Agalsidase treatment for Fabry disease: Uses and rivalries

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In this issue, three articles are relate to various aspects of enzyme replacement therapy (ERT).[1–3] The studies discuss the use of existing α-galactosidase A preparations and are based on two registries of patients with Fabry disease. The two enzyme preparations for ERT in Fabry disease are agalsidase alfa, produced by Shire Human Genetic Therapies, and agalsidase beta, produced by Genzyme Corporation. Both are approved in Europe and other countries, but only agalsidase beta is currently approved for general use in the United States. Since completion of the randomized controlled trials that led to the approval of these two compounds,[4,5] most studies describing the efficacy of ERT have been open labeled and increasingly based on patient registries. The three articles in this issue exemplify this trend.

The use of patient registries for a variety of diseases and treatments has increased in recent years.[6] The Agency for Healthcare Research and Quality (http://effectivehealthcare.ahrq.gov/repFiles/DEcIDEs_Registries.html#execsum) defines a registry as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose."

The goal of a patient registry is to collect "real-world" data on the safety and effectiveness of a new but already approved treatment by following typical patients. Those patients receiving a novel treatment are included in registries to evaluate how their condition progresses and whether any untoward events occur that seem to be related to the treatment.[7] Registries have been used to expand indication of a drug, of an interventional procedure, or of the use of a diagnostic method.[6] The drug inserts of most ERT products contain a recommendation to the physician to include the patient in the appropriate registry. The advantages of a registry include the enrollment of a large number of patients with the full spectrum of the disorder and the potential detection of rare events. However, limitations of registries include possible patient selection bias (e.g., inclusion of more severely affected or more compliant patients in registries), incomplete and missing data leading to misclassification, and, most importantly, absence of concurrent untreated controls or controls treated by an alternative approach.[8] Some of the findings in the three articles exemplify these advantages and limitations. The deficiencies can, however, be partially corrected by the use of various statistical tools such as sensitivity analysis and other predictive modeling techniques.[9,10]

In the first article, Watt et al.[1] have found a significant increase in quality of life (QOL) in 71 men and 59 women on their registry in the first 2 years on agalsidase beta. Patients with lower baseline QOL score, especially men, tended to have the greater increase in QOL. Because of a more severe and uniform type of the disease, hemizygous male patients with Fabry disease tended to benefit more than heterozygous female patients with Fabry disease, in particular in the physical component of the SF-36 questionnaire. The authors acknowledge the limitations of their study. The most remarkable of them was the inclusion in this study of only 71 men who filled the SF-36 questionnaire out of the 898 men in the registry or 7.3%. A similar proportion of women were studied (13%). It is possible that patients with greater improvement in QOL were more likely to fill the form, thus introducing a bias toward a positive treatment effect. Increased QOL in patients on placebo ERT has been observed, further emphasizing the difficulty of assessing treatment effect, especially in a subjective parameter.[4] Nevertheless, the frequent recurrence of symptoms in patients whose ERT had to be stopped or curtailed (because of the recent shortage in the supply of agalsidase beta) suggests that these QOL improvements had been significant (R. Schiffmann, personal observation). Importantly, improved QOL was also shown in patients receiving agalsidase alfa.[11] The mean QOL scores tended to be uniformly lower at the 2 years time point than at the 1-year time point, particularly in men.[4] This may be due to a ceiling effect or to a change in the frame of reference over time.[1] A similar waning effect of ERT was, however, seen in studies on the effect of ERT on left ventricular mass and may represent decreased treatment effect in the face of a progressive disease.[11]

Lidove et al.[2] review the ERT literature on both agalsidase alfa and agalsidase beta. They found evidence of a stabilizing effect on kidney function, a reduction of neuropathic pain and improvement of small fiber peripheral nerve function, and a positive effect on the heart, predominantly by a reduction of left ventricular hypertrophy in the early stage of the disease, although prevention of heart failure or increased survival have not been demonstrated. No effect on cardiac rhythm or conduction abnormalities has been described other than increased heart rate variability in male children.[12] Lidove et al.[2] confirm the lack of evidence of any preventive effect of ERT on ischemic strokes in patients with Fabry disease. These therapeutic effects are modest overall but would probably be enhanced if ERT is initiated at an early age. These authors also conclude that, although very few studies were performed comparing the two commercially available forms of α-galactosidase A, the therapeutic effect of the two agalsidases is similar overall.

