every 2 weeks, the rate of loss of eGFR was not significantly different from 0 (29). The response was much better than previously reported for patients with overt proteinuria and eGFR  $<60$  ml/min per  $\text{m}^2$  (14,15,24,30) but requires confirmation in an ongoing multicenter study (31).

Effective ACEI/ARB therapy is challenging for the physician and the patient when the baseline BP is relatively low. In addition, hyperkalemia and anemia and other adverse effects,

such as persistent cough with ACEIs, can complicate the use of antiproteinuric therapy in patients with CKD. Recent studies of Fabry disease revealed disappointing rates of use of renin-angiotensin-aldosterone system inhibitors under 50% despite multiple indications: Hypertension, proteinuria, reduced GFR, hyperfiltration, and others (14,15,17,18). This suggests that real barriers limit the use of ACEIs and ARBs in Fabry disease. Because most physicians who care for patients with Fabry disease are not nephrologists and may not be familiar with use of these agents, education about the optimal use of these therapies is paramount. Referral to a nephrologist of all patients with Fabry disease and any of the aforementioned indications is strongly recommended.

#### **What Do We Not Know?**

The validation of microvascular endothelial GL-3 clearance as a surrogate outcome measure for the clinical efficacy of ERT is not established at this time and is being addressed in an accompanying article in this series (32).

#### *Proteinuria, ERT, and Progression of Fabry Nephropathy*

The response of ACEI/ARB therapy has to be optimized by adjusting the dosages to achieve reduction of proteinuria to a predefined target level, but the optimal target has not been established for Fabry nephropathy. In addition, it is not known whether stabilization of kidney function can be achieved with control of proteinuria and ERT given at lower dosages than used in the pilot study (29) or the ongoing Fabrazyme and ARBs and ACE Inhibitor Treatment (FAACET) trial (31).

Whether differences between  $0.2$  and  $1.0$  mg/kg or between agalsidase-alfa and agalsidase-beta have an effect on renal outcomes is as of yet unknown. For example, in comparing the low-risk groups of male patients who had Fabry nephropathy and baseline proteinuria  $<1.0$  g/d and were treated with ERT, West *et al.* (19) reported a progression rate of  $-2.1 \pm 1.3$  ml/min per  $1.73 \text{ m}^2/\text{yr}$ , and Germain *et al.* (21) reported a progression rate of  $-1.01 \pm 0.97$  ml/min per  $1.73 \text{ m}^2/\text{yr}$  (Table 2). Statistically, these rates are not different (19) by *t* test; however, there is a possibility of a type I error in the comparison of such studies when there is not a randomized allocation of patients to either treatment arm.

The ongoing Canadian Fabry Disease Initiative study (33) will evaluate the effects on progression of both dosages of agalsidase in randomly assigned patients for whom ACEI or ARB therapy are dosed to achieve reduction of proteinuria to a similar degree. It is also important to demonstrate that the progression rate in Fabry nephropathy be reduced to the “normal” rate (20,22) with optimal ACEI or ARB therapy and agalsidase-alfa given at  $0.2$  mg/kg every 2 weeks.

The clinical significance of an absolute reduction of the progression rate by  $-1.0$  ml/min per  $1.73 \text{ m}^2/\text{yr}$  could be questioned, but to put this change in perspective, this is exactly the magnitude of the reduction or the progression rate reported in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) (34) and Irbesartan Diabetic Nephropathy Trial (IDNT) (35) studies, which are generally accepted as important advances in the treatment of diabetic

Table 2. Progression rates, baseline proteinuria and GFR, and ERT dosing in Fabry nephropathy

