Enzyme Replacement Therapy in Pregnant Women with Fabry Disease: A Case Series

Pehuén Fernández • Shunko Oscar Fernández •
Jacqueline Griselda Mariela Gonzalez •
Tabaré Fernández • Cinthia Claudia Fernández •
Segundo Pastor Fernández

Received: 11 May 2018 / Revised: 27 August 2018 / Accepted: 30 August 2018 / Published online: 08 November 2018
© Society for the Study of Inborn Errors of Metabolism (SSIEM) 2018

Abstract Fabry disease is a rare inherited lysosomal storage disorder caused by the deficiency of the enzyme alpha-galactosidase A. There is uncertainty regarding the safety of enzyme replacement therapy during pregnancy. We describe the course and outcome of seven pregnancies in six patients with Fabry disease who continued or reinitiated enzyme replacement therapy during pregnancy. No adverse events, in both mothers and children, were observed.

Introduction

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by the deficiency of the enzyme alpha-galactosidase A (α -Gal A). This condition results in the accumulation of glycosphingolipids, mainly globotriaosylceramide (gb3), in the lysosomes of cells throughout the body (Germain 2010) and impairs the function of major organs, including the heart, the kidneys, and the central and peripheral nervous systems, often leading to death at an early age (Tuttolomondo et al. 2013).

Communicated by: Carla E. Hollak, M.D.

We describe the course and outcome of seven pregnancies in six patients with Fabry disease who received enzyme replacement therapy during their pregnancies and lactation, without reporting any adverse events.

P. Fernández (✉) • S. O. Fernández • J. G. M. Gonzalez •
T. Fernández • C. C. Fernández • S. P. Fernández
CIDTEF, Centro de Investigación, Diagnóstico y Tratamiento de
Enfermedad de Fabry (Research, Diagnosis and Treatment Center for
Fabry Disease), San Fernando del Valle de Catamarca, Argentina
e-mail: pehuenfernandez@hotmail.com

Men with classical FD typically present more severe clinical manifestations than women and nonclassically affected male patients. Because of X-chromosome inactivation, women with FD may experience a variable range of symptoms (Echevarria et al. 2016). The efficacy of enzyme replacement therapy (ERT) has been demonstrated (Baehner et al. 2003) among these female patients.

There are few publications addressing the use of ERT in pregnant women, with only nine cases reported worldwide treated with agalsidase alfa (Wendt et al. 2005; Dehout et al. 2006; Kalkum et al. 2009; Hughes et al. 2012). The largest case series to date was presented by Hughes in 2012, who reported on the administration of ERT during five pregnancies (Hughes et al. 2012). No experimental studies specifically assessing drug safety during pregnancy have been conducted in humans.

Methods

In this series, we retrospectively reviewed the medical records of all FD patients receiving ERT during pregnancy and lactation at the *Centro de Investigación, Diagnóstico y Tratamiento de Enfermedad de Fabry* (CIDTEF, Research, Diagnosis and Treatment Center for Fabry Disease) in Catamarca, Argentina, between January 2012 and December 2017. Relevant clinical, laboratory, and imaging findings are provided for all patients. Data were collected from each pregnant woman at diagnosis and during the course of pregnancy and lactation. Baseline characteristics, including age (in years), mutation of the GLA gene, signs and symptoms at presentation, activity of the α -Gal A enzyme, imaging studies, indication, and dose of ERT, were registered. During pregnancy, age (in years), initiation or resumption of ERT, potential treatment-emergent adverse effects and/or complications, mode of administration, and

gestational age at the time of delivery (in weeks) were recorded. For newborns, gender, weight (in grams), length (in centimeters), and Apgar score at birth were recorded, including data on whether or not they were breastfed (exclusively or partially) and for how long (in months), their current age (in years), and subsequent health issues, if any.

To calculate the newborns' weight and height percentiles, international standards were used according to gestational age and sex (Villar et al. 2014).

Results

Six women with FD who received ERT during their pregnancies were included. Patient 3 had two previous pregnancies.

