Letter to the Editor

Successful long-term enzyme replacement therapy in a young adult with Fabry disease

To the Editor:

Fabry disease (FD) is an X-linked lysosomal storage disorder with a deficiency of α-galactosidase A (AGLA), leading to accumulation of globotriaosylceramide (Gb3) mainly in the lysosomes. The clinical manifestations of FD show inter-individual variations, and the time between the onset of symptoms and a correct diagnosis is around 13 years (1), including symptoms such as hypohidrosis, pain, gastrointestinal complications, and hearing loss. With progression, complications such as cardiomyopathy, stroke and renal failure are common. Before the introduction of enzyme replacement therapy (ERT) in 2001 only symptomatic treatment was available. Post-marketing experience over the last years has shown to be beneficial (2, 3). We report a 28-year-old male patient, who has been treated with ERT using agalsidase alfa over 12 years.

In 1998, the, then 27-year-old patient presented the first time at our center, suffering from pain crises since age 7–9 and angiokeratomas, noticed at age 15. The diagnosis was confirmed by showing reduced enzyme activity for AGLA in leucocytes (nonsense mutation Q257X). At time of diagnosis the examination revealed multiple angiokeratomas and arterial hypertension (200/120 mmHg) without left ventricular hypertrophy. Antihypertensive treatment was initiated with an angiotensin-II-receptor antagonist (ARB). Glomerular filtration rate (GFR) was reduced to 79 ml/min/1.73 m², but urine albumin was normal. The patient (BMI: 19.5 kg/m²) complained of frequent abdominal pain, nausea and diarrhea.

Daily aspirin for thromboembolic prophylaxis, ARB and carbamazepine were prescribed as chronic concomitant medication.

Despite well-controlled arterial hypertension, left ventricular mass increased from 47.6 to 50.7 by 3.1 g/m²/year and the GFR declined by 7 ml/min/1.73 m² per year to 71 ml/min/1.73 m² before the initiation of ERT.

Fig. 1. Long-term follow-up of glomerular filtration rate (GFR) (ml/min/1.73 m²) and urine albumin (mg/24 h) excretion in a patient followed over 13 years.
Due to observed progression, ERT was offered as part of a pre-clinical study program in 1999. The treatment was well tolerated and the patient showed excellent compliance.

After initiation of ERT, GFR increased within a year to 81 ml/min/1.73 m². During long-term treatment the GFR normalized completely, and urine albumin remained normal (Fig. 1). During the first 3 years of ERT, LV mass declined from 51 to 34 g/m².7, and stayed normal over a period of 12 years.

The patient described his self-defined health status as being significantly improved since starting ERT. Nevertheless, he continued to complain of pain attacks, gastrointestinal problems, tinnitus, mild attacks of chest pain and fatigue. Although the patient presented palpitations several times, 23 Holter ECGs performed during follow-up did not reveal any arrhythmias. Carbamazepine could be reduced to an on-demand pain medication.

**Discussion**

This patient case is a good example to show the importance and benefits of early initiation of ERT. In hemizygous male patients, ERT, starting soon after confirmed diagnosis, might be essential to improve the long-term prognosis of patients with FD. The primary focus of the treatment should be the prevention of renal, cardiac and vascular complications. The increased GFR and the improvement from CKD stage II to CKD stage I with long-term stabilization is the first report in a male patient under ERT. This improvement is even more prominent in the light of a natural decline in GFR in healthy individuals and in patients under symptomatic therapy.

Short- and mid-term effects of ERT with agalsidase alfa on the heart and the LV mass have been reported. Until now, no information about the long-term effect of ERT has been available. In untreated patients left ventricular mass increases, leading in the long-term to a worsening of the heart function (4) and to the development of arrhythmias, which again contribute to the occurrence of strokes.

A patient with the same nonsense mutation has been reported with multiple brain infarctions (5). The prevention of arrhythmias in combination with ERT and anti-platelet medication may be helpful in preventing cerebrovascular complications.

This report indicates that an early start of ERT in a male patient could have prevented renal, cardiac and cerebrovascular complications over 12 years.

**Acknowledgements**

The authors have received travel grants and honoraria for lectures from Genzyme Co, Shire HGT, Actelion and Biomarin.

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