Enzyme replacement therapy for Fabry disease: proving the clinical benefit

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Introduction

Fabry disease is an X-linked lysosomal storage disorder that results from a deficiency of the enzyme α-galactosidase A (α-Gal A). The lack of α-Gal A leads to incomplete metabolism and progressive lysosomal accumulation of glycosphingolipids, particularly globotriaosylceramide (GL3). This process causes damage to endothelial, perithelial and smooth-muscle cells of the vascular system, glomerular and tubular cells of the kidney, myocardial cells and valvular fibrocytes, epithelial cells of the cornea and ganglion cells of the dorsal root and autonomic nervous system, as well as cortical and brain-stem structures [1]. Therefore, the disease presents as a multi-system disorder, clinical features being typical but highly variable in affected individuals. One of the earliest and most debilitating symptoms is the onset of acroparaesthesias in childhood. Other common manifestations are lenticular and corneal opacities, angiokeratomas, hypohidrosis, oedema and abdominal pain. During the third and fourth decade of life, the disease is characterized by a progressive course and severe morbidity due to cardiac, renal and cerebrovascular involvement [1,2].

One of the most severely affected organs in Fabry disease is the kidney. Renal involvement can be detected in early adulthood as mild to heavy proteinuria and microhaematuria. The majority of patients show progressive renal failure and eventually develop end-stage renal disease (ESRD) [3].

The leading cardiac manifestation in Fabry disease is concentric left ventricular hypertrophy (LVH) [4,5]. Some studies report constrictive cardiomyopathy [6] and congestive heart failure [7,8] as well as disturbances in the conduction system with reduced PR interval [9]. Late cardiac manifestations are hypertrophic cardiomyopathy [10], myocardial ischaemia, heart failure and ventricular arrhythmias associated with sudden cardiac death [11].

The average age of onset of cerebrovascular symptoms in hemizygous individuals is 33 years. It includes hemiparesis, vertigo/dizziness, diplopia, dysarthria, nausea/vomiting, headache and hemiataxia [12]. There is an elevated risk for transient ischaemic attacks, premature stroke and dementia [13].

Therapeutic options

Since Fabry disease cannot be cured at present, clinical management is symptomatic. Chronic pain therapy includes membrane stabilizers such as gabapentin, carbamazepine and phenytoin. ACE inhibitors and antihypertensive drugs may delay progressive loss of renal function. Because of endogenous enzyme production, kidney transplants stay free of glycosphingolipid deposits [14]. However, enzyme production by the graft is not sufficient to prevent progression of systemic disease [15]. Kidney donation from female relatives who are heterozygous carriers for Fabry disease should be avoided because females may also develop impaired renal function with increasing age. Appropriate therapy of cardiovascular disease may require anti-arrhythmic medication, artificial pacemakers, interventional therapy and coronary-artery bypass grafting. Heart transplantation in case of end-stage cardiomyopathy due to Fabry disease has been successfully performed [8]. Among future potentially curative therapies, gene therapy [16] is certainly the most promising.

Enzyme replacement therapy (ERT)

In 1986 the α-Gal A gene was cloned [17] and as a result of further advances in molecular genetic techniques recombinant α-Gal A (rhα-GAL A) is produced at present by genetically engineered cell lines (cultured...
human fibroblasts/agalsidase \( \alpha \); Chinese hamster ovary (CHO) cell line/agalsidase \( \beta \) in sufficient quantities.

Safety and efficacy of enzyme replacement therapy has been shown with the two enzyme formulations. The enzymes were tested in several clinical trials [18–21]. In one trial agalsidase \( \alpha \) was administered intravenously every 14 days in a dose of 0.2 mg/kg/bodyweight for 24 weeks to 26 hemizygous male patients [19]. A significant decrease in neuropathic pain (primary end-point) was observed in the treatment group. Renal function (inulin clearance) remained stable as compared to a deterioration in the placebo group. Renal histology showed a 21% increase in the fraction of normal glomeruli, whereas a 27% decrease occurred in the placebo group.