The patients' baseline characteristics are shown in Table 1. All FD diagnoses were made by family screening of the index case. All six patients share the same genetic mutation (exon 3 of the GLA gene coding region c.520T>G, missense-type mutation, C174G genotype, late-onset phenotype). The median age at diagnosis was 22 years old (range 16–35 years). During follow-up, all women showed signs or symptoms of FD. Patient 1 presented mainly with peripheral nervous system involvement (compromise of A-delta fibers in lower limbs) with severe neuropathic pain (acroparesthesias) and heat intolerance that affected her quality of life. The remaining six patients presented kidney involvement, with a decrease in glomerular filtration rate (patients 2, 4, 5, 6) and microalbuminuria (patient 3), confirmed by typical histological

findings of FD in renal biopsies (patients 3, 4, 6). Pain crises occurred in patients 1, 2, and 3. Most patients (1, 2, 4, 5) had reduced activity of the α -Gal A enzyme. All six women had started ERT prior to their pregnancies and received intravenous infusions of agalsidase alfa at a dose of 0.2 mg/kg every 14 days.

The patients' characteristics during pregnancy and the follow-up of their child are shown in Table 2. The median age at the time of pregnancy diagnosis was 26 years old (range 19–38 years). In patients 1, 2, and 3, ERT was discontinued during the first trimester. Given the recurrence of severe untreatable pain crises (pain visual analog scale 8–9/10), it was decided to resume therapy, thereby leading to a major improvement of symptoms. Pregnancy in patient number 4 was confirmed late (Week 10), so ERT was continued. Patients 5 and 6 had impaired renal function and experienced kidney disease progression. The decision to continue ERT was agreed with each patient and their relatives upon the assessment of the risk-benefit balance. All patients underwent close medical follow-up during pregnancy. No drug-related adverse effects were reported.

End of pregnancy occurred between Weeks 36 and 39 of gestational age by means of five vaginal deliveries and two cesarean sections (C-section). Patient number 3 had developed eclampsia at Week 36 during her first pregnancy. She had proteinuria, a hypertensive crisis, and seizures, which led to an emergency C-section, without further complications.

The median newborns' birthweight was 2,890 g (range: 2,370–3,800 g), and the median birth length was 50 cm (range: 46–51 cm). No infant had their weight or size

Table 1 Baseline characteristics of women with Fabry disease at the time of diagnosis

ID	Age (years)	Mutation	Clinical involvement. Enzymatic dosage	Drug dose
1	35	C174G	<ul style="list-style-type: none"> Symptoms: acroparesthesia, pain crisis, heat intolerance Peripheral nervous system: compromise of A-delta fibers in lower limbs Hearing: moderate mixed hearing loss Dosage of alpha-galactosidase A: 0.94 $\mu\text{mol/L/h}$ (reference value: 2.10–10.50 $\mu\text{mol/L/h}$) 	Agalsidase alfa 0.2 mg/kg/ 14 days
2	35	C174G	<ul style="list-style-type: none"> Symptoms: acroparesthesia, heat intolerance, pain crisis Renal: creatinine clearance, 71 mL/min $\times$ 1.73 m² Dosage of alpha-galactosidase A: 1.27 $\mu\text{mol/L/h}$ (reference value: 2.10–10.50 $\mu\text{mol/L/h}$) 	Agalsidase alfa 0.2 mg/kg/ 14 days
3	22	C174G	<ul style="list-style-type: none"> Symptoms: severe pain crisis Renal: microalbuminuria 240 mg. Biopsy: microvacuoles in visceral and mesangial cells. Ultrasound: parapelvic renal cyst 	Agalsidase alfa 0.2 mg/kg/ 14 days
4	16	C174G	<ul style="list-style-type: none"> Renal: creatinine clearance: 72 mL/min $\times$ 1.73 m². Biopsy: glomeruli with intracytoplasmic microvacuoles in some cells. Electron microscopy: podocytes with intracytoplasmic inclusions resembling zebra bodies and myelin figures 	Agalsidase alfa 0.2 mg/kg/14 days
5	28	C174G	<ul style="list-style-type: none"> Renal: creatinine clearance, 69 mL/min $\times$ 1.73 m² Dosage of alpha-galactosidase A: 1.55 $\mu\text{mol/L/h}$ (reference value: 2.10–10.50 $\mu\text{mol/L/h}$) 	Agalsidase alfa 0.2 mg/kg/14 days
6	18	C174G	<ul style="list-style-type: none"> Renal: creatinine clearance, 63 mL/min $\times$ 1.73 m². Biopsy: microvacuolated podocytes with foamy cytoplasm Dosage of alpha-galactosidase A: 1.17 $\mu\text{mol/L/h}$ (reference value: 2.10–10.50 $\mu\text{mol/L/h}$) 	Agalsidase alfa 0.2 mg/kg/14 days

