Journal of Rare Cardiovascular Diseases 2018; 3 (6): 209–212
www.jrcd.eu

CASE REPORT
Rare diseases of the heart

Biventricular cardiomyopathy improvement by shifting therapy from agalsidase alfa to agalsidase beta in Anderson-Fabry Disease (RCD code: III-3B.2)

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Abstract

Treatment of Fabry disease has improved since the introduction of enzyme replacement therapy (ERT). Two preparations of the recombinant enzyme α-galactosidase A are available: agalsidase alfa and agalsidase beta. We aim to report on a disease improvement after switching therapy from agalsidase alfa to agalsidase beta in a patient with Fabry cardiomyopathy. We present a case of a 60-year-old male with chronic renal failure and hypothyroidism, diagnosed with Fabry disease in 2010. We investigated clinical changes in this patient during the 12-months follow-up. At the time of diagnosis, transthoracic echocardiogram (TTE) and cardiac magnetic resonance (CMR) showed widespread transmural inferolateral late enhancement (LE), poor ejection fraction and severe left ventricular hypertrophy. Despite of initiation of ERT with agalsidase alfa, clinical status of the patient did not improve. A shift to agalsidase beta was made, what resulted in marked betterment. Effectiveness of ERT on Fabry cardiomyopathy primarily depends on the stage of disease at baseline, since ERT may provide limited benefits in patients with evidence of fibrosis in CMR. Switch from agalsidase alfa to agalsidase beta may be needed in some patients, who do not improve on the first-line therapy. JRCD 2018; 3 (6): 209–212

Key words: rare disease, echocardiography, cardiac magnetic resonance imaging, Fabry disease, enzyme replacement therapy

Introduction

Fabry disease is an X-linked, inherited, lysosomal storage disorder caused by a deficiency in α-galactosidase A. This results in the accumulation of globotriaosylceramide (Gb3 or ceramide trihexoside) and other neutral glycolipids in many tissues and cell types throughout the body, ultimately leading to cellular abnormalities and triggering inflammation and fibrosis. The consequences of these biochemical changes can include cardiac and renal dysfunction [1,2].

Fabry disease is rare, with an incidence estimated to be between 1 in 40 000 and 1 in 117 000 worldwide [3]. Life expectancy is reduced by 20 years in untreated men and by 15 years in untreated women [3,4,5].

Mortality is usually related to heart failure, but recently, organ transplantation and dialysis have increased the life span of patients with Fabry disease [6,7].

Treatment of Fabry disease has improved since the introduction of enzyme replacement therapy (ERT) in 2001 [8]. Since then, two preparations of the recombinant enzyme α-galactosidase A are available: agalsidase alfa (Replagal; Shire Human Genetic Therapies, Lexington, MA) and agalsidase beta (Fabrazyme; Sanofi Genzyme, Cambridge, MA)

We aim to report on a disease improvement after switching therapy from agalsidase alfa to agalsidase beta in a patient with Fabry cardiomyopathy. We investigated the potential clinical changes by evaluating a patient from baseline for a duration of 12 months.

Please cite this article: Serra W, Pastorini G, Biventricular cardiomyopathy improvement by shifting therapy from agalsidase alfa to agalsidase beta in Anderson-Fabry Disease (RCD code: III-3B.2). J Rare Cardiovasc Dis. 2018; 3 (6): 209-212; doi: https://doi.org/10.20418/jrcd.vol3no6.315

Conflict of interest: none declared. Submitted: November 18, 2017. Accepted: March 6, 2018.

