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Enzyme Replacement Therapy of Fabry Disease

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Abstract

Fabry disease is an X-linked lysosomal storage disease caused by deficiency of the enzyme α-galactosidase A and results in pain, progressive renal impairment, cardiomyopathy, and cerebrovascular disease. The results of two major randomized, double-blind, placebo-controlled clinical trials and open-label extensions have shown that replacement of the deficient enzyme with either of two preparations of recombinant human α-galactosidase A, agalsidase-alfa, and agalsidase-beta is safe. Biweekly IV infusions of 0.2 mg/kg of agalsidase-alfa were associated with a significant decrease in pain and stabilization of renal function. Biweekly infusions of 1 mg/kg of agalsidase-beta were associated with virtually complete clearing of accumulated glycolipid substrate from renal and cutaneous capillary endothelial cells. Several smaller, open-label studies, along with observations made in the course of monitoring large numbers of patients on enzyme replacement therapy, indicated that treatment stabilizes renal function and produces significant improvements in myocardial mass and function. Treatment of Fabry disease by enzyme replacement has a significant impact on at least some serious complications of the disease.

Index Entries: Fabry disease; enzyme replacement therapy; lysosomal storage disease; glycosphingolipids; α-galactosidase.

Introduction

Fabry disease is a rare, X-linked hereditary disorder of neutral glycosphingolipid metabolism caused by deficiency of lysosomal α-galactosidase A *(1)*. Deficiency of the enzyme results in accumulation of globotriaosylceramide (Gb3, or CTH) in various tissues throughout the body, especially in the walls of small arteries, renal glomerular, and tubular epithelium; myocardium; small unmyelinated nerves; and dorsal root ganglion neurons. Another neutral glycosphingolipid, galactosylgalactosylceramide, also accumulates in the organ in much lower concentrations than Gb3. The extent to which it contributes to clinically significant pathology in patients with Fabry disease is not clear.

Brady *(2)* originally demonstrated the defect in the degradation of Gb3 in Fabry disease using radiolabeled glycolipid. During the time that I was a research fellow working in Leon

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Wolfe's lab, we unambiguously demonstrated that the terminal glycosidic linkage in Gb3 is in the α-anomeric configuration *(3)*. This provided proof of the direct relationship between the enzyme defect in Fabry disease (shown previously by Kint to be deficiency of an α-galactosidase) and the structure of the principal glycolipid accumulating in the disease *(4)*.

Clinical Characteristics of Fabry Disease

Much has been written about the clinical manifestations of Fabry disease *(5–7)*. The earliest, often most debilitating, and most bizarre clinical manifestation of the disease is pain caused by accumulation of glycolipid in small, unmyelinated nerves *(8)*. The pain may take many forms. The most common is sudden attacks of intense paresthesias and burning pain in the hands and feet, often precipitated by exposure to heat, fever, or physical exertion and lasting from a few hours to several days. Patients with Fabry disease generally sweat poorly or not at all, adding to their intolerance of environmental heat. Patients also experience lancinating pain in the extremities and back, as well as acute abdominal pain. The joint pain is often indistinguishable from acute juvenile rheumatoid arthritis. The pain responds poorly to conventional non-narcotic analgesics, although it is often relieved or preventable by treatment with phenytoin, carbamazepine, or gabapentin.

Glycosphingolipid accumulation in the small arteries of the skin produces lesions called angiokeratomata, which are almost pathognomonic of Fabry disease. The skin lesions generally develop in affected males in the late teen years, are typically distributed diffusely around the torso and in the groin, and are small (1–2 mm), red-black, slightly raised, vascular lesions that do not blanch with pressure and are not associated with any inflammatory reaction. They may occur as a small number of single lesions (often in the umbilicus) or as a large number of diffusely scattered lesions covering large areas of the trunk, genital area, buttocks, and thighs. They will bleed if scratched. Since we reported patients with the disease who had no angiokeratomata *(9)*, which once was considered to be necessary and virtually pathognomonic of the disease, a significant proportion of Fabry patients have been found to lack angiokeratomata.

The most serious clinical complications are the result of accumulation of Gb3 in the walls of small arteries, renal epithelium, and myocardium. Small vessel disease often presents as transient ischemic attacks or complete strokes *(10)*. These may be so subtle that they are missed clinically but show up on magnetic resonance imaging as scattered lacunar lesions in the cerebrum. Occasionally, they are associated with sudden, complete, and irreversible loss of vision in one eye or with the loss of hearing in one or both ears. We have even observed transient ischemic attacks in young female carriers of Fabry disease *(11)*. The prevalence and severity of symptoms and complications of Fabry disease in many female carriers *(6)* has prompted investigators to drop the historical reference to the term X-linked recessive disorder in favor of X-linked disorder.

