Fabry Disease: Dose Matters

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Fabry disease is an X-linked disorder resulting from mutations of the gene that encodes the lysosomal hydrolase α-galactosidase A, and leads to progressive lysosomal accumulation of globotriaosylceramide (GL-3) and related glycosphingolipids. In classically affected male patients, clinical onset occurs in childhood or adolescence and is characterized by several symptoms as well as kidney failure, cerebrovascular manifestations, heart failure, and eventually premature death.

Nephropathy is a dominant feature in Fabry disease. Proteinuria predicts and may also contribute to the progressive decline in GFR, which may eventually lead to ESRD in the third to fifth decade of life. Fabry nephropathy is generally less severe in women than in men; however, heterozygous female patients with progressive kidney involvement reach ESRD at the same median age as hemizygous male patients.

Enzyme replacement therapy (ERT) with recombinant α-galactosidase, including agalsidase-α (Replagal; Shire Pharmaceuticals) and agalsidase-β (Fabrazyme; Genzyme Corporation), is currently the only approved, specific treatment for Fabry disease. ERT stabilizes or slows the progression of Fabry nephropathy in patients with Fabry disease, especially if proteinuria can be controlled to <0.5 g/dL. Patients are treated with 1 mg/kg agalsidase-β intravenously every other week or 0.2 mg/kg agalsidase-α every other week; other than the amount of infused protein, there appears to be a very little difference between the two products. There may be differences in the response to ERT, and it appears that the 5-fold difference in the delivered dose could affect the stabilization of renal function, at least in some patients. The issue of effective ERT dosing for Fabry disease was brought into sharp focus by an unfortunate lapse in manufacturing practices that resulted in a worldwide shortage of the Genzyme product (Fabrazyme) between June 2009 and January 2012.

In this issue of JASN, Weidemann and a collaborating group in Germany report their patient experiences during the period of the Fabrazyme shortage that resulted in a change of treatment regimen in many patients. Systematic and complete data collections were obtained before any change in ERT dose, at the time of dosing adjustment, and 1 year after the change in dosing. This is an especially impressive effort considering that the dose reductions caused by the shortage were unanticipated and acutely imposed with very little warning. As Weidemann et al. fully acknowledge in their article, decisions about dosing regimens during the shortage were based on consensus-based clinical criteria and not on a randomized prospective study design, which substantially limits comparisons between the treatment arms. More severely affected patients were in the stable agalsidase-β group, and more mildly affected patients were in the agalsidase-α group. Approximately one third of the 105 patients were maintained on standard ERT dosing at 1 mg/kg every 2 weeks, whereas the remainder receiving reduced dosing of agalsidase-β (0.3–0.5 mg/kg every 2 weeks) or were switched to agalsidase-α at 0.2 mg/kg every 2 weeks.

Although patients in the standard dosing group remained stable, patients in the dose reduction group self-reported worsened pain attacks, pain crises, and disease severity scores and patients in the switch group reported worsened pain attacks, chronic pain, gastrointestinal symptoms, and disease severity scores. The eGFR decreased by approximately 3 ml/min per 1.73 m² in both male and female participants in the dose reduction group and showed a similar trend in the more mildly affected switch group (P = 0.09), but the eGFR was unchanged in the group maintained on standard dosing. However, the albumin/creatinine ratio increased only in the switch group. Although there were no major target organ events during the 1-year follow-up, this was a short follow-up time for such analyses and most patients had been on stable ERT dosing for at least a year before the shortage.

Two much smaller studies—with 10 patients and 11 patients, respectively, and with no comparison groups maintained on full dose ERT—reported no increases in symptoms or organ injury indicators 12 months after the switch to 0.2 mg/kg agalsidase-α every other week. The study by Weidemann et al., with very different outcomes of dose reduction, illustrates the risk of coming to potentially incorrect conclusions on the basis of statistically underpowered observations.

