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Short Communication

Breast development in a 7 year old girl with CF treated with ivacaftor: An indication for personalized dosing?

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ABSTRACT

Substantial progress has been made in the treatment of Cystic fibrosis due to introduction of CFTR modulators. However, little is known about the long term side effects of treatment with these drugs. We here present a 7 year old girl with CF who presented with breast development as a rare dose dependent side effect of treatment with ivacaftor and we report data on the correlation between drug plasma concentration and clinical effect, bodyweight, and BSA in 16 patients.

Higher plasma concentrations did not correlate with clinical effect, as change in FEV1 and sweat chloride concentration. Patients with low bodyweight or BSA tended to have higher plasma concentrations. This might indicate that the current recommended dose of ivacaftor is at the top of the dose-response curve and that some patients can be treated with lower doses of ivacaftor with similar clinical effect.

1. Introduction

Treatment of patients with Cystic Fibrosis (CF) has been challenging for decades, but Cystic Fibrosis Transmembrane conductance Regulator (CFTR) modulators such as ivacaftor, lumacaftor, tezacaftor and lately elexacaftor impressively changed the perspectives [1,2]. Initially, treatment with CFTR modulators started in adults and children aged 12 years and older, but treatment is now becoming available to younger children from the age of 6 months [3–5].

Ivacaftor, a CFTR-potentiator, is prescribed in adults and children aged 6 years and older with a body weight above 25 kgs (kg) in a dose of 300 mg /day (mg/day). Little research is available on the optimal dose for younger children. Davies et al. [3] and Rosenfeld et al. [4] treated children aged 2–5 years and 1,2 years, respectively, with 100–150 mg/day. No data is available on the effect of lower doses of ivacaftor in these young children.

Extensive research into the short term effects and safety of treatment with ivacaftor shows positive results [3,4,6]. However, the safety on the long term remains unclear.

Here we report a rare side effect of treatment with ivacaftor in a pediatric patient, which appears to be related to the prescribed dose of ivacaftor. Additionally, we report data on the correlation between plasma concentrations of ivacaftor and body weight, body surface area (BSA) and clinical effect.

1.1. Case presentation

A female CF patient aged 7 & 5/12th years old, who harbored the 711+1G>*T* and S1251N mutation, was presented to the outpatient clinic with breast development. She was being treated with ivacaftor for 3 years. At presentation, she was being treated with ivacaftor 300 mg/day, i.e. 10 mg/kg/day. The girl was in a stable condition, was pancreas sufficient, and had a normal FEV1 (121% of the predicted value) and sweat chloride concentration (SCC) was 22 mmol/L (pre-treatment 91 mmol/L). At physical examination she had clearly visible breast development (Tanner stadium III-IV), without any other symptoms of pubertas praecox. Additional work-up showed a slightly elevated Luteinizing Hormone (LH) 2,1 U/I (reference range prepubertal girls < 1,0 U/I) and normal Follicle Stimulating Hormone (FSH) 2,9 U/I (reference range prepubertal

Abbreviations: CF, Cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; FEV1, Forced expiratory volume in 1 sec, SCC, Sweat chloride concentration; BSA, body surface area; HPLC, High pressure liquid chromatography.

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girls 3–10 U/l) and estradiol < 40 pmol/L (reference range prepubertal girls <60 pmol/L). Bone age assessment was performed, which was in accordance with her calendar age. An ultrasound of the breast showed symmetric development of glandular breast tissue without other abnormalities.

As breast disorders are a known side effect of ivacaftor, the dose was reduced and later treatment was discontinued. Cessation of treatment led to quick total regression of the breast development to Tanner stadium I. Several weeks after discontinuation, she presented with increased symptoms of dyspnea, productive cough, and reduced physical functioning. A decline of FEV1 (112% of predicted value) was observed, SCC was not reevaluated. Therefore, treatment with low-dose ivacaftor (25% of original dose, i.e. 75 mg/day, 2.5 mg/kg/day) was restarted. The symptoms improved significantly within several weeks, lung function restored to earlier values (FEV1 120% of predicted value) and SCC at this dose was 6 mmol/L. As clinical symptoms improved significantly and the SCC decreased to normal levels, there was no reason to increase the dose of ivacaftor, so a dose of 75 mg/day was continued. No breast development was observed until now after being treated with this dose for 17 months.

