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J Cyst Fibros. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

J Cyst Fibros. 2018 November ; 17(6): 779–782. doi:10.1016/j.jcf.2018.05.009.

Measured fetal and neonatal exposure to Lumacaftor and Ivacaftor during pregnancy and while breastfeeding

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Abstract

With the growing class of CFTR modulator therapy available to more patients and with increasing pregnancies in individuals with CF, there is a growing need to understand the effects of these agents during pregnancy. There are few reports of their continued use in the literature, although it is likely that this is not an uncommon occurrence. We report the uncomplicated and successful pregnancy of a woman treated with lumacaftor/ivacaftor, as well as the clinical course of the infant during the first 9 months of life. We also report drug levels in plasma from the mother, cord blood, breast milk, and infant to estimate fetal and infant drug exposure.

Introduction:

The advent of CFTR modulator therapy and other treatments has significantly increased the life expectancy for individuals with cystic fibrosis (CF) [1–4]. As a result, adults with CF are more likely to have families than they have in the past [2]. Although the overall pregnancy rate among women with CF age 18–44 is declining (mirroring trends in general population) [5, 6], the overall number of pregnancies is increasing due to the increasing number adults with CF [2]. However, little is known about CFTR modulator use in pregnant or breastfeeding mothers, as outlined in a recent review of CF-therapies in pregnant and breastfeeding women [7]. Presently, there is one report of an uncomplicated pregnancy during ivacaftor use [8], and one case of a woman who became pregnant after initiating ivacaftor who discontinued the drug after her positive pregnancy test [9]. As previously reported, pregnancy rates decreased during phase III trials of CFTR modulators among

Conflict of Interest Statement:
The authors have no financial relationships with organizations pertaining to this work to report.

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women with eligible genotype but increased after FDA approval, suggesting that CFTR modulator use in pregnancy may be underappreciated [6]. Here we report an uncomplicated pregnancy of a woman treated with lumacaftor/ivacaftor combination therapy and describe the clinical course of her infant who was breastfed while her mother continued on this therapy. Drug levels were measured in plasma from maternal blood during and after pregnancy, cord blood after delivery, and infant blood as well as breast milk to estimate fetal and infant exposure.

Methods:

Study oversight and sample collection.

This study was approved by institutional review board at the University of North Carolina at Chapel Hill, and informed consent was obtained prior to the collection of any samples. Maternal peripheral blood was collected pre-, peri-, and post-partum. A sample of cord blood was obtained at delivery. Breast foremilk samples were collected concurrently with all post-natal maternal blood samples on an ad-hoc basis. Blood samples were obtained from the infant whenever excess blood could be obtained from a clinically-indicated sample. Lumacaftor and ivacaftor concentrations in blood samples were measured by mass spectrometry as previously described [10]. Similar methods were employed for breast milk samples: firstly an organic extraction was performed using methyl *tert*-butyl ether followed by lyophilization and resuspension in methanol solution and analysis with LC-MS. For validation, maternal and infant plasma as well as breast milk samples were spiked with known concentration of drug then processed and analyzed as above, which yielded similar results among the sample types. None of the collections were controlled for maternal dosing times of lumacaftor/ivacaftor, and thus there was limited utility to comparison of values across time points, but mean, 25^{th}, and 75^{th} percentile values were calculated as descriptors of the range. After establishing normal distribution of maternal plasma levels for both lumacaftor and ivacaftor using the D'Agostino-Pearson omnibus test, t-scores were calculated from the cord blood samples to evaluate if these were significantly different than maternal plasma values.

Case Report and Results:

A twenty-three-year-old woman Gravida 1 Para 1 (genotype F508del/F508del, BMI 21.6, baseline FEV_1 90% of predicted) became pregnant while being treated with lumacaftor/ivacaftor combination therapy. She discontinued this treatment at 13 weeks gestation at the advice of her CF provider, but her respiratory function worsened, and she self-reinitiated treatment after two weeks. She then established care at a new CF center due to a family relocation. She was again counseled on the lack of evidence regarding the use of combination CFTR modulator treatment in pregnancy, and she made the informed decision to remain on therapy for the duration of her pregnancy. Her obstetric care was provided by the maternal-fetal medicine program at the same institution as her CF center. The patient made a similar informed decision to breastfeed her infant following a pre-natal consultation with the breastfeeding medicine program as well as her pediatrician who agreed to provide monitoring following delivery. At 38 weeks 6 days gestation, she delivered a healthy, 2850 g

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baby girl by spontaneous vaginal delivery after an uncomplicated labor. Formal ophthalmologic evaluation of the baby was normal. Liver function testing at 33 hours was significant only for a direct bilirubin of 1.10 mg/dL, and both mother and baby were discharged home after 36 hours.