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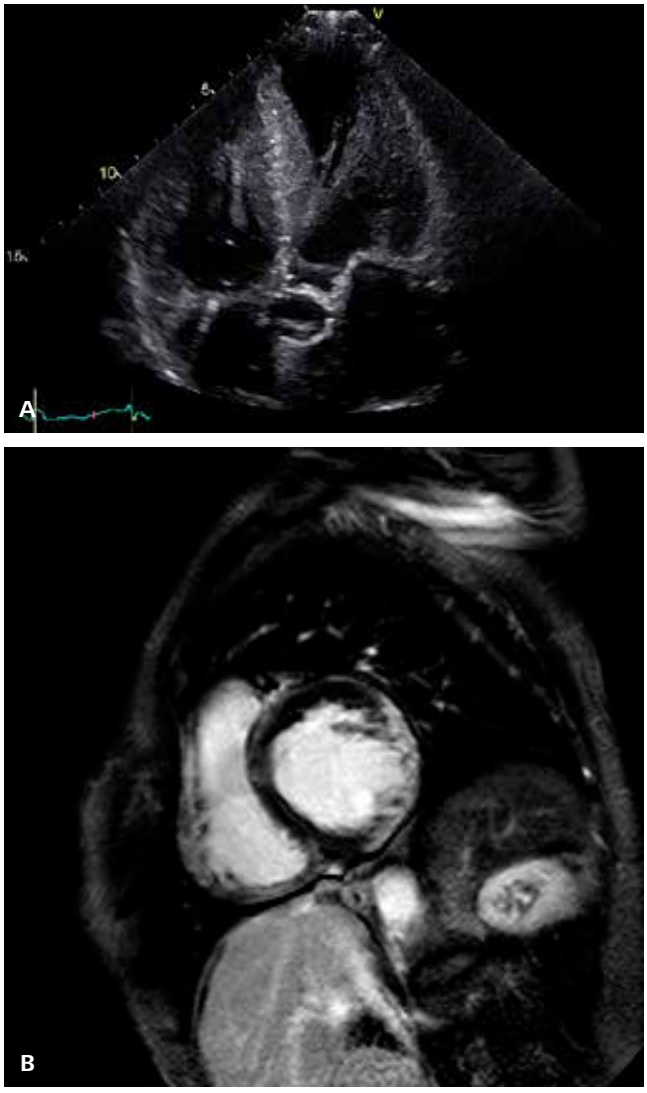

Figure 1. A. Transthoracic echocardiography showing severe left ventricular hypertrophy. **B.** Late gadolinium enhanced magnetic resonance imaging showing widespread septal enhancement

Case report

A 60-year-old male with chronic renal failure (Kidney Disease: Improving Global Outcomes, KDIGO stage 5) and hypothyroidism was diagnosed with Fabry Disease in 2010. Transthoracic echocardiogram (TTE) and cardiac magnetic resonance (CMR) showed widespread transmural inferolateral and lateral late enhancement (LE) with poor ejection fraction (EF) and severe left ventricular hypertrophy (LVH) (Figure 1A–B).

During the same year, the patient suffered from sustained ventricular tachycardia (VT) and had received an implantable cardioverter-defibrillator. In February 2011, following another episode of VT with the left bundle branch block morphology, the patient underwent epicardial catheter ablation (Figure 2).

He was seen in our cardiology outpatient clinic, where he continued to receive Replagal® (agalsidase alfa). However, in December 2015, he was admitted to our cardiac unit, presenting with severe congestion and worsening of dyspnoea. Electrocardiogram showed ventricular paced rhythm (65 bpm). A TTE showed dilated left ventricle (left ventricular end-diastolic volume, LVEDV of 224 ml), with increased interventricular septal thickness (17 mm), diffuse hypokinesia of the inferior wall (global EF of 25%), very low strain deformation, hypertrophy of the papillary muscle, moderate mitral regurgitation (MR) caused by bilateral leaflet tethering, diastolic restrictive pattern (grade III, E/e' of 17), severe tricuspid regurgitation with a hypokinetic (Tricuspid annular plane systolic excursion, TAPSE of 14.5 mm) dilated right ventricle, and severe pulmonary hypertension (pulmonary artery pressure, PAP of 64 mm Hg).

Laboratory findings: complete blood count (CBC) within normal limits, alteration of renal function (creatinine of 440 umol/L, blood urea nitrogen, BUN of 44 mmol/L, estimated glomerular filtration rate, eGFR of 16 ml/min), potassium of 4.6 mEq/L, severe hyponatremia of 120 mEq/L, brain natriuretic peptide (BNP) 567 pmol/L with metabolic acidosis.

Chest X-ray showed interstitial oedema and bilateral pleural effusion, which was then confirmed by chest computed tomography. High dose loop diuretic therapy with continuous intra venous infusion was administered along with bicarbonate supplementation and inotropic support.