In this case the appearance of premature telarche seems to be related to the dose of ivacaftor. Based on these findings we studied the relation between the plasma concentration of ivacaftor and a patient's weight and clinical effect to treatment, in a group of patients that was treated with ivacaftor.

2. Patients and methods

As part of an investigator initiated clinical trial (Berkers et al. [7]), we studied the plasma levels of ivacaftor in samples from 16 patients, who were treated with ivacaftor 150 mg twice daily. After 8 weeks of treatment, change from baseline in lung function (FEV1% predicted) and SCC were measured as well as plasma ivacaftor levels. All blood samples were taken 4 h after dosing. Ivacaftor levels were measured with high-performance liquid chromatography (HPLC). Plasma levels were correlated to patient body weight and change in clinical parameters (FEV1 and SCC) using the Pearson correlation coefficient.

3. Results

An overview of patient characteristics are shown in Table 1. The mean age of the patients was 21 (6–44) years and mean body weight was 55.4 (19.8- 95,8) kilograms. Only three patients were pancreas sufficient. Nine patients were treated with drugs that inhibit cytochrome 450 (CYP)3A4. One patient was treated with a strong inhibitor and 8 patients with weak inhibitors) [8,9]. An full overview of co-medication prescribed during the trial can be found in Supplemental table 1 in the appendix.

After 8 weeks of treatment mean FEV1 improved 12,5%, mean SCC decreased 54,5 mmol/L. The mean post-dosing plasma level of ivacaftor was 5,03 umol/L

We found no significant correlation between the plasma concentrations of ivacaftor and changes in FEV1 (Fig 1A) or SCC (Fig 1B). Patients with low body weight or low body surface area tended to have higher plasma concentrations of ivacaftor (Fig. 1C and 1D respectively). Especially, patients with a body weight of approximately 20 kg demonstrated higher plasma concentrations compared to the other patients.

4. Discussion

We describe breast development in a young girl during treatment with ivacaftor, which disappeared after cessation of treatment and did not reappear after resuming treatment with 25% of

Table 1
baseline characteristics of patients.

	Mutation	Age (years)	Sex	Weight (kg)	Body surface area (m^2)	FEV1 (%)	SCC (µmol/L)	Pancreatic insufficiency	Use of CYP3A4 inhibitors
1	S1251N/ R117H	41	male	95.8	2.18	83	45	no	azithromycin, omeprazole
2	S1251N/ delta F508	44	female	71.4	1.85	73	41	yes	omeprazole
3	S1251N/ 1717-IGA	38	male	57.2	1.68	28	72	yes	azithromycin
4	S1251N/ delta F508	6	male	19.8	0.81	82	146	yes	none
5	S1251N/ delta F508	35	male	76.5	1.98	56	117	yes	azithromycin, esomeprazole
6	S1251N/ delta F508	32	female	59.5	1.68	65	110	yes	azithromycin
7	S1251N/ delta F508	9	male	30.5	1.11	73	64	yes	itraconazol, azithromycin
8	S1251N/ delta F508	13	female	42.1	1.34	63	70	yes	none
9	S1251N/ delta F508	17	female	67.8	1.81	73	63	yes	azithromycin
10	S1251N/ delta F508	15	female	49.1	1.48	66	67	no	none
11	S1251N/ delta F508	12	male	44.2	1.39	72	80	yes	none
12	S1251N/ A455E	16	male	68.2	1.83	95	86	no	none
13	S1251N/ delta F508	9	male	29.5	1.06	109	109	yes	none
14	S1251N/ delta F508	26	male	82.0	2.05	101	115	yes	azithromycin, omeprazole
15	S1251N/ delta F508	16	male	69.5	1.89	87	76	yes	azithromycin
16	S1251N/ R117H	6	male	23.0	0.9	97	21	yes	none
	Mean	21		55.4	1.56	76	80		