Progressive accumulation of Gb3 in kidney *(12)* is associated with the development of proteinuria and isosthenuria, usually in the late 20s or early 30s, followed within a decade by the development of progressive renal failure *(13)*. Advanced renal complications may occur in males or females with Fabry disease who do not have a history of the characteristic pain or skin lesions. Recently reported surveys of male dialysis patients in Japan *(14)* and both male and female dialysis patients in Europe *(15)* showed that up to 1.2% of patients with end-stage renal disease may have previously unrecognized Fabry disease.

Cardiac manifestations of the disease include episodes of palpitations associated with conduction defects that often begin in later childhood. In some patients, treatment requires the use of implanted pacemakers. Accumulation of Gb3 in cardiac myocytes is associated with progressive cardiac hypertro-

phy in most patients with the disease *(16,17)*. In some patients, the progressive impairment of cardiac function is particularly severe, often resulting in the need for cardiac transplantation *(18)*. Surveys of both males *(19)* and females *(20)* with late-onset hypertrophic cardiomyopathy (HCM) without other characteristic features of Fabry disease showed that 6 of 79 men and 4 of 34 women tested had previously unrecognized Fabry disease. The total numbers examined were small in both studies; surveys of much larger populations of patients with HCM are in progress.

In addition to these severely debilitating or life-threatening complications, patients of both genders with Fabry disease commonly experience tinnitus and vertigo as well as loss of hearing (which may be precipitate) apparently unrelated to the effects of the disease on the cerebral circulation. Gastrointestinal problems, such as recurrent abdominal pain and chronic diarrhea, are very common. Chronic fatigue is also reported by the majority of males with Fabry disease as well as many female carriers of the disease. Taken together, the quality of life of patients with the disease is severely impaired *(21,22)*.

Although in the past attention has focused predominantly on adults with the disease, the onset of symptoms—particularly in affected males—generally dates from childhood *(23,24)*. In addition to pain and characteristic skin lesions, affected boys and many affected girls report chronic gastrointestinal manifestations of the disease. However, unless the child is known to be at risk for Fabry disease because of his or her family history, the diagnosis is generally delayed, sometimes for decades.

Symptomatic and Supportive Treatment

Until the advent of enzyme replacement therapy (ERT), treatment for Fabry disease was limited to symptomatic and supportive measures. The pain often responds to the administration of phenytoin, carbamazepine, or gabapentin, and some patients also appear to respond to tricyclic antidepressants. The renal manifestations of the disease are managed in the same manner as the renal complications of other diseases causing progressive renal failure. Peritoneal dialysis, hemodialysis, or renal transplantation relieves symptoms caused by progressive renal failure; however, none of these alter the progression of other manifestations of the disease, such as cerebrovascular or cardiac complications *(25)*. Treatment of the cerebrovascular and cardiac complications is empirical, drawing on experience with other diseases associated with similar complications. The management of cardiac arrhythmias sometimes requires the use of implanted pacemakers, and cardiac transplantation is occasionally necessary for relief of symptoms caused by severe hypertrophic cardiomyopathy. The need to control risk factors, such as smoking and arterial hypertension, is particularly important.

Enzyme Replacement Therapy

Research undertaken by Brady and others in the 1960s showed that many inherited metabolic diseases, including Fabry disease, are caused by deficiencies of lysosomal enzymes *(26)*. Sly *(27)* recently reviewed the sequence of events that ultimately led to the development of practical ERT for the lysosomal disorders in general. More than 30 yr ago, Brady *(28)* showed that iv administration of purified lysosomal enzymes in patients with deficiency diseases produced biochemical evidence of enzyme replacement. However, the successful ERT of patients affected with any of the several lysosomal storage diseases that were known at the time required enormous amounts of enzyme, more than could be reasonably produced in an academic research laboratory.

The field experienced a series of major breakthroughs as a result of some important discoveries in research labs, coupled with key legislative initiatives in the United States. On

the biology side, methods were found to produce large quantities of purified lysosomal enzymes *(29)*, and scientists discovered that the nature of the oligosaccharide of lysosomal enzyme glycoproteins played a central role in targeting intravenously administered enzymes to specific tissues *(30)*. On the legislative side, the US Bayh–Dole Act (1980) stimulated the entrepreneurial activities of academic institutions by enabling them to patent their discoveries and licensing them to private corporations. In 1983, the US Orphan Drug Act stimulated research and development of new therapies for rare disorders by granting companies fast-track approval by the Food and Drug Administration as well as market exclusivity for several years (at least in the United States) after approval of a new therapy.