Despite these efforts, the patient was still suffering from persistent oliguria and worsening of renal parameters (creatinine of 528 umol/L, BUN 102 mmol/L, eGFR 13 ml/min). Arterial blood gas analysis showed a tendency to hypercapnia. Therapeutic thoracentesis was performed and the patient was placed on non-invasive ventilation (BiPAP). In the following days, the patient showed progressive improvement in terms of symptoms and haemodynamic compensation. A shift from Replaglal® to Fabrazyme® (agalsidase beta) at a dose of 1 mg/kg every two weeks was made. Despite recovery of diuresis, another round of haemodialysis was performed in order to decrease urea levels (BUN was 107 mmol/L).

Due to improvement in the patient's clinical status and laboratory parameters, he was discharged and assigned to the outpatient clinic for continuation of care. Haemodynamic status was stable during subsequent follow-up visits, and the patient no longer complained of dyspnoea at rest or during low intensity activities. Echocardiographic parameters and cardiac biomarkers confirmed clinical improvement. TTE in May 2016 demonstrated marked improvement compared to previous results: LVEDV was 179 ml, EF was 32%, hypo-akinesia of inferior wall reduced, interventricular septal wall thickness was 16mm and posterior wall was 9 mm, mild MR, type II diastolic dysfunction (E/e' <10), TAPSE of 16 mm and PAP of 34 mm Hg (Figure 3).

Laboratory findings from June 2016 showed CBC within normal limits, stable renal parameters (creatinine of 486 umol/L, BUN of 15 mmol/L) and non-elevated liver function tests and decreased BNP (112 pmol/L).

Discussion

Cardiac involvement is frequent in Fabry disease, with LVH being the most common finding [9]. Angina pectoris, conduction abnormalities, valvular disease, aortic root dilatation and coronary artery disease (often leading to congestive heart failure and myocardial infarction) are other manifestations of the disease,