Reference/Patient Nos.	No. of Patients	Male/Female	ERT	Duration (Months)	Baseline Values			Proteinuria during ERT (mg/d)	Progression Rate <sup>a</sup>
					Age (Years)	MDRD eGFR	Proteinuria (mg/d)		
Warnock (16)	1	1	Agalsidase-alfa 0.2 mg/kg EOW	16	40.4	72	1510	350	-13.70 ± 1.50
Schwartz et al. (23), 7, 10, 12, and 14	4	1/3	Agalsidase-alfa 0.2 mg/kg EOW	12	57 ± 5	45 ± 5	203 ± 162	295 ± 208	-5.00 ± 4.08
Schiffmann et al. (15), 3, 7, 8, and 9	4	4/0	Agalsidase-alfa 0.2 mg/kg EOW	46	46 ± 7	90 ± 15	216 ± 79	287 ± 175	-6.63 ± 2.06
Feriozzi et al. (18)	40	?	Agalsidase-alfa 0.2 mg/kg EOW	36	37 ± 8; males 50 ± 12; females	85 ± 26	<500	<500	-1.68 ± 3.59
Feriozzi et al. (18)	14	?	Agalsidase-alfa 0.2 mg/kg EOW	36	37 ± 8; males 50 ± 12; females	92 ± 27	>500	>500	-3.98 ± 7.86
West et al. (19)	58	58	Agalsidase-alfa 0.2 mg/kg EOW	>48	34 ± 9	90 ± 31	<1000	<1000	-2.10 ± 1.30
West et al. (19)	22	22	Agalsidase-alfa 0.2 mg/kg EOW	>48	34 ± 9	90 ± 31	>1000	>1000	-6.30 ± 1.80
Warnock (16)	1	1	Agalsidase-beta 1.0 mg/kg EOW	65	41.9	48.7	350	555 ± 237	-2.92 ± 0.44
Breunig et al. (24), 9, 10, 11, 12, 20, 21, and 22	7	4/3	Agalsidase-beta 1.0 mg/kg EOW	22	40 ± 12	95 ± 20	152 ± 188	146 ± 171	-4.66 ± 6.86
Schiffmann et al. (15), 3, 7, 8, and 9	4	4/0	Agalsidase-alfa 0.2 mg/kg per wk	24	50 ± 7	62 ± 15	203 ± 60	260 ± 1725	4.20 ± 5.40
Germain et al. (21)	42	40/2	Agalsidase-beta 1.0 mg/kg EOW	52	29 ± 10	137 ± 50	277 ± 213	245 ± 247	-1.01 ± 0.97
Tahir et al. (29), 3, 4, 5, and 8	4	2/2	Agalsidase-beta 1.0 mg/kg EOW	30	32 ± 10	97 ± 17	449 ± 433	361 ± 245	1.18 ± 2.78

eGFR calculated with the MDRD equation (ml/min per 1.73 m<sup>2</sup>). EOW, every other week.<sup>a</sup>Annualized rate of change of the slope of the linear regression of eGFR over time (ml/min per 1.73 m<sup>2</sup>/yr).

renal disease (36). A similar effect was reported in the recent study of strict BP control and progression of kidney disease in children (37). In that study, there was not a significant difference between the eGFR slopes, but the intensively treated group of children had a significant delay in reaching the primary composite end point, which was defined as a 50% reduction in the eGFR or progression to ESRD.

### What Can We Do with What We Know?

Because of the rarity of Fabry disease, there are not any adequately powered outcome studies. Open-label studies, case series, and expert consensus opinions will have to inform treatment decisions, in conjunction with what has been learned about more common forms of CKD.

In addition to proteinuria, other potentially treatable factors in patients with CKD, including hypertension, smoking, and hyperlipidemia, may contribute to progressive loss of GFR (38). There is every reason to expect that this approach will apply to patients with Fabry nephropathy, so correction of these other risk factors should also be considered for interventions to slow CKD progression. Systemic BP is generally lower in patients with Fabry disease (39,40).  $\beta$  Blockers and diuretics may cause hypotension and limit the use of antiproteinuric therapy. The current approach to Fabry nephropathy is outlined in Table 3.

Regular assessment of eGFR and proteinuria is mandatory, with a frequency that should be related to the baseline severity. Changes in eGFR can be followed over time, recognizing the limitations of the estimating equations, especially when “hyperfiltration” is present (19). Plasma clearance techniques with radionuclide tracers for GFR measurement are currently the only accurate available methods for determining true GFR, because indirect methods overestimate GFR above 90 ml/min per 1.73 m<sup>2</sup> (41). It can be expected that the extended validation range of the CKD-EPI estimating equation for GFR (41) will reduce the prevalence of apparent hyperfiltration in patients with Fabry nephropathy.

The goal for treatment of Fabry nephropathy is reduction in the rate of loss of GFR to  $\leq -1.0$  ml/min per 1.73 m<sup>2</sup>/yr (20,22). What can be done if this goal is not reached? Measuring proteinuria and urinary sodium excretion are important first steps. Repeated measures of eGFR are needed; basing treatment decisions on only two measurements of serum creatinine is not recommended. If proteinuria is not controlled, then antiproteinuric dosing increases are recommended, with the understanding that systemic BP may further decrease. The doses can be split to minimize acute falls in BP, and small dosage increments are preferable. It may be necessary to reduce the dosage of other antihypertensive agents (*e.g.*,  $\beta$  blockers, diuretics, calcium channel blockers) so that ACEI or ARB dosing can be increased. Aldosterone receptor blockers may lower proteinuria with modest effects on BP (42). The possibility of another form of kidney disease could be addressed with a kidney biopsy (17).