The first new treatment for a lysosomal storage disease to emerge from these developments was ERT of Gaucher disease. During the 1990s, treatment by intravenous infusions of human glucocerebrosidase, extracted and purified from pooled human placentas and then chemically modified to enhance uptake by macrophages, was shown to dramatically alter the natural history of the disease in patients with severe type I disease *(31,32)*. The original enzyme product has since been replaced by recombinant human glucocerebrosidase produced on a large scale in genetically modified Chinese hamster ovary (CHO) cells *(33)*. Experience with several thousand patients worldwide, who were treated with the enzyme for up to 20 yr, has shown that ERT of Gaucher disease is safe and almost uniformly effective in the treatment of type I disease *(34)*.

The emergence of new recombinant techniques for the production of large amounts of virtually any lysosomal enzyme spawned a flurry of activity in this area in the past 8 yr. The development of ERT for Fabry disease was among the first to be tackled after Gaucher disease. Two companies, employing different recombinant technologies, produced two versions of recombinant human α-galactosidase A and subjected them to rigorous clinical trials, which included patients from across Canada studied in Toronto.

In 2001, Eng et al. *(35)* showed that treatment with agalsidase-beta (a form of recombinant α-galactosidase A produced in CHO cells), given intravenously at a dosage of 1.0 mg/kg of body weight every 2 wk for 20 wk produced a dramatic decrease in plasma Gb3 levels in men with Fabry disease. They also showed marked improvements in the amount of Gb3 accumulating in renal capillary endothelial cells. In the same year, Schiffmann et al. *(36)* showed that treatment with agalsidase-alfa (a form of the enzyme produced in human cells in culture), given intravenously at a dosage of 0.2 mg/kg every 2 wk for a similar period, was associated with a significant decrease in the neuropathic pain experienced by men with the disease. In the same study, they showed that the creatinine clearance of patients on the drug was stabilized, whereas patients in the placebo-treated group experienced a significant decrease over the same period.

Since the publication of the results of the large-scale, randomized, placebo-controlled studies, other reports have appeared describing the effects of ERT. In a series of papers reporting the results of a randomized, placebo-controlled study of 26 males with Fabry disease and 10 healthy control subjects, Schiffmann's group at the National Institutes of Health showed (via positron-emission tomography and transcranial Doppler studies) a paradoxical increase in regional cerebral blood flow in the patients with Fabry disease. The effect was reversed by treatment with agalsidase-alfa *(37–40)*. Transient ischemic attacks and stroke are common complications of Fabry disease, but the clinical significance of these studies is still unclear. The impact of ERT on the incidence of cerebrovascular events has not yet been determined with confidence.

Reporting on the results of a 6-mo open-label extension of the Eng study, Thurberg et al. *(41)* confirmed that treatment with agalsidase-beta was associated with complete clearing of Gb3 from capillary endothelial cells and partial clearing of mesangial and arteriolar smooth muscle cells in the kidney. They also reported some evidence of decreased Gb3 in glomerular

podocytes and distal tubular epithelial cells. De Schoenmakere et al. *(42)* reported a single case of stabilization of moderately impaired renal function in a male patient with Fabry disease on the same enzyme preparation. Summarizing the renal data from a large, longitudinal, observational study of patients on ERT, Dehout et al. *(43)* concluded that treatment with agalsidase-alfa "can significantly improve renal function in patients with Fabry disease, at least in those with a mild decrease in glomerular filtration rate and may be able to slow down the natural decline in renal function in patients with moderate reduction in glomerular filtration rate."

In separate open-label studies, Weidemann et al. *(44)* and Mignani et al. *(45)* showed improved left ventricular mass and myocardial function in a total of 18 males with Fabry disease after 12 to 18 mo of treatment with agalsidase-beta. Baehner et al. *(46)* reported a significant decrease in left ventricular mass and improvement in quality of life in 15 severely symptomatic female patients with Fabry disease on ERT with agalsidase-alfa. ERT with either agalsidase-alfa *(47)* or agalsidase-beta *(48)* was shown to produce a statistically significant improvement in peripheral nerve function. Similarly, ERT with agalsidase-alfa has been reported to produce improvement in hearing *(49,50)* and vestibular function *(51)* in patients with the disease, but only after at least 12 mo of treatment. Although the results of these studies showed statistically significant changes, the patients did not report clinically significant improvements. Furthermore, longer term studies are necessary to evaluate the long-term impact of ERT on hearing. Dehout et al. *(52)* reported relief of gastrointestinal symptoms by treatment of patients suffering from Fabry disease with agalsidase-alfa—perhaps one of the earliest and most consistently beneficial effects of ERT of the disease. In the first report of the long-term safety and efficacy of ERT, Wilcox et al. *(53)* summarized the changes in 58 patients who had been on treatment with agalsidase-beta for 30 to 36 mo. They showed that the treatment was safe and resulted in continuous decreases in plasma Gb3 levels, sustained clearance of glycolipid from capillary endothelial cells, and stabilization of renal function.

