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Do we need more intensive enzyme replacement therapy for Anderson-Fabry disease?

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Running title: Enzyme replacement therapy for Fabry disease

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Anderson-Fabry disease (AFD) is a rare, X-linked, lysosomal storage disease caused by deficient activity of the lysosomal enzyme α-galactozidase A, with accumulation of globotriaosylceramide and related glycosphingolipids in different organs and tissues. The disease manifests primarily in affected males, with severe pain from the childhood, kidney failure, heart disease and strokes occurring during the 4^{th} and 5^{th} decade of life, or even earlier. Heterozygous females may also develop serious clinical manifestations (1).

In recent years, enzyme replacement therapy (ERT) has become standard treatment of patients with AFD. Two enzyme preparations are currently available for ERT: agalsidase alfa (Replagal, TKT Europe), and agalsidase beta (Fabrazyme, Genzyme) (2). Both preparations were approved on an expedited basis because of beneficial effect on target organs with reduction of lysosomal inclusions. It was shown that agalsidase beta after 24 weeks of treatment slows the decline of glomerular filtration in patients with AFD (3). Study performed with agalsidase alfa failed to demonstrate significant change in inulin clearance from baseline after 20 weeks of double-blind treatment or after 6 months of open-label treatment. However, authors showed that ERT cleared globotriaosylceramide deposits from the target organs (4). Both studies were underpowered and suffered from serious disadvantages. The main problem of both studies was limited number of patients. While standard medical treatment used for treatment of proteinuria or prevention of stroke and cardiac disease is likely to be beneficial in patients with AFD, more patients are needed for demonstration of ERT efficacy. Additional problem is production of neutralizing antibodies which decrease enzyme activity. The effect of anti-agalsidase antibodies on the likelihood of therapeutic success should be evaluated. However, the main problem remains the extremely expensive therapy with annual cost per patient exceeding € 150.000. Considering ERT as „moderately effective“ life-long therapy, we believe that more evidence is needed to demonstrate its cost-effectiveness.

We have recently described two patients who received the renal allograft from a female deceased donor who died from the heart attack and had empty medical anamnesis. Deterioration of graft function with persistent proteinuria of 2 g/l demanded graft biopsy. Pathohistological finding was suggestive of Anderson-Fabry disease. This graft was lost because of the bleeding after drainage of the lymphocele which demanded graftectomy. Kidney biopsy performed three months later (9

months after transplantation) in other recipient who received organ from the same donor demonstrated significant clearance of globotriaosylceramide deposits from the kidney (5). Protocol biopsy performed one year later (21 month after transplantation) showed almost complete clearance of globotriaosylceramide deposits from the graft. More importantly, proteinuria decreased from 1.66 g/l at 3 months after transplantation, to 0.98 g/l at 12 months, and 0.17 g/l at 20 months after transplantation. Glomerular filtration rate was stable at 75-85 ml/min as determined by the Cockroft-Gault formula. Enzyme activity measured in leukocytes at 20 months after transplantation was 98 (normal laboratory value 89 nmol/h/mg of protein). The patient was not treated with ACE inhibitor because of the rise in serum creatinine concentration.

Our experience demonstrates that proper enzyme activity may not only clear globotriaosylceramide deposits from the kidney but may decrease proteinuria and maintain glomerular filtration rate even without the additive effect of ACEi. This is very important while shows that higher than currently recommended doses are needed to achieve therapeutic targets (Fabrazyme 1.0 mg/kg, and Replagal 0.2 mg/kg every other week). It has recently become evident that more intensive treatment may improve outcome in patients with AFD (6,7). Our case demonstrates that structural and functional changes in target organs may be almost completely reversible in the setting of normal enzyme activity and raises the possibility that the same results may be achieved with increase dosage of ERT in patients with AFD. Enzyme replacement therapy in AFD nephropathy should probably been instituted earlier and in higher doses, together with the standard concomitant medications (ACE inhibitors or angiotensin receptors blockers). Higher doses of ERT could probably solve the problem of neutralizing antibodies as was observed in patients with haemophilia (8). Individualized dosing of ERT seems promising (6), but needs an appropriate surrogate marker for assessment of treatment efficacy.

Larger trials are urgently needed to find an optimal dosing regimen, and possibly, to identify more efficient enzyme formulation. Modest effect of expensive, but perhaps inadequate dose of ERT should probably be changed to the full dose treatment that will be cost-effective and associated with improved outcome.

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