### What Are the Key Research Questions and Answers Needed to Move Forward?

The current target for proteinuria reduction to 0.5 g/24 h was adopted (29) from an analysis of ACEI therapy in nondiabetic

Table 3. Recommendations for the diagnosis and management of Fabry nephropathy in adults

Diagnosis and assessments
confirm diagnosis of Fabry nephropathy
GFR <90 ml/min per 1.73 m <sup>2</sup> (stages 2 through 5 CKD)
albuminuria >30 mg/d or >30 mg/g creatinine
proteinuria >300 mg/d or >300 mg/g creatinine
other renal conditions rigorously excluded, which may require renal biopsy
kidney biopsy
histologic injury can precede clinical signs and provides a compelling indication for institution of ERT
excludes other conditions, especially in patients with atypical presentation or concurrent disease ( <i>e.g.</i> , diabetes)
confirms diagnosis and stage and can be used to assess response to therapy
initial assessment and follow-up
measure serum creatinine and use CKD-EPI equation to estimate GFR
use isotopic methods for precise GFR if eGFR >90 ml/min per 1.73 m <sup>2</sup>
standard CKD assessment schedule, depending on local practice standards, with more frequent visits for patients with more severe baseline kidney involvement
quantify BP, routine laboratory tests, serum creatinine, urine albumin, and protein and creatinine levels at every visit
calculate and follow eGFR slope
Treatment
ERT
agalsidase at approved dosage
start ERT as soon as practical when definite diagnosis is made
start ERT as soon as definite diagnosis is made in patients with residual enzyme activity if there is any evidence of kidney involvement
ERT will not reduce proteinuria
control of proteinuria
use ACEIs and/or ARBs in addition to ERT
titrate dosages to achieve urine protein <500 or even <300 mg/d, even if BP is <130/80 mmHg
slowing of progression requires both control of proteinuria and optimal ERT dosing

Adapted from reference (39).

forms of kidney disease (43). Whether achieving this goal will improve outcomes and the adverse effect profile are issues being addressed in an ongoing study (31).

In other forms of proteinuric kidney disease, the prespecified goal for reduction of proteinuria seems to be 0.3 g/d (27,28,38). Whether this same goal can be achieved in Fabry disease is an important issue to be addressed. In contrast to the usual BP treatment goals in CKD (44,45), many patients with Fabry nephropathy have low baseline BP levels (11,46) that are reduced even further with antiproteinuric therapy (29). The Canadian Fabry Disease Initiative Enzyme Replacement Therapy Study (33) will address optimal ERT dosing in Fabry nephropathy, but final results will not be available until 2012 or 2013.

Adult patients with “hyperfiltration” should have thorough baseline evaluation and then be started on ERT with antiproteinuric therapy to <0.30 g/24 h. After the immediate fall in GFR (29,47), the questions to be answered include what is the rate of GFR decline once titration of antiproteinuric therapy is completed and whether control of proteinuria in patients with hyperfiltration has any benefit on outcome.

Once the factors that drive progressive loss of GFR in Fabry nephropathy are identified and optimal treatment strategies are established, there may be opportunities to evaluate alternative dosing strategies (e.g., amount, frequency). Preliminary studies suggest that antibody titers may have an impact on ERT effectiveness (48). Optimizing ERT dosing for the individual patient will require an effective biomarker that reflects disease burden and response to therapy. The significance of increased of urinary GL-3 levels in the presence of anti-agalsidase antibody (48) remains to be defined (49), and the search for a reliable biomarker in Fabry disease continues (50).

Study of the pathology of Fabry nephropathy may identify predictors of progressive disease. A recent international collaborative effort by nephrologists and pathologists resulted in a scoring system for Fabry nephropathy that may serve as a tool to identify predictors of progressive disease in future studies (8).

Finally, it should be emphasized that renal events have dominated the largest trials to date (14,19,21). If kidney function can be stabilized with antiproteinuria therapy and optimal ERT dosing, then outcome events for other target organs, such as the heart and brain, can be more clearly defined with respect to the use of ERT as well as other adjunctive therapies, such as the use of ACEIs and ARBs, in Fabry nephropathy.

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