Another trial included 58 patients (56 male, 2 female), who received agalsidase \( \beta \) intravenously in a dose of 1 mg/kg/bodyweight or placebo every 14 days [21]. Primary end-point was the disappearance (‘0’ score) of microvascular endothelial GL3 deposits in renal biopsy specimens after 20 weeks of treatment. Twenty of 29 (69%) patients in the \( \alpha \)-Gal A group reached this end-point, compared to none in the placebo group. Thereafter all patients were enrolled in an open label extension treatment study [21]. After 6 months of treatment in the extension trial, a ‘0’ score level was achieved in 42 of 43 (98%) patients biopsied. GL3 deposits from endothelial cells, mesangial cells and interstitial cells cleared almost completely while podocytes were the most difficult cells to clear. In endomyocardial biopsies the percentage of patients achieving a ‘0’ score in the coronary capillary endothelium increased from 67% (week 20) to 82% at the end of the trial, demonstrating an enhanced effect with prolonged treatment. Baseline serum creatinine and GFR were normal (treatment 0.8 mg/dl and 83.0 ml/min; placebo 0.8 mg/dl and 96.6 ml/min, respectively) and remained substantially unchanged after week 20 and at the end of the open label trial. A significant improvement in the severity of pain and quality of life was observed in both the ERT and the placebo groups but there was no difference between groups.

Assessing the benefit: does ERT meet clinical expectations?

Short term (1-year) clinical studies have positively correlated ERT with improvement of clinical symptoms and microvascular endothelial cell clearance. Whether histological improvements also correlate with clinical outcome in more severe forms of Fabry organ manifestation, such as proteinuria and renal function impairment, left ventricular hypertrophy and heart insufficiency is still unknown. It appears that patients with advanced organ damage need longer treatment periods until a definite improvement in organ function, or at least stabilization, can be demonstrated. Therefore treatment should probably be started early, without waiting for organ manifestations such as proteinuria or LVH.

There may be a point in the process of organ damage beyond which ERT cannot reverse existing tissue damage or delay organ failure in the short term. Specifically, one of the future challenges will be to identify patients before progression to ESRD is inevitable. However, De Schoenmakere and colleagues in this issue of the Journal report effective ERT in a 36-year-old male with advanced kidney disease (creatinine 2.78 mg/dl). A 19 month treatment period with Fabrazyme\(^\text{\textregistered}\) resulted in stabilization of renal function and regression of left ventricular hypertrophy [22]. The most pertinent and frequent questions currently asked are when is the appropriate time to start therapy and how should children and heterozygous females be managed? In particular, females appear to be affected to a much greater extent than previously assumed [23].

Similar questions are asked about the heart, since screening studies among risk populations, such as patients suffering from unexplained myocardial hypertrophy, revealed a surprisingly high prevalence of unrecognized Fabry disease as the underlying cause [10,24].

Future objectives

To judge the benefit of a new therapy in a rare disorder like Fabry disease, it is important to collect sufficient and comparable baseline and long-term clinical data on every patient under treatment. Since genotype and plasma or leukocyte \( \alpha \)-Gal enzyme activities are not reliable predictors of treatment outcome, the assessment of ERT benefit will ultimately depend on clinical outcome, not on histological or structural changes. At present it is not known whether enzyme replacement is worthwhile in dialysis or transplant patients. The rationale for treating such patients is to prevent future cerebrovascular and cardiac events, for which they are at increased risk. Consequently, one of the main future challenges is to evaluate the therapeutic efficacy of ERT in the long term. Sufficient numbers of patients should be enrolled in evaluation programmes (e.g. registries) to assess the efficacy and safety of ERT in clinical practice. Ambulatory ERT should be initiated by specialized centres to obtain a baseline data set and to document the subsequent clinical course. In selected cases this may include tissue sampling as well. According to our personal experience and data from the phase III trial [21], patients with no obvious clinical signs of organ failure such as LVH, impaired renal function or proteinuria may have extensive depositions of GL3 in pre-treatment kidney biopsies.

Critical issues to be investigated are whether treatment can delay progression of disease and what is the pathophysiology of renal insufficiency in Fabry disease. Is it possible to reverse organ damage or should the primary goal simply be to stabilize and prevent further deterioration? Last, but not least, we must...
learn for how much time the start of therapy can be delayed without compromising treatment benefit, and whether there is a point of no return, beyond which treatment is no longer effective. Agalsidase α and β were approved a year ago in the European Union and undergo continued regulatory review in the United States. Both preparations have been shown to be safe and efficient in major clinical trials. The two enzyme preparations are administered at different doses (0.2 and 1.0 mg/kg, respectively). Understanding how the two enzymes compare, and determining the dose required to achieve the best clinical outcome, are important future objectives. This is particularly important when considering the cost of therapy which for one patient in Europe is estimated at €200 000 per year. Additional treatment options in the future may include gene therapy and substrate synthesis inhibition, perhaps in combination with ERT. Fabry disease is a rare disease qualifying for orphan disease status; therefore it is difficult to conduct large clinical trials. Given the small patient population and considerable disease heterogeneity, a particular challenge will be to demonstrate to physicians, patients and health insurers that early therapeutic intervention with ERT is the most effective way to treat Fabry disease.

References

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