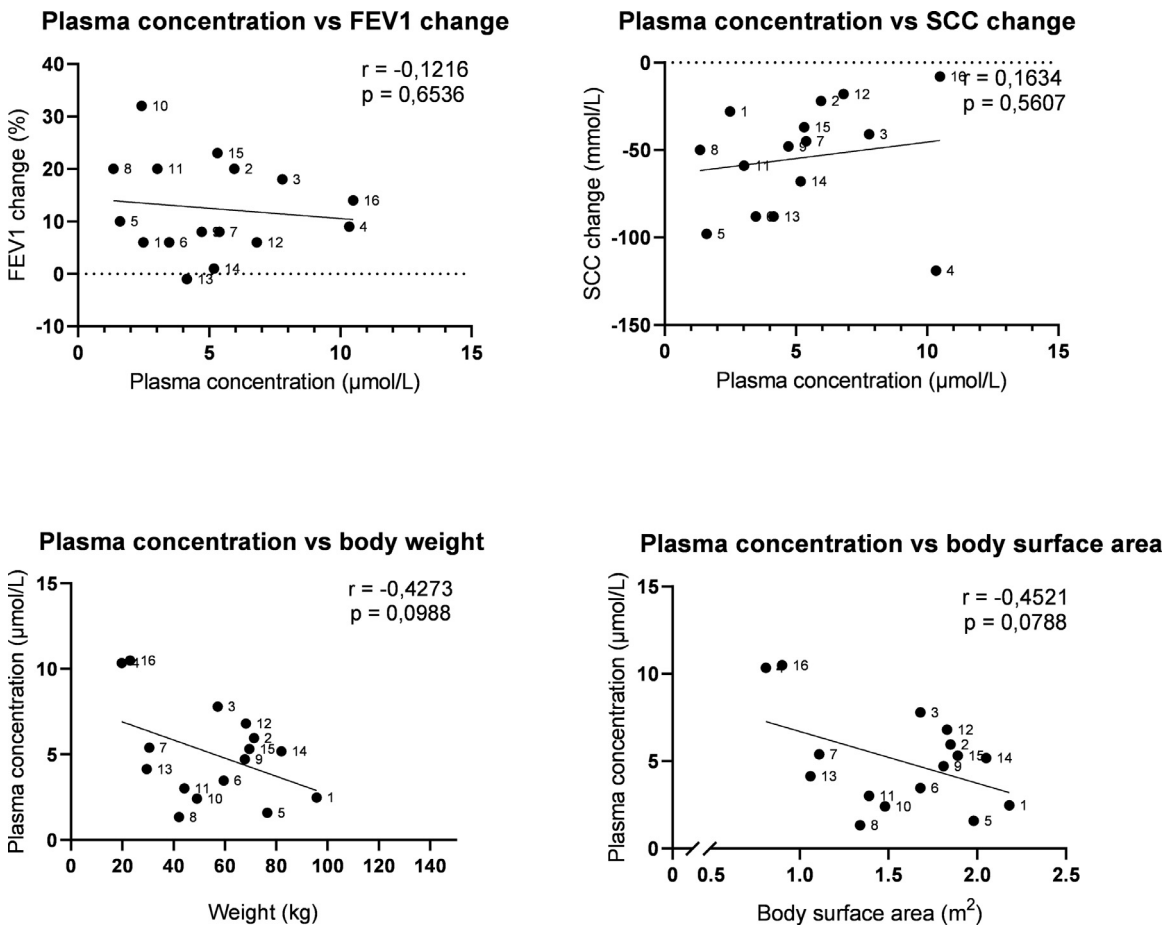

Fig. 1. Correlation between plasma concentration and change in FEV1 and SCC, body weight and BSA.

the recommended dose. Her clinical response was comparable to treatment with the full dose.

This raises the question whether the currently advised dosage of ivacaftor may be too high and can thereby lead to side effects, such as premature breast development.

Accurso et al. [6] reported that the incidence of adverse events was lowest in patients treated with 50 mg/day. The incidence of adverse events was similar in patients treated with 150, 300 or 500 mg/day. Frequently reported adverse events included cough, pulmonary exacerbations, erythema, diarrhea, abdominal pain and vomiting. However, these results should be interpreted with caution considering the small sample size within these groups and most of the adverse events are inherent to the disease cystic fibrosis. Breast development in children under 12 years old has not yet been reported as a side effect of ivacaftor. However, other breast disorders such as breast mass, breast swelling and gynecomastia have been described in both male and female patients aged 12 years and older [10,11].

