Enzyme Replacement in Fabry Disease: The Essence Is in the Kidney

Fabry disease is an X-linked, single-gene defect caused by a deficiency of lysosomal α-galactosidase A resulting in failure to catabolize α-D-galactosyl glycolipid moieties, mostly globotriaosylceramide (1). It is a panethic disorder with an estimated incidence of 1 in 117 000 live births in males, but recent neonatal screening suggested an incidence of up to 1 in 3100 live births (2). Female heterozygotes often express delayed heterogeneous signs and symptoms ranging from no disease expression to full-blown disease as seen in hemizygous men (3).

Fabry disease has been classified as a lysosomal storage disorder because of the conspicuous presence of membranous inclusions in lysosomes of most types of cells and tissues. However, its salient characteristic, the systemic increase in glycolipids, is better considered as a risk factor for developing organ damage whose manifestations are relatively common in the general population. These include a painful small-fiber peripheral neuropathy (4), cerebrovascular stroke (5), progressive renal failure (6), and manifold cardiac abnormalities (7). This view of Fabry disease leads directly to the preferred therapeutic approach, which is to prevent the progressive and irreversible deterioration of major organ systems.

In the past 15 years, enzyme replacement therapy (ERT) has been successfully used in Gaucher disease and, more recently, in other lysosomal disorders, including Fabry disease. There are currently 2 preparations of α-galactosidase A for ERT—agalsidase alfa (Replagal, Shire Human Genetic Therapies, Cambridge, Massachusetts) (8) and agalsidase beta (Fabrazymel, Genzyme Corp., Cambridge, Massachusetts) (9). Both preparations are used in most countries, but the U.S. Food and Drug Administration (FDA) approved only agalsidase beta. They approved it on an expedited basis because of a demonstration that it markedly reduced the number of lysosomal inclusions in renal vascular endothelial cells (9) and on the condition that a later study of agalsidase beta would show a beneficial effect on relevant clinical end points, particularly in the kidney. That long-awaited study is published in this issue (10).

The study by Banikazemi and colleagues is a multicenter, double-blind, placebo-controlled trial involving 82 patients with Fabry disease (12% were women), with median time in treatment of 18.5 months (10). The study sample included only patients whose renal glomerular function was clearly declining. The composite primary outcome measure was time to first clinical renal, cardiac, or cerebrovascular event or death. The study ended when only about one third of the patients had experienced a total of 27 clinical events, 17 (63%) of which were renal events. After adjustment for baseline proteinuria, the intention-to-treat analysis showed that fewer clinical events occurred in patients receiving agalsidase beta than in those receiving placebo in the intention-to-treat population—a difference that was not statistically significant. When only the 74 protocol-adherent patients were analyzed, the reduction in risk for a clinical event with agalsidase beta was statistically significant. Furthermore, a secondary analysis showed that treatment benefit occurred mostly in patients with a relatively preserved baseline glomerular filtration rate (GFR) (>55 mL/min per 1.73 m²) (10).

Overall, these data strongly suggest that agalsidase-beta ERT slows the decline of glomerular function in patients with Fabry disease. Banikazemi and colleagues’ study is the first controlled trial to show an effect of ERT on a major complication of Fabry disease, but the study was underpowered, and we are left with some uncertainty about whether the differences were due to chance or to agalsidase-beta ERT. If the study was performed in a larger study sample, the effect would probably have been more conclusive by statistical criteria, but we can’t be sure. Nevertheless, we can estimate that the effect size of agalsidase beta was rather large when compared with the renal-sparing effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Using similar study structures, other studies have found that 583 patients, who were followed for 3 years, were needed to demonstrate a 50% risk reduction with benazepril (11) and that 1513 patients, who were followed for an average of 3.4 years, were needed to show a 16% mean risk reduction with losartan (12). The authors’ choice of an outcome measure may have made detection of an effect of ERT more difficult. Categorical efficacy measures, such as clinical events, are clinically meaningful but are known to be less sensitive than continuous measures, such as the mean rate of change in GFR (13).