On the basis of their conclusions regarding the effect of ERT, the authors of the third paper, Mehta et al.,[3] describe what they consider should be the therapeutic goals for the treatment of Fabry disease. In considering the therapy for a disease such as Fabry, one has to take into account that virtually all the complications of the disease are "nonspecific" in nature—i.e., they

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have similar presentation and clinical characteristics as they would be in non-Fabry patients (atherosclerosis, diabetes, etc.).[13] As a consequence, other standard therapies developed for the general population, e.g., therapies for proteinuric renal insufficiency or for various cardiac ailments have similar beneficial effects in patients with Fabry disease.[14] Such therapies range from low-cost remedies such as angiotensin converting enzyme inhibitors/angiotensin receptor blockers to more definitive but costly interventions such as renal transplantation which clearly prolong life. These "nonspecific" therapies are efficacious but confound the evaluation of a specific treatment such as ERT, especially in open-labeled, uncontrolled, long-term observational studies.

Mehta et al.[12] correctly emphasize that the main goal of therapy for Fabry disease is prevention of its cardinal cerebrovascular, renal, and cardiac manifestations. They also appropriately state the very high likelihood that a typical patient with no residual α-galactosidase A will develop renal insufficiency or some cardiac anomaly. However, they usually recommend initiating specific therapy only when some renal (e.g., proteinuria or albuminuria), cardiac, or cerebrovascular abnormalities are already present. Given the high likelihood that male patients with this X-linked disease will develop major complications, why not provide ERT to them as soon as they are diagnosed and well before any clinical or laboratory evidence of organ damage is present? It is likely that once proteinuria, cardiac hypertrophy, or any other abnormality is present, substantial damage has already occurred. The evidence presented thus far supports such an approach. A controlled trial of early versus delayed ERT is highly desirable but such a study has not materialized thus far. In addition, preventive therapies have been in use for diseases in which complications are far less likely than is the case in Fabry disease.[15] Preventive therapy in Fabry disease may include not only ERT but also angiotensin converting enzyme inhibitor/angiotensin receptor blocker even before the onset of overt albuminuria.[16] In the same vein, because ERT has not been shown to prevent strokes, why do we expect its use to prevent or delay the occurrence of stroke, or why should a clinical sign of cerebrovascular involvement constitute an indicator to start ERT? Because strokes occur at about a 20-fold higher rate in patients with Fabry disease than in the general population, primary prevention using effective antiplatelet agents such as clopidogrel or aspirin and extended-release dipyridamole should probably be the desired approach in patients with no residual enzyme activity.

Since the advent of ERT for Fabry disease, there has been a heated debate about the dose that should be used. Agalsidase alfa has been used at a fifth the dose of agalsidase beta. However, the much higher dose does not seem to be associated thus far with measurable clinical superiority. The lack of a significant dose effect is not surprising because no real dose effect on the substrate biomarker globotriaosylceramide in urine or blood was seen in studies using agalsidase alfa.[17,18] Rather than the dose, it is delayed timing of ERT initiation, the intermittent administration (while a healthy individual has a constant supply of α-galactosidase A in every cell), uneven organ distribution, and tissue penetration that are more likely explanations of the limited effect of ERT.[19–21] It is important to remember that unlike type 1 Gaucher disease, for example, which is essentially a one-cell (macrophage) disorder, Fabry disease affects multiple organ systems and various cell types.

The clinical application of the two agalsidases has been a source of controversy and competition between the makers of these two enzyme preparations, one in which physician investigators too often seem to serve as surrogates. In reality, most of the difficulties encountered in evaluating ERT for Fabry disease have been due to the nature of the disorder. Similar obstacles are likely to lie in the path of investigators testing other specific therapeutic approaches such as increasing the level and activity of the mutated enzyme with pharmacological chaperones or substrate reduction therapy.[22]

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