In Canada, ours was the first center to enroll patients in formal clinical trials of the treatment of Fabry disease by ERT. As part of a large, industry-sponsored, multicenter, randomized, double-blind, placebo-controlled trial, we studied nine males, ages 24 to 53 yr (35.6 ± 3.4 yr, mean ± standard error mean). The subjects were randomly assigned to ERT or placebo. After 24 wk, all subjects were treated with agalsidase-alfa and followed for another 55 wk in an open-label extension study. The drug was infused intravenously at a dosage of 0.2 mg/kg every 2 wk. The five subjects on placebo received intravenous infusions of drug-free vehicle. All infusions were administered over 40 min.

Baseline studies included measurements of serum creatinine concentrations and 24-h urinary protein excretion. These were repeated at wk 9, 17, 24, 37, 51, 65, and 79. Additionally, the Toronto center assessed the effect of treatment on heart size and function by echocardiography. Echocardiograms were done at baseline and repeated at after 6, 12, and 18 mo of ERT. The results of the study are still being analyzed.

Discussion

The results of formal studies of ERT in Fabry disease convincingly show that the treatment is safe. Infusion reactions are relatively common but generally mild, and after several dozens of patient-years experience with both agalsidase-alfa and agalsidase-beta, not a single death from the treatment has been reported. Both enzyme preparations have been shown to produce significant improvements in key surrogate markers of disease progression, such as Gb3 levels in plasma and glycolipid accumulation in vascular endothelium. However, the relationship between these surrogates and clinically significant outcomes, such as the progression of the renal and cardiac complications and the prevention of cerebrovascular manifestations of the disease, is still not entirely clear. Stabilization of renal function has been reported, and improvements in myocardial left ventricular mass and

function have been reported in patients on both enzymes. Nonetheless, several questions remain to be answered. For example, some of the results of clinical trials indicate that renal impairment resulting from Fabry disease is only partially reversible, and beyond a certain stage, progression to end-stage renal disease becomes inevitable. More experience with the treatment is needed to determine the point during the course of the disease at which ERT must be initiated to prevent progression to renal failure. Similarly, although the data indicate an effect of ERT on myocardial function, it is still not clear which patients are most likely to benefit and when treatment must be started to achieve optimum results. The impact of ERT on the cerebrovascular complications of Fabry disease is still unknown. The results of preliminary analysis of the unpublished observations from a large, placebo-controlled study of the effect of treatment with agalsidase-beta on the time-to-major, disease-associated, events in numerous male patients with advanced Fabry disease are promising. Studies are also in progress to establish the safety and efficacy of ERT in children with Fabry disease as well as in female carriers who are often severely symptomatic and develop most of the complications that occur in affected males, albeit generally at an older age.

The effect of different dosages of enzyme is still incompletely understood. In this regard, the recommended dosage of agalsidase-alfa (0.2 mg/kg every 2 wk) is five times lower than the manufacturer's recommended dosage of agalsidase-beta (1 mg/kg every 2 wk). Although the effects of the two products at different dosages are not dramatically different, no head-to-head study of their comparative clinical effectiveness has ever been reported, and the outcomes evaluated in various clinical trials have been sufficiently different to make direct comparisons impossible using existing data. Studies are in progress to assess the safety and efficacy of different dosage regimens for the treatment of Fabry disease in adults.

Fabry disease is rare, and the clinical course of the disease is unpredictable in individual patients and is highly variable between patients. Further study is required regarding the place of ERT in the management of the disease, including the identification of patients most likely to benefit from treatment, the optimum time to initiate therapy, the dosage of enzyme to use, and those aspects of the disease most likely to respond well to therapy. Large registries of patients with Fabry disease, including many who are currently receiving ERT, have been established in Europe and North America. Analysis of the data emerging from these registries will provide valuable insights regarding the natural history of the disease and will help determine answers to some of the many questions that early experience with the therapy has raised. For now, the treatment of Fabry disease by ERT should be undertaken by specialists experienced in the management of the disease to ensure that data relevant to the long-term evaluation of clinical outcomes of therapy are collected, rigorously analyzed, and reported.

Finally, the high cost of ERT, which is in the range of $200,000 to $300,000 per patient per year, has some health policy decisionmakers concerned. The high price tag will inevitably produce pressure on the manufacturers to support further observational studies to answer some of the questions raised above, to confirm the long-term effectiveness of treatment, and to develop treatment guidelines that optimize cost-effectiveness.

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