Other factors may have diminished the effect of ERT in Banikazemi and colleagues’ study. The organ complications of Fabry disease cited previously obey the same physiologic rules as those that govern similar illnesses in the general population. Therefore, standard medical therapy used to prevent stroke, kidney failure, and cardiomyopathy that are caused by common diseases is likely to be useful in Fabry disease. In particular, ACE inhibitors and ARBs are likely to slow the progression of kidney disease and may confound the assessment of the net effect of ERT. Because about one third of the patients in each group were receiving ACE inhibitors and ARBs, the use of these drugs may have tended to diminish the difference between the ERT and placebo groups.

Many other factors are likely to influence the results of the study. Most patients receiving ERT (68%) developed IgG antibodies to agalsidase beta. These antibodies are likely to be inhibitory in enzyme assays and diminish the effect of the infused enzyme on the patients’ glycolipid deposits (14). Banikazemi and colleagues do not report on...
the effect of anti-agalsidase-beta antibodies on the likelihood of a clinical event. Future studies should determine whether tolerizing patients to the infused enzyme would increase the efficacy of ERT. A decrease in the difference in treatment effect between the 2 study groups would have occurred if more patients with milder variants of the disease had been randomly assigned to placebo. Such patients are known to have delayed onset of disease complications (15). Uneven allocation of patients to study groups is a risk in relatively small randomized trials, such as Banikazemi and colleagues’ trial. The authors also do not report the outcomes in female patients. The inclusion of women in the trial is laudable. Affected women are heterozygous for this X-linked disease, and the heterogeneity and lesser severity of their clinical manifestations make evaluating therapy more difficult in heterozygotes than in hemizygous men (3). Including women may have further decreased the likelihood of observing an effect of therapy on clinical events in the study sample.

Banikazemi and colleagues focused on kidney disease and did not describe evidence for an effect of agalsidase beta on cerebrovascular or cardiac complications. Indeed, strokes continue to occur in patients taking either enzyme preparation (16, 17). It is, therefore, important for all susceptible patients to receive effective antiplatelet agents (such as clopidogrel) and statins.

Most of the effect of agalsidase beta occurred in patients in an early phase of renal deterioration, which suggests that introducing ERT early in the disease, particularly in children, would be more effective than waiting until renal function starts to decline. Because of the confounding effect of standard general medical therapy for Fabry disease, confirming this hypothesis would require a clinical trial that randomly assigned children to immediate versus delayed ERT (18).

The high cost of lifelong therapy with agalsidase beta is a major concern. The yearly cost of agalsidase beta for a patient weighing 70 kg is about $240,000. This suggests that lifelong therapy cannot be cost-effective even if it completely prevents the medical complications of Fabry disease and extends life for 30 years or more. Therefore, fair cooperation between society and industry in setting reasonable and agreed-upon prices should govern decision making for ERT in this and other orphan disorders (19).

On the basis of Banikazemi and colleagues’ study, hemizygous male patients with the classic form of Fabry disease at possibly any age and symptomatic patients with milder variants should receive ERT with the particular goal to preserve renal function. Because a therapeutic effect on the cardiac and cerebrovascular aspects of the disease remains to be demonstrated, ERT should be supplemented with the best standard medical care with particular emphasis on the most effective stroke-preventing medications.

Even as this landmark trial is finally published, promising new developments are on the horizon. Better results with ERT in Fabry disease may be achievable by modifying the infused enzyme to allow more thorough cellular and tissue uptake. In addition to ERT, many novel therapies for Fabry disease and other lysosomal disorders are being developed that include chemical chaperones to improve trafficking of the mutated enzyme, thereby increasing endogenous enzyme activity; molecules that reduce substrate storage; therapy based on an understanding of the downstream biochemical effects; and possibly gene or stem cell therapy further in the future (20). As part of this effort, the work by Banikazemi and colleagues provides a crucial path toward lowering the morbidity of Fabry disease.

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References