Given the known risk of hepatic dysfunction with lumacaftor/ivacaftor, the infant's liver function was carefully monitored over time (Table 1). Based on the elevated aspartate aminotransferase and total bilirubin at day 29, the patient was advised to switch to formula for infant feeding, supplementing one feeding in four with breast milk to maintain supply. With normalization of these values at day 37, she increased her breastfeeding to 50%. The infant also had follow-up ophthalmologic evaluation at 37 days of age, which was normal. Her LFTs remained normal at 59 days, and she resumed full breast-feeding. At her 90-day appointment, the infant was well, and was meeting all of her developmental milestones, with near-normal LFTs. At 135 days, the infant was again noted to have LFT abnormalities, however, the patient's mother was being treated with levofloxacin and sulfamethoxazole/trimethoprim at that time. Again, formula supplementation was used for 50% of feeds while on antibiotics, after which formula supplementation ceased. However, around this time, solid food was introduced to the infant corresponding with a steady reduction in breastfeeding. At 154 days, the LFT abnormalities had resolved, and remained normal until the infant had almost completely been weaned from breastfeeding by 267 days.

Concentrations of lumacaftor and ivacaftor in maternal plasma, cord blood, breast milk, and infant plasma are shown over time in Figure 1. The mean lumacaftor concentration in maternal plasma was 8.07 μM (25^{th}: 5.15, 75^{th}: 12.00), while the average concentration of ivacaftor was 3.18 μM (25^{th}: 0.99, 75^{th}: 5.40). The concentration of lumacaftor in cord blood (18.09 μM) was significantly higher than the maternal plasma concentration over the study period ($p = 0.02$), while the concentration of ivacaftor in cord blood (0.81 μM) was not different than maternal plasma ($p = 0.48$). Both lumacaftor and ivacaftor could be detected in breast milk (average concentrations 0.06 and 0.09 μM). Average infant plasma concentrations (excepting day 1 when values were more reflective of placental transfer) were 0.20 and 0.01 μM respectively, with an average corresponding fraction of maternal plasma levels of 2.7% and 0.5% respectively. The final infant plasma level of ivacaftor was not detected, but infant breastmilk intake was lower at this time point than during previously assessed values.

Discussion:

We present here a case report of a woman with cystic fibrosis delivering a healthy, term infant while remaining on combination lumacaftor/ivacaftor therapy for the duration of her pregnancy. She continued on therapy and was able to breastfeed her child beyond six months, although with some reductions due to transient abnormalities in liver function tests.

The reported half-lives for lumacaftor and ivacaftor (when co-administered) are approximately 26 and 9 hours respectively, and both drugs are reported to be approximately 99% protein bound to plasma proteins[11]. Their apparent clearances are 2.38 and 25.1 L/hr respectively for patients with CF, though these pharmacokinetic parameters have not been

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tested in pregnant women. Lumacaftor metabolism occurs principally by oxidation and glucuronidation, although it is primarily excreted unchanged into feces, while ivacaftor is readily metabolized by CYP3A into active metabolites M1 and M6[11]. Our findings suggest that both lumacaftor and ivacaftor readily traverse the placenta, and it is highly likely that the infant experienced therapeutic levels of these drugs *in utero*. Indeed, lumacaftor concentration in the cord plasma sample was higher than in maternal plasma concentrations. It is possible that lumacaftor accumulates in the continually exposed placenta or fetus, particularly since lumacaftor is not readily metabolized. The consequences of such exposure are unknown, although neither drug had significant teratogenic effects in animal studies [11]. Both drugs appeared to pass into breast milk at low levels, but enough to maintain detectable levels in infant plasma. Our data suggest that exposure from breastfeeding is small, but of unclear consequence. There were some mild fluctuations observed in the infant's LFTs, but these may be attributed to other causes (normal early-life variation observed at day 29, and antibiotic exposure at day 135). The decision to curtail breastfeeding was made out of an abundance of caution.