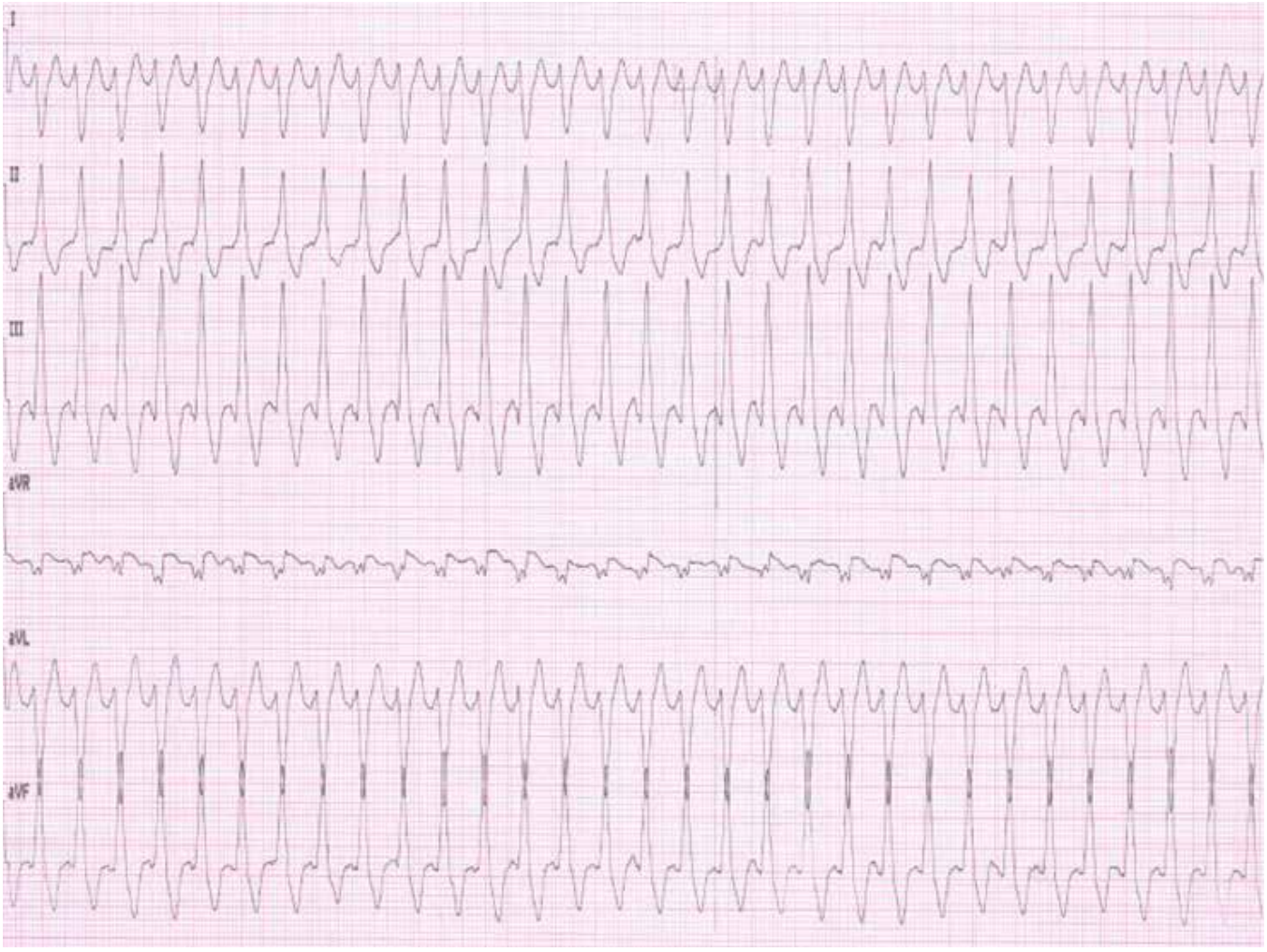

Figure 2. 12-lead ECG showing sustained ventricular tachycardia with the left bundle block morphology

caused by accumulation of glycosphingolipids in the vascular endothelium and cardiomyocytes [1,11]. Prompt diagnosis of Fabry disease is imperative, since specific ERT is now available. Furthermore, it has been suggested that early initiation of treatment, before myocardial fibrosis has developed, results in better long-term outcomes in terms of myocardial morphology and cardiac function [9]. ERT has been proven to be effective in clearing glycosphingolipid accumulation in affected tissues, improving clinical parameters, and slowing the progression of cardiac, renal, and cerebrovascular complications in Fabry disease [1,6–9].

Studies in small cohorts have also documented a reduction or stabilization in LV mass and improvement of LV function and exercise capacity [6,9,11]. Previous clinical studies have evaluated the long-term effects of therapy, but not the shift from agalsidase alfa to agalsidase beta replacement therapy in patients with end stage heart failure. Our patient was a 60-year-old male with end-stage cardiac and renal disease. Clinical improvement was evident after 2 weeks of treatment with agalsidase beta, demonstrated by the resolution of cardiac oedema and improvement in heart function This improvement could be due to the superior efficacy of agalsidase beta in patients with low enzyme levels along with extensive myocardial fibrosis and severe contractile dysfunction. In previous studies, the reduction in plasma lyso-GL-3 and GL-3 observed in patients after switching from agalsidase alfa to agalsidase beta indicates that the recommended dose of agalsidase beta (1.0 mg/kg every other week) has a greater pharmacodynamic effect on these markers. A study by Goker-Alpan et al. demonstrated that in male patients with Fabry disease, increasing the dose of ERT by switching from agalsidase alfa at 0.2 mg/kg to agalsidase beta at 1.0 mg/kg can further reduce plasma lyso-GL-3 and GL-3 concentrations beyond reductions previously achieved with agalsidase alfa [12]. Another study has revealed similar effects on clinical parameters (cardiac hypertrophy and glomerular filtration rate) and on plasma and urinary GL-3 reduction after 12 and 24 months of treatment with either agalsidase alfa or beta at a dose of 0.2 mg/kg biweekly [13]. Although the number of patients in these studies is small, it is unlikely that large differences in clinical potency exist between the two enzymes at equal dose. Treatment failure appears to be related to patient age and severity of the disease before the initiation of treatment, supporting the hypothesis that early initiation of ERT may be the only method of preventing long term complications. We report that agalsidase beta contains a significantly higher level of mannose-6-phosphate (M6P), present on the side chains of oligomannose, which could explain the residual efficacy of ga-

