

# Enzyme Replacement Therapy and Fabry Kidney Disease: Quo Vadis?

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The advent of effective enzyme replacement therapy (ERT) has kindled considerable interest in Fabry disease; ERT offers the promise of altering the natural history of this unusual form of proteinuric chronic kidney disease (CKD). Fabry disease is a rare, X-linked, lysosomal storage disorder caused by deficient activity of the lysosomal enzyme  $\alpha$ -galactosidase A, with accumulation of its substrates (globotriaosylceramide and related glycosphingolipids), particularly in the vascular endothelial cells of the kidney and heart (1). Early manifestations typically include debilitating chronic acroparesthesias, episodic excruciating pain "crises," hypohidrosis, and gastrointestinal complaints. Subsequently, kidney failure, heart disease, and strokes lead to early death, typically between ages 40 to 50 yr for men (1). Heterozygous women can have serious disease manifestations including kidney failure (2,3). Phenotypic variation in females is more marked than in males, presumably as a result of nonrandom X-chromosomal inactivation (4–7). Later-onset variants that can be limited to a single organ system have been described (8–11).

Two forms of ERT are currently available worldwide for treating Fabry disease: (1) Replagal (agalsidase-alpha; Shire Human Genetic Therapies, Inc., Cambridge, MA) and (2) Fabrazyme (agalsidase-beta; Genzyme Corporation, Inc., Cambridge, MA). The US Food and Drug Administration has only approved agalsidase-beta for use in the US (12). Both forms of agalsidase are essentially identical (13,14), except that the approved dose for agalsidase-alpha is 0.2 mg/kg body wt and for agalsidase-beta is 1.0 mg/kg body wt. Both agents are approved for intravenous use every 2 wk. Approval for both agents was based on Orphan Drug provisions with the use of surrogate end points (12) such as clearing of vascular endothelial deposits (15) and symptomatic improvement of pain scores (16). Furthermore, when ERT was initiated in patients with relatively mild disease, there appeared to be favorable responses in terms of slowing or preventing serious organ dysfunction (16,17).

Less favorable results have been reported in open-label longitudinal studies in patients with more advanced kidney disease, particularly with overt proteinuria (18,19). These concerns

are echoed by the recently published results of a phase IV, randomized, prospective, placebo-controlled trial in which 82 patients with initial GFR values  $<80$  ml/min per  $1.73$  m<sup>2</sup> were randomized (2:1) to agalsidase-beta or placebo (20). *Post hoc* analysis of this study revealed that the patients who had initial GFR values  $>55$  ml/min per  $1.73$  m<sup>2</sup> did quite well compared with their placebo control group, but those with more severe disease and proteinuria did not exhibit the same benefits from ERT (20). Interpretation of this study is complicated by a baseline imbalance in the urine protein excretion between the placebo- and agalsidase-beta groups (20), and the relatively small number of patients included in what was designed to be an outcome study (21).

Proteinuria has emerged as an important risk factor for progression of kidney involvement in a number of kidney diseases (22), including Fabry disease (17). In this issue of *JASN*, two important papers that underscore the importance of proteinuria in Fabry patients and describe the limitations of ERT in addressing this issue are published. Germain *et al.* (23) provide a prolonged follow-up of the original agalsidase-beta phase III cohort. The favorable outcome of most of these patients is now extended to  $>4.5$  yr, but, as was noted in an earlier publication (17), a small subset of patients who initially had well-preserved GFR values and overt proteinuria suffered continuing decline of their kidney function at a rate that approached  $-10$  ml/min per  $1.73$  m<sup>2</sup> per yr (23). Similarly, Schiffmann *et al.* (24) describe a subset of their previous cohort (19) that had marked rates of GFR decline and benefited from increasing the infusions of agalsidase-alpha to a weekly basis from every 2 wk. Although the finding of a possible dose-dependent effect of ERT is clearly important, it should also be noted that agalsidase-alpha is not approved by the US Food and Drug Administration for use in the US, and the dosing interval used by Schiffmann *et al.* (24) is not approved in any country where agalsidase-alpha is approved for treatment of Fabry disease.

A common thread in all of the published outcome studies with agalsidase-alpha (19,24) and agalsidase-beta (15,17,18,20,23) is that ERT at the currently approved doses simply does not impact on urinary protein excretion. The association between pathologic changes (focal and global glomerular sclerosis, tubular atrophy, interstitial fibrosis, *etc.*) and proteinuria is not surprising (23,25), but to date there has not been a systematic attempt to reduce the proteinuria and slow the progressive GFR decline in Fabry disease with antiproteinuric therapy, as has been so successful in type I

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and type II diabetes and other forms of proteinuric kidney disease (26,27). A number of patients in the various trials (15,17–20,23,24) were treated with angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB), but in none of these studies was systematic reduction of urinary protein excretion identified as a primary or secondary objective in the study (20). Schiffmann *et al.* did include the use of ACEI and ARB in a multivariate analysis of progression rates, but this was treated as a dichotomous variable without regard for their critical effects on measured urinary protein excretion (24).

Even although the baseline blood pressure (BP), especially in males, is not typically elevated in Fabry disease (17–20,23,24,28), it is possible to achieve sustained reductions in urinary protein excretion and stabilization of GFR with careful titration of ACEI and ARB (29,30). The safety and efficacy of this approach is now being addressed in a recently organized, prospective, observational study of 40 Fabry patients with significant kidney involvements who are being treated with agalsidase-beta (31). There is reason to hope that kidney function can be stabilized even in advanced cases with the combined use of ERT and antiproteinuric therapy (29,32). We can now be fairly certain that ERT alone will not reduce overt proteinuria in Fabry disease, and that baseline urine protein excretion at the time of ERT initiation will predict the progression rate of GFR decline (23). There may be important dosing issues that need to be addressed in patients with more advanced kidney involvement (24,32).

Fabry disease should be of general interest to practicing nephrologists because it now represents one of the treatable causes of proteinuric CKD. Many of these patients are not overtly hypertensive, so the usual clinical practice guideline for CKD of reducing systemic BP to <130/80 mmHg is not particularly helpful if the baseline BP is already below that target. Fabry disease with proteinuria may well provide a clear-cut example where the therapeutic target needs to be defined in terms of sustained reduction in the urine protein excretion rate rather than achieving some predetermined goal for reduction of systemic BP (33).

The immediate task is to apply the results of the available outcome studies to the treatment of the individual patient with Fabry disease. Schiffmann *et al.* has emphasized the importance of focusing on the preservation of kidney function with our current state of knowledge (21); the obvious implication is that the sooner effective ERT is started, the more likely it is that this goal will be achieved.

## Disclosures

D.G.W. serves as a consultant for Genzyme Corporation, and participates on Registry Advisory Panels and the Speakers Bureau on Fabry disease. He has received research support from Genzyme Corporation and participated in the phase IV agalsidase-beta trial. The preparation of this editorial was carried out entirely independently of Genzyme Corporation, including any and all medical writers and data analysis.

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See the related articles, "Sustained, Long-Term Renal Stabilization after 54 Months of Agalsidase-Beta Therapy in Patients with Fabry Disease" on pages 1547-1557, and "Weekly Enzyme Replacement Therapy May Slow Decline of Renal Function in Fabry Patients on Long-Term Biweekly Dosing" on pages 1576-1583.