Table 2 Patients with FD treated with ERT during pregnancy (mother and child)

Mother		Child											
ID	Age (years)	Drug	AE	PC	Delivery mode	Gestational age (weeks)	Gender	BW, g (perc ^a)	BL, cm (perc ^c)	Apgar score	BF (months)	Current age (years)	Follow-up
1	36	Agalsidase alfa	No	No	VD	37	F	3,800 (97)	46 (10–50)	9/10	P (5)	5	RUTI up to 2 yo No AM
2	38	Agalsidase alfa	No	No	VD	39	M	3,190 (10–50)	50 (50)	8/10	E (12)	3	Normal
3a	24	Agalsidase alfa	No	Eclampsia	CS	36	F	2,370 (10–50)	47 (50)	6/10	No	2	FD
3b	26	Agalsidase alfa	No	No	CS	37	M	2,890 (50)	51 (97)	8/10	E (12)	1	Normal
4	19	Agalsidase alfa	No	No	VD	39	M	3,085 (10–50)	51 (90)	8–9/10	E (12)	1	Normal
5	29	Agalsidase alfa	No	No	VD	39	F	2,730 (10–50)	51 (90)	8–9/10	P (12)	1	Normal
6	22	Agalsidase alfa	No	No	VD	38	F	2,530 (10)	49 (50–90)	8–9/10	P (10)	4	Asthma

AE adverse events, *PC* pregnancy complications, *VD* vaginal delivery, *CS* cesarean section, *F* female, *M* male, *BW* birth weight, *BL* birth length, *perc* percentile, *BF* breastfeeding, *E* exclusive, *P* partial, *RUTI* recurrent urinary tract infection, *yo* years old, *AM* anatomical malformations

^a Percentiles of BW and BL according to Villar J. et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project¹⁰

below the tenth percentile for their gestational age. The first child of patient number 3 (eclampsia and emergency C-section) had a first-minute Apgar score of less than 8 but recovered spontaneously without any resuscitation maneuvers. This was the only non-breastfed child. Three babies were exclusively breastfed for 6 months and continued breastfeeding during the first year. Babies 1, 5, and 6 were partially breastfed for 5, 12, and 10 months, respectively. One girl experienced five episodes of recurrent uncomplicated urinary tract infections in her first 2 years of age. Urine reflux and anatomical malformations were ruled out by renal and urinary tract ultrasound and a cystourethrography. She has not had any recurrent infections to date. Another child had controlled asthma and received treatment with the leukotriene receptor blocker montelukast and inhaled corticosteroids (fluticasone). FD was diagnosed only in newborn 3a by family screening and was ruled out in the remaining six babies by enzyme activity dosage in males and molecular methods in females. Currently, children's median age is 2 years old (range: 1–5 years old), and no health issues potentially associated with the use of ERT during pregnancy and breastfeeding have been reported.

Discussion

In this report, we describe six related patients with FD treated with agalsidase alfa during pregnancy and lactation. They share the same genetic mutation and have different clinical manifestations of FD. Although this mutation is phenotypically characterized by late disease onset, these patients presented early manifestations and therefore received ERT. Two patients (2 and 5) with decreased glomerular filtration rate refused to undergo kidney biopsy. Kidney damage was attributed to FD due to histologically confirmed early renal involvement in their female relatives harboring the same mutation (patients 3, 4, and 6). In patients 2 and 5, there were no clinical signs or symptoms suggestive of other kidney function-impairing conditions.

In all six cases, the decision of whether or not to continue with ERT during pregnancy was challenging. Beck et al. suggested that the medication could be safely used during pregnancy in light of missing evidence on any harmful effect for the mother or the newborn (Beck 2009). Of note, however, this statement was based on only two cases reported worldwide. In our experience, patients presented either disabling clinical symptoms related to the disease that interfered with daily activities or impairment and progression of their kidney disease. The risks and benefits were carefully weighed, and, in agreement with the patients and their families, a decision was made to continue or resume treatment. The medication was well tolerated in all cases, and no ERT-related complications were reported neither in mothers nor in newborns. Although one pregnant

woman developed eclampsia, she was at increased risk, with factors including nulliparity, chronic hypertension, and a family history of preeclampsia (Bartsch et al. 2016).

