Rapid Communication

Enzyme replacement therapy in Anderson–Fabry’s disease: beneficial clinical effect on vital organ function

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Abstract

Two recent randomized trials pointed out the beneficial effect of enzyme replacement therapy on biochemical parameters in patients with Anderson–Fabry’s disease. Clinical end-points, such as amelioration or stabilization of renal function deterioration, or improvement of left ventricular hypertrophy have not been evaluated in depth. We report the case of a patient whose moderately impaired renal function was stabilized with the start of enzyme treatment. In addition, left ventricular hypertrophy tended to regress. To our knowledge this is the first observation of clinical efficacy of the enzyme replacement therapy in Anderson–Fabry’s disease in patients with moderately impaired renal function.

Keywords: Anderson–Fabry’s disease; beneficial clinical effect; enzyme replacement therapy; vital organ function

Introduction

Anderson–Fabry’s disease is an X-linked disorder affecting all hemizygous males and to a variable extent also heterozygous females. The symptoms are caused by a deficiency in lysosomal α-galactosidase A, resulting in the defective clearance of glycosphingolipids. Consequently, these glycosphingolipids accumulate intracellularly, with a particular predilection for endothelial and vascular smooth muscle cells. However, various other cell types are implicated, e.g. renal podocytes and myocardial cells. The main cause of morbidity and mortality is cardiovascular [1] and renal involvement, leading to end-stage renal disease in the majority of patients during the fifth decade of life [2]. Recently, human α-galactosidase A became available in clinical practice. The administered enzyme is targeted to the lysosome, and thus degrades the intracellular glycosphingolipid stores. Whether this results in clinical stabilization—in particular of renal and cardiac function—remains to be proven.

A report by the International Collaborative Fabry Disease Study Group [3] demonstrated the efficacy of a 20 week treatment with recombinant human α-galactosidase (agalsidase β; Fabrazyme, Genzyme, Cambridge, MA, USA; dose of 1 mg per kilogram of body weight every other week) on renal capillary endothelial clearance of globotriaosylceramide in patients with Anderson–Fabry’s disease. The patients enrolled had normal to slightly impaired renal function [mean serum creatinine concentration 0.8 ± 0.2 mg/dl (70.7 ± 17.6 µmol/l)]. The evolution of creatinine clearance during treatment was not reported.

Another article addressing the same issue [4] in patients with normal or slightly impaired renal function also reported an improvement in renal glomerular pathology scores after a 6 month treatment period with a genetically engineered human α-galactosidase A (Transkaryotic Therapies, Inc., Cambridge, MA, USA; dose of 0.2 mg per kilogram of body weight every other week). Remarkably, creatinine clearance decreased by 16.1 ml/min/m² per 6 months in the placebo group vs. 2.1 ml/min/m² in the treated group. The results in the placebo group are somewhat surprising, since the annual loss of estimated creatinine clearance in untreated male patients with Anderson–Fabry’s disease is 12.2 ± 8.1 ml/min/m² per year [1].

Case report

Given the scarce literature data on the clinical evolution of kidney and cardiac function during enzyme replacement therapy, we report the case of a 36-year-old male with Anderson–Fabry’s disease who started enzyme replacement therapy with Fabrazyme®. We used the infusion protocol described by Eng et al. [3].

The serum creatinine concentration at the beginning of replacement therapy was 2.78 mg/dl (245 µmol/l),
corresponding to a calculated creatinine clearance of 38.9 ml/min. Prior to treatment, the loss of creatinine clearance was 6.4 ml/min/year. During the ensuing 19 months of treatment, the progression of renal failure was significantly slowed: the slope of clearance loss during enzyme replacement is presently −2.2 ml/min/year, contrasting significantly with the pre-treatment slope (Figure 1). During the entire follow-up period there was no major change in blood pressure and proteinuria (0.4–0.6 g/l), and the initial anti-hypertensive treatment with lisinopril (5 mg daily, instituted before 1994) was substituted by irbesartan (150 mg daily, as from December 2001) because of invalidating chronic cough without any significant blood pressure change. This demonstrates a beneficial effect of enzyme therapy on deterioration of renal function, even in the setting of moderate renal insufficiency at treatment start.

Furthermore, there was a marked left ventricular hypertrophy, which was gradually increasing before the treatment period with enzyme infusion up to a left ventricular mass index of 202 g/m² (Figure 2). In addition, septum and posterior wall thickness were increased to 15 and 12 mm, respectively. After treatment start, we performed an echocardiography at 6-monthly intervals to evaluate disease progression: the left ventricular mass index was steadily decreasing to reach 145 g/m² after 19 months of treatment. In
parallel, we observed a decrease in septal thickness to 13 mm. The posterior wall thickness remained stable.

**Discussion**

The comparison of the slopes of progression before and during enzyme replacement therapy is of great value for assessing the clinical effects. This technique is reminiscent of the mode of comparison used in the 1980s to demonstrate the beneficial effects of strict blood pressure control on the progression of diabetic nephropathy.

Based on the favourable histopathological and biochemical data reported in the above-mentioned trials [3,4], it is hoped that enzyme replacement therapy will clear vascular glycosphingolipid deposits and prevent renal and cardiovascular complications in Anderson–Fabry’s disease. We present evidence that this therapy is also able to slow the progression of established renal disease and that it can possibly reverse left ventricular hypertrophy. A more extensive follow-up period with larger numbers of patients is undoubtedly required to confirm this statement.

It remains to be seen whether there may be a point-of-no-return or not for the efficacy of the enzyme substitution therapy both in the heart and kidney, beyond which organ function deteriorates independently of intracellular glycosphingolipid clearance because of fibrotic and degenerative processes.

**References**


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