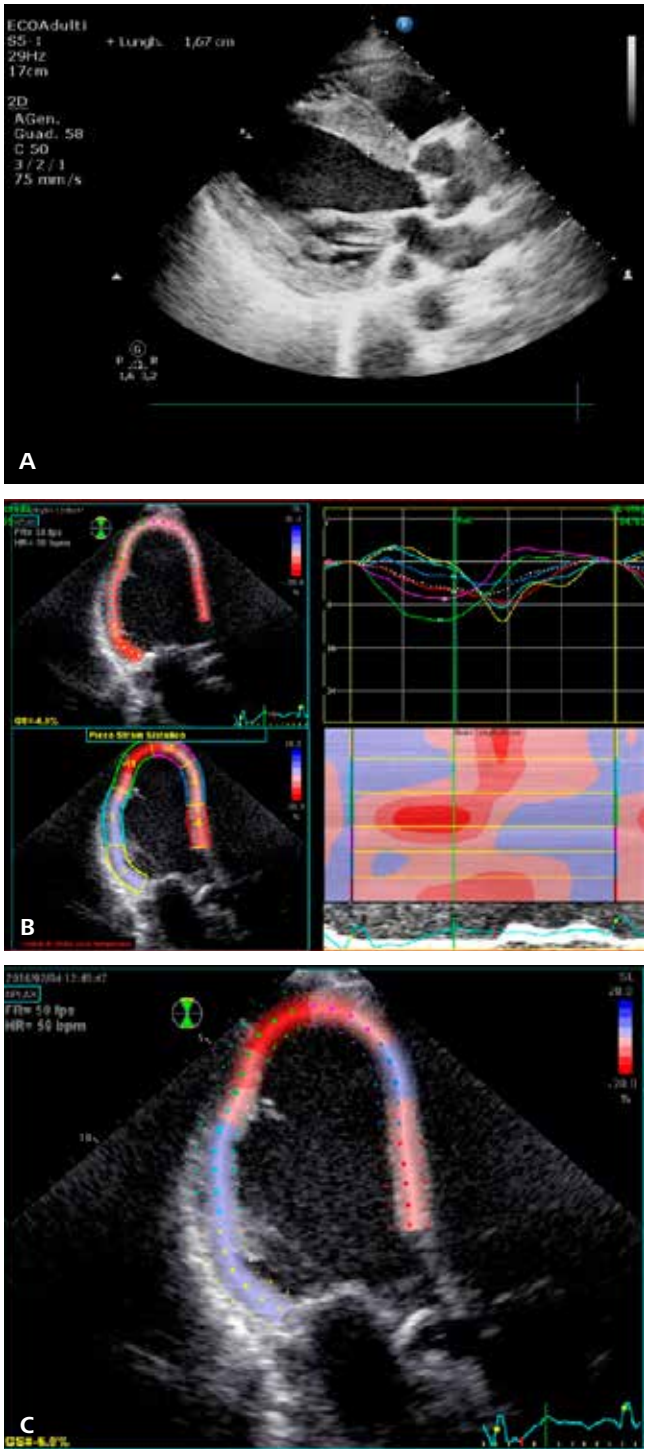

Figure 3. Transthoracic, spackle tracking echocardiography. **A.** Diffused thickening of the left ventricular walls. **B.** Dilatation of the left ventricle (left ventricular end-diastolic volume of 179 ml) and low ejection fraction of 32%. **C.** Hipo-akinesia of the inferior left ventricualr wall

lactosidase beta. This is very important because the level of M6P influences the bioactivity of the protein. M6P is indispensable for binding α-galactosidase A to target cells through its attachment to M6P receptors, with subsequent transport of the enzyme into the lysosome. Lee and co-workers have shown that significantly higher amounts of agalsidase beta bind to receptors compared to agalsidase alfa (at all concentrations studied), and that better binding capacity is related to improved absorption of agalsidase beta in fibroblasts [14].

In Fabry disease, ERT has been proved effective in removing glycosphingolipids from affected tissues, however, there is growing evidence that the beneficial effects may be variable in different tissues and patients. Moreover, the effectiveness of ERT on Fabry cardiomyopathy primarily depends on the stage of disease at baseline, since ERT may provide limited benefits in patients with evidence of fibrosis in CMR. Treatment is most effective when initiated before the onset of myocardial fibrosis in order to achieve stabilization of cardiac function. Therefore, a shift from agalsidase alfa to agalsidase beta replacement therapy should always be considered in patients with severe cardiac involvement to improve heart function and prognosis.

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