This study is limited by including only one mother-infant dyad, and results cannot be extrapolated to the entire CF population. Furthermore, the drug measurement method did not include known active metabolites of ivacaftor and may have underestimated drug exposure. It is also possible that plasma drug concentrations do not adequately assess drug exposure, since both lumacaftor and ivacaftor can accumulate intracellularly [10]. Additionally, our methods for sample analysis in breast milk had limited validation, and it is possible that matrix effects may have distorted our measured concentration in this body fluid. However, the scope of this work is more qualitative, reporting estimates of drug exposure, rather than a fully quantitative analysis. The findings pertaining to ivacaftor reported here are more likely to be relevant to future CFTR modulator treatments, as recent and planned studies with Vertex compounds use tezacaftor *in lieu* of lumacaftor since the former yielded similar clinical benefits and fewer reported side effects and drug interactions compared to the latter in their respective clinical trials[4, 12, 13]. With individuals affected by CF living longer, and up to 85% having the potential to be treated with highly active modulators in the foreseeable future, modulator use in pregnancy is an important consideration, necessitating additional study to better guide patients and practitioners. A recent review of CF therapies in pregnancy recommended avoiding lumacaftor and ivacaftor in both pregnancy and breastfeeding due to lack of data[7]. This single report of successful delivery and breastfeeding does not provide sufficient data to support an alternative conclusion, and further highlights the vital role of including pregnancy information in registry data to help guide clinicians in the use of these medications during and after pregnancy.

Acknowledgements:

The authors would like to thank Tara Guhr Lee for her technical assistance in this work, as well as Dr. Carl Seashore for his advice. The authors would like to especially thank the patient and her daughter described in this case for their participation in this study during a major life event.

Funding Source:

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The corresponding author was supported by an NIH training grant (T32 HL007106) and a grant from the CF Foundation during the time this work was performed (TRIMBL17A0). Drug analysis was supported by NIH/NIEHS P30-ES10126, NIH/NHLBI P30-DK065988, and Cystic Fibrosis Foundation RDP R026-CR11

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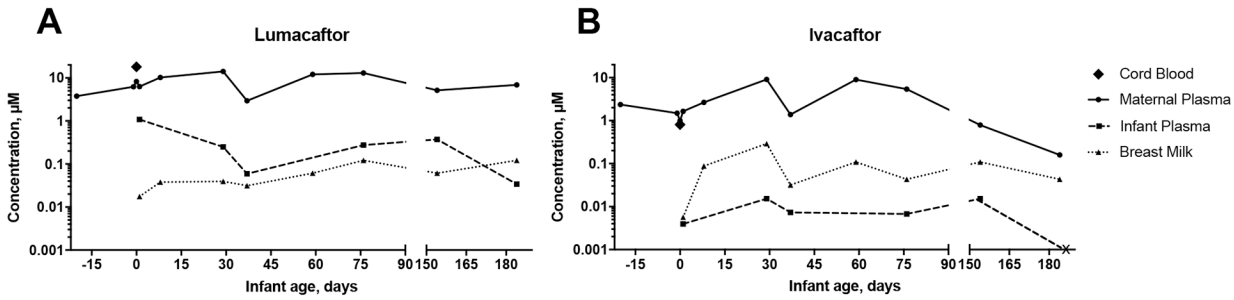

Figure 1 –.

Plasma and breast milk levels (log scale) of A: lumacaftor and B: ivacaftor over time. Sample collection was not timed in relation to maternal dosing of medication, which may account for some variability. Drug levels in plasma obtained from umbilical cord blood (diamonds) were comparable to levels obtained from plasma from peripheral maternal blood (circles plotted with solid lines). Infant levels of lumacaftor at day of life 1 were elevated, likely reflecting higher pre-natal values, although this effect was not seen with ivacaftor. After 135 days of life, breastmilk intake declined and was approximately 50% at day 184. Ivacaftor was not detected in the infant plasma at this time point.

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Table 1 –

Infant liver function test (LFTs) over time, with corresponding amount of dietary intake from breastmilk at the time the samples were obtained. Bold values marked with * indicate values above the lab's reference range. †Denotes concurrent maternal treatment with levofloxacin and sulfamethoxazole/trimethoprim.

Infant age (days)	**1**	**14**	**29**	**37**	**59**	**76**	**94**	**135†**	**154**	**184**	**267**
% of intake from breastmilk	**100%**	**100%**	**100%**	**25%**	**50%**	**100%**	**100%**	**100%**	**75%**	**50%**	**<25%**
Total Bilirubin (mg/dL)	2.0	1.0	***1.4****	0.7	0.7	0.9	0.8	0.9	0.4	0.5	<0.1
Direct Bilirubin (mg/dL)	1.10	0.50	***0.70****	0.30	0.40	0.40	0.40	***0.80****	<0.10	0.50	<0.10
Aspartate aminotransferase (AST, U/L)	76	28	***113****	33	42	48	51	***77****	53	48	47
Alanine transaminase (ALT, U/L)	24	16	17	22	35	46	48	46	54	39	31
Alkaline Phosphatase (U/L)	105	259	***375****	266	204	216	222	192	186	153	206