In this case the appearance of premature breast development seems to be related to the dose of ivacaftor as sex hormone levels were normal and total regression was observed after cessation of ivacaftor. Nevertheless, hormone levels were not measured with ultra-sensitive assays, which demonstrate a more reliable depiction of hormone levels in children.

The mechanism by which drugs can cause gynecomastia is not always clear. However, various pathophysiologic mechanisms have been described. Some are directly related to increased serum estradiol levels or activation of estrogen or progesterone receptors in breast tissue, for example exogenous estradiol therapy. Other are related to blockage of dopamine D2 receptors, which may lead to hyperprolactinemia and can subsequently cause secondary hypogonadism by inhibiting LH and FSH. Other mechanisms include inhibition of CYP3A4, which is catalyzer of estradiol to 2-hydroxyestradiol [12,13].

The exact mechanism by which ivacaftor can cause breast development is unknown. However, ivacaftor is a mild inhibitor of CYP3A4. Therefore, it is plausible that ivacaftor can increase the serum concentration of estradiol, especially when used concomitantly with other CYP 3A4 inhibitors [10].

In the presented clinical study all patients were treated with the same, recommended dose of ivacaftor [10]. As Tmax of ivacaftor is 3–6 h, blood samples were taken 4 h after ingestion. In 5 patients additional blood samples were taken 3 and 5 h after ingestion which showed similar plasma concentrations as observed in the samples taken 4 h after ingestion. No dose-response relationship was found, which might suggest that the current recommended dose of ivacaftor is at the top of the dose-response curve.

Absorption of ivacaftor is enhanced when taken with fatty foods, which suggests that the absorption rate might be higher in pancreas sufficient patients. Most dose finding studies for ivacaftor are performed with pancreas insufficient patients and it is likely that plasma concentrations are higher when pancreas sufficient patients are treated with the same recommended dose. Moreover, studies have reported preservation or even restoration of pancreas function after treatment with ivacaftor [14,15]. This might implicate that some patients, especially pancreas sufficient patients, can also be treated with a lower dose with the same effect. More-

over, concomitant use with other CYP 3A4 inhibitors could lead to higher plasma concentrations.

As described by Guimbellot et al. [16] plasma concentration is a reliable indicator of the cellular concentration of ivacaftor. They describe a positive correlation between plasma concentrations and the in vivo cellular concentrations of ivacaftor. The cellular concentrations were considerably higher than the plasma concentrations, which suggests cellular accumulation of ivacaftor.

5. Conclusion

Findings from our case and patient cohort suggest that the currently advised dosages of ivacaftor might be at the top of the dose-response curve and in some patients can even be too high. Besides body weight, pancreas sufficiency and use of co-medication could possibly play a role in the plasma concentration of ivacaftor and occurrence of side effects. In patients with side effects of ivacaftor, a dose decrease should be considered while monitoring the clinical parameters. In patients without side effects studies with lower dosages are advocated to evaluate the added value of implementing personalized dosing regimens and to improve cost-efficacy of treatment.

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Declaration of Competing Interest

Dr. Jeyaratnam, Dr. van der Meer, Dr. Berkers and Dr. Heijerman have nothing to disclose.

Dr. Beekman reports grants from proteostasis, personal fees from proteostasis, outside the submitted work; In addition, Dr. Beekman is inventor on a patent related to Intestinal Organoid swelling and received royalties paid from Hubrecht Organoid Technology. Dr. van der Ent reports grants from GSK, grants from Nutricia, grants from TEVA, grants from Gilead, grants from Vertex, grants from ProQR, grants from Proteostasis, grants from Galapagos NV, grants from Eloxx, outside the submitted work; In addition, Dr. van der Ent has a patent 10,006,904 with royalties paid.

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Appendix. Supplementary materials

Table name: Supplemental table S1: co-medication during treatment with ivacaftor.

Medication	N
beta-mimetics	6
inhaled steroids	8
nasal steroids	11
pulmozyme (dornase alfa)	11
inhaled antibiotics (tobramycine or colistin)	12
oral antibiotics	16
pancreatic enzymes	13
insulin	2
ursochol	1
vitamins, minerals	16

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