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Case Report

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Treatment with Agalsidase Alfa during Pregnancy in a Heterozygous Female with Fabry Disease

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Abstract

Introduction: Enzyme replacement therapy (ERT) is the cornerstone of the treatment of Fabry disease (FD), with either agalsidase alfa or beta. Both preparations have been shown to be safe and effective in patients with FD, but there are very few data on the safety of ERT during pregnancy.

Here we report a case of a 22-year-old woman with FD who received ERT with agalsidase alfa during the pregnancy.

Case report: The patient, a 22-year-old woman, was diagnosed with FD three years prior to pregnancy. Because of the presence of pain and proteinuria, she started treatment with agalsidase alfa (0.2 mg/kg every 2 weeks) with a substantial amelioration of the disease over time. When the patient informed us that she was pregnant, consensus was reached on continuation of ERT during pregnancy. The dose and frequency of intravenous ERT remained unchanged throughout pregnancy and agalsidase alfa infusions were well tolerated. At a gestational age of 39 weeks, the patient gave birth a healthy boy via a natural delivery.

Discussion: In our opinion, and supported by the findings of literature, pregnancy should not be a contraindication of ERT. ERT with agalsidase alfa during pregnancy seems to be well tolerated, without negative effects on the mother or child.

Keywords

Fabry disease; Enzyme replacement therapy; Agalsidase alfa; Pregnancy

Introduction

Fabry disease (FD) is an X-linked disorder caused by lysosomal enzyme α-galactosidase A (GLA) deficiency [1], with subsequent intracellular accumulation of undegraded glycosphingolipids, mainly globotriaosylceramide (Gb3), in multiple organs [2,3]. Renal failure, cardiomyopathy, and peripheral and central nervous system alterations are the main causes of morbidity and reduced life expectancy [4]. FD and familial Mediterranean fever (FMF) have typical clinical similarities, and both diseases may progress to end-stage renal diseases (ESRD). The similarities between the symptoms of FMF and FD might lead to a diagnostic dilemma in physicians at countries where FMF is observed frequently [5]. Currently, treatment options for FD patients include long-term enzyme replacement therapy (ERT) in addition to supportive management [6,7]. Two distinct recombinant protein replacement drugs are used for the treatment of Fabry patients: agalsidase alfa (Replagal, Shire) and agalsidase beta (Fabrazyme, Genzyme), produced using different methods and approved for administration at different doses [6]. Both preparations have been shown to be safe and effective in patients with FD [6,8] but there are very few data on the safety of ERT during pregnancy [9-13]. Here we report a case of a 22-year-old woman with FD who received ERT with agalsidase alfa during the pregnancy.

Case Report

The patient, a 22-year-old woman, had been healthy until since childhood, except for peripheral neuropathic pains, hypohidrosis, fatigue and gastrointestinal pain. Her family history included a father diagnosed with FD at the age of 47 for chronic kidney disease and left ventricular hypertrophy. Therefore, the diagnosis of FD in the patient was performed at the age of 19 years old for family screening. The diagnosis was confirmed by molecular analysis, that showed a single nucleotide point mutation in heterozygosis at nucleotide c.901 C>T in exon 6 (p.Arg301X) of GLA gene.

Because of the finding of mild proteinuria (500 mg/24 h), with a normal creatinine clearance rate (eGFR 117 mL/min/1.73 m^2), she underwent renal biopsy, that showed the presence of typical myeloid or zebra bodies at the ultra-structural analysis. Therefore, the patient started treatment with ACE-inhibitors and ERT with agalsidase alfa (0.2 mg/kg every 2 weeks). The patient performed periodic follow-up every six months, and showed a substantial amelioration of her symptoms and proteinuria (100 mg/24 h) 1 year after starting the treatment. When the patient informed us that she was pregnant, she immediately stopped treatment with ACE-inhibitors because of the high risk of fetal malformations [14] while, based on a risk/benefit assessment, consensus was reached on continuation of ERT during pregnancy. The patient was fully informed and agreed to continue the treatment, accepting any possible risk. The dose and frequency of intravenous ERT remained unchanged throughout pregnancy and agalsidase alfa infusions were well tolerated. The patient was followed closely at the Department of Nephrology and Obstetrics, and all evaluations were performed in accordance with criteria for standardized follow-up of pregnancy in Italy, revealing no abnormalities. Prenatal diagnosis was offered, but declined by the patient. Patient's clinical condition and proteinuria remained stable throughout the pregnancy. At a gestational age of 39 weeks, the patient gave birth a healthy boy via a natural delivery (birth weight 3250 g, birth length 48 cm, head circumference 33 cm and Apgar score 9/10/10). After the delivery, patient's clinical condition remained stable and she continued to perform periodic follow-up for FD.

Discussion

ERT is the cornerstone of the treatment of FD [7] and recombinant human α-galactosidase A is available in two forms: agalsidase alfa, given as an intravenous infusion at a dose of 0.2 mg/kg biweekly, and agalsidase beta, given as an intravenous infusion at a dose of 1

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mg/kg biweekly [4]. Studies comparing the two forms showed no significance [6] and current guidelines recommend that all affected females should be treated as soon as there are early signs of organ involvement (kidney, heart and/or central nervous system signs) consistent with FD and not fully explained by other pathology [15]. Despite the well-known efficacy of both preparations of ERT, there are very few data on the safety of ERT during pregnancy and evidence is limited only to case-reports [9-13] that showed no difference in the pregnancy outcomes with the two drugs.

In 2005, Wendt and colleagues described the first successful pregnancy outcome in a 34-year-old woman who continued ERT with agalsidase alfa during pregnancy without any problem; at a gestational age of 37 weeks, the patient gave birth to a healthy boy, not affected by FD, after an uneventful delivery [9]. Two more pregnant cases receiving agalsidase alfa were described by Kalkum and colleagues in 2009 [10]. No reports describing a patient receiving agalsidase beta was available since Germain [11] and Politei [12] who described 2 uneventful pregnancy outcomes with agalsidase beta: the first author reported the case of a patient whose conception had presumably occurred after the second infusion of Fabrazyme [11] and the second reported the case of a 37-year-old woman receiving agalsidase beta for the last 2 years before pregnancy [12]. In both cases, patients' clinical conditions remained stable throughout the pregnancies and they gave birth two healthy boys at a gestational age of 38 weeks. More recently, Senocak described 2 patients with FD who received agalsidase beta during their pregnancy [13] the first was a 26-year-old woman who started ERT with agalsidase beta when she was 8-week pregnant, with regression of her proteinuria, and gave birth to a healthy girl at week 40; the second was a 29-year-old woman who started her pregnancy at the 2nd month of treatment, giving birth to a healthy girl at 40 week.

Similarly, in Gaucher Disease, another lysosomal storage disorder, no effects of continuation of ERT during pregnancy had been reported on the mothers or the unborn children, and the ERT was well tolerated and maintained the therapeutic response [16].

Presently, is unclear whether ERT crosses the placental barrier or if the possible clearance of placental vessels has any benefit for the fetus. Our patient started ERT prior to conception and continuation of treatment during pregnancy was carefully evaluated. In fact, its continuation is theoretically contraindicated, given the lack of reproductive studies and of data on the drug labels of both ERT preparations. However, on the basis of the risk/benefit assessment, considering the well-known efficacy of ERT in the control of symptoms, organ involvement and quality of life, consensus was reached on continuation of therapy during pregnancy.

In our opinion, and supported by the findings of literature, pregnancy should not be a contraindication of ERT. In conclusion, ERT with agalsidase alfa during pregnancy seems to be well tolerated, with no negative effects on the mother or child.

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