In conclusion, there is limited evidence in current literature on pregnant women with FD treated with agalsidase alfa. At the time of this writing, the total number of women with FD treated during their pregnancies worldwide was 9 (Wendt et al. 2005; Dehout et al. 2006; Kalkum et al. 2009; Hughes et al. 2012), with the largest series (5 patients) belonging to the Fabry Outcomes Survey (FOS) (Hughes et al. 2012). The outcomes of these pregnancies during ERT are promising.

We present the largest series available in the literature to date, raising the total number of pregnant women receiving treatment for FD with agalsidase alfa to 16. In our case series, agalsidase alfa was safe and well tolerated during pregnancy and lactation, with no adverse events reported in mothers and children. Nevertheless, we believe there is still poor evidence to support its universal use among all pregnant women with symptomatic FD.

Conflicts of Interest

The authors received no funding for this work/manuscript.

Compliance with Ethics Guidelines

- Details of the contributions of individual authors:
 - Pehuén Fernández and Shunko Oscar Fernández: planning (conception and design), conduct (analysis and interpretation of data), and reporting (draft and thorough review)
 - Tabaré Fernández, Jacqueline Griselda Mariela Gonzalez, Cinthia Claudia Fernández, and Segundo Pastor Fernández: planning (conception and design), conduct (analysis and interpretation of data), and reporting (thorough review)
- The name of the corresponding author and guarantor: Pehuén Fernández
- Conflict of interest:
 - Tabaré Fernández and Jacqueline Griselda Mariela Gonzalez declare no conflict of interest.
 - Pehuén Fernández and Cinthia Claudia Fernández have received travel reimbursement for symposia attendance from Shire.
 - Shunko Oscar Fernández and Segundo Pastor Fernández have received travel reimbursement for symposia attendance and speaker honoraria from Shire.
- This study did not receive funding.
- Informed consent

- All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study authorizing the use of their data for this publication.
- This project was approved by the Bioethics Committee of the Hospital Interzonal San Juan Bautista in Catamarca, Argentina.

References

- Baehner F, Kampmann C, Whybra C, Miebach E, Wiethoff CM, Beck M (2003) Enzyme replacement therapy in heterozygous females with Fabry disease: results of a phase IIIB study. *J Inher Metab Dis* 26(7):617–627
- Bartsch E, Medcalf KE, Park AL, Ray JG (2016) Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ* 353:i1753
- Beck M (2009) Agalsidase alfa for the treatment of Fabry disease: new data on clinical efficacy and safety. *Expert Opin Biol Ther* 9(2):255–261
- Dehout F, Roland D, Henry F, Langlois A, Van Maldergem L (2006) Successful pregnancy in a patient with Fabry disease receiving enzyme replacement therapy. *Acta Paediatr* 451(95):137–138
- Echevarria L, Benistan K, Toussaint A et al (2016) X-chromosome inactivation in female patients with Fabry disease. *Clin Genet* 89(1):44–54
- Germain DP (2010) Fabry disease. *Orphanet J Rare Dis* 5(1):30
- Hughes D, Deegan P, Romero B, Hollak C, Giugliani R (2012) Pregnancy events in females with Fabry disease in the Fabry Outcome Survey. *Mol Genet Metab* 105(2):S37
- Kalkum G, Macchiella D, Reinke J, Kölbl H, Beck M (2009) Enzyme replacement therapy with agalsidase alfa in pregnant women with Fabry disease. *Eur J Obstet Gynecol Reprod Biol* 144(1):92–93
- Tuttolomondo A, Pecoraro R, Simonetta I, Miceli S, Pinto A, Licata G (2013) Anderson-Fabry disease: a multiorgan disease. *Curr Pharm Des* 19(33):5974–5996
- Villar J, Ismail LC, Victora CG et al (2014) International standards for newborn, weight, and circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 384(9946):857–868
- Wendt S, Whybra C, Kampmann C, Teichmann E, Beck M (2005) Successful pregnancy outcome in a patient with Fabry disease receiving enzyme replacement therapy with agalsidase alfa. *J Inher Metab Dis* 28(5):787–788