The licensed dose of agalsidase-β (1 mg/kg every 2 weeks) was based primarily on the findings that 20 weeks of treatment in adults substantially cleared endothelial cells of accumulated GL-3 primarily in renal peritubular capillaries, but also in the heart and skin. This was sustained at 11 months although
there were fewer effects on distal tubular and vascular smooth muscle cells and on podocytes. After 54 months of this dose of ERT, repeat renal biopsies showed that podocytes were only partially cleared of GL-3 in four patients and were unchanged GL-3 in two patients. In Europe, the approval of agalsidase-α (Replagal) at 0.2 mg/kg every other week was based on 6-month data from placebo controlled trials as well as 18-month data from an open-label maintenance study. The primary endpoint in the TKT003 study was the effect of the enzyme replacement on serious debilitating pain. The regulatory summary reported that the study demonstrated improvement in kidney function and reductions in pain, cardiac mass, and GL-3 content in kidney, heart, and liver cells (http://www.fda.gov/ohrms/dockets/ac/03/briefing/3917b2_02_fda-backgrounder.pdf).

It is noteworthy that there is no progressive increase in glomerular endothelial cell GL-3 accumulation with age in children with Fabry disease, whereas podocyte GL-3 accumulation is not only progressive with increasing age but also correlates with podocyte foot process width, and both foot process width and podocyte GL-3 deposits are correlated with proteinuria. Similar findings are emerging in patients studied into adulthood while average glomerular endothelial cell GL-3 remains constant (B. Najaian and M. Mauer, unpublished observations). A recent case report describes podocyte GL-3 deposits and foot process effacement in a young Japanese male patient with severe neuropathic pain and confirmed Fabry disease with normal kidney function but with very low levels of proteinuria.

Proteinuria in adults was previously recognized as an important risk factor for progression of Fabry nephropathy, especially if proteinuria is >1 g/d. ERT appears not to have beneficial effect on overt proteinuria in adults, especially in men, but stabilization of renal function may be seen with ERT if proteinuria can be controlled using renin-angiotensin system blockers. Recent studies in younger patients and female patients have described effects of ERT on lower levels of proteinuria (specifically, reductions in albumin excretion in patients with relatively mild or early onset renal involvement treated with higher doses of ERT [1 mg/kg every 2 weeks]). The study by Tøndel et al. is especially notable because systemic renal biopsies were carried out before and 5 years after ERT. Tøndel et al. described a reduction in and even clearing of podocyte GL-3 deposits that was related to the cumulative dose of ERT received, and the reductions in urinary albumin excretion paralleled the reductions in podocyte GL-3 deposits. At lower doses of administered ERT, neither podocyte GL-3 scoring nor albuminuria decreased. Similarly, women with Fabry disease whose glomerular and tubular protein excretion decreased had received 1 mg/kg per 2 weeks of agalsidase-β for at least 1 year. These studies emphasize the importance of starting ERT early, before there is major, irreversible organ damage, and illustrate the importance of systematic histologic evaluation to assess the adequacy of response to ERT as well as the importance of the podocyte in relation to proteinuria, an important indicator of disease progression in Fabry nephropathy. We are hopeful that additional biomarkers will be validated in the future that will assist in the treatment decisions (e.g., when to start, what dose); however, for now, histologic evaluation should be seriously considered in every patient.

What lessons were learned from the 2.5-year shortage of agalsidase-β? Clinical trials are difficult to carry out in rare disorders, such as Fabry disease, especially with already approved treatments resulting in a paucity of treatment-naïve patients. Thus, albeit an imperfect set-up, studies such as that of Weidemann et al., which took advantage of an unfortunate and quite prolonged drug shortage, are important. Using the patients as their own controls, important effects of dose reductions were noted even though these reductions were not below the levels approved in Europe for agalsidase-α. These effects were primarily on patient-reported outcomes and renal function, and did not include major target organ events during the relative short-term follow-up period described by Weidemann et al. Patient-reported outcomes require more systematic evaluation as important aspects of the response to ERT and other future treatments for Fabry disease. Finally, there may be instances of Fabry disease in which the currently approved maximal ERT doses may be suboptimal because of individual pathophysiologic variables, the presence of relatively more advanced disease, or both. In these patients, more personalized care approaches with dose adjustments for inadequate clinical or tissue responses might be considered and new add-on treatment modalities need to be explored for patients with residual risks despite current standards of care.

DISCLOSURES

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REFERENCES


See related article, “Patients with Fabry Disease after Enzyme Replacement Therapy Dose Reduction Versus Treatment Switch,” on pages 837–849.