

CASE REPORT

REAL-world clinical effectiveness of ivacaftor therapy in the first 24 months in two infants with cystic fibrosis and different gating mutations—A case report

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Abstract

This study summarizes efficacy of ivacaftor treatment in 2 infants in a real-world setting. A distinct decline of sweat chloride and lung clearance index plus increase in fecal elastase was seen. The results underline the early and sustainable effect and give cause for discussing whether a reduction in standard cystic fibrosis therapy is possible.

KEYWORDS

cystic fibrosis, highly efficient CFTR modulator therapy, pancreas insufficiency, sweat chloride

1 | INTRODUCTION

The cystic fibrosis transmembrane conductance regulator (CFTR) potentiator ivacaftor (IVA) has been a significant innovation in the treatment of cystic fibrosis (CF) with gating mutations.^{1–4} In this study, we summarize effectiveness and safety of this highly effective modulator in the first 24 months in a real-world setting in two male infants with two different gating mutations. Modulator therapy was started off-label in both patients at the age of 11 and 2 months. At this time in Austria, IVA was approved for patients with CF, from 12 months of age, carrying at least one gating CFTR mutation.

2 | CASE HISTORY

Diagnosis of CF in each case was confirmed within the framework of the Austrian Newborn Screening Program by repeated pathological sweat chloride in the second

month of life. In both cases, fecal elastase (FE) was depressed, pancreatic insufficiency was diagnosed, and enzyme substitution therapy was started. FE values above 200 $\mu\text{g/g}$ indicate normal exocrine pancreatic function. Due to alternating FE (<16–133 $\mu\text{g/g}$) and increasing impaired growth status, therapy with IVA $\times 2$ 50 mg was started at the age of 11 months in patient 1. In patient 2, therapy with IVA $\times 2$ 50 mg was started at the age of 2 months. Both parents gave their consent to start therapy off-label.

To prove safety and efficacy of IVA therapy, changes in following measurements and parameters from baseline were collected at days 0 and 14, weeks 4 and 16, and months 10, 17, and 24: sweat chloride, lung clearance index ($\text{LCI}_{2.5\%}$), anthropometry, laboratory examination, and analysis of FE as assessment of endocrine pancreatic function. Multiple breath washout (MBW)–Exhalyzer[®] was performed on sleeping child, using sulfur hexafluoride SF_6 under 1 year of age and oxygen from 1 year and older.

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3 | OUTCOME

In patient 1, sweat chloride gained normal values after two weeks of therapy from 88 to 8 mmol/l and remains normal to the present day. MBW-Exhalyzer[®] showed an improvement (9.86 vs. 5.8) of LCI_{2.5%} by 41% until week 16 with a slight increase until month 24 (6.07), however, still within normal values. After 4 weeks of therapy, patient 1 showed FE >200 µg/g indicating exocrine pancreatic sufficiency; therefore, pancreatic substitution therapy was successfully terminated. Over the course of time, vitamin values increased and no further substitution except for vitamin D was necessary.

Patient 1 showed insufficient growth progress before start and during therapy with an improvement of nutritional status toward the end of the observational period (z-score for weight −1.2 vs. −0.5 at month 24).⁵

In patient 2, sweat chloride declined by 65.6% until day 14 (90 vs. 31 mmol/l). Values remained in the lower borderline range until month 10. Subsequent sweat chloride concentration showed normal values to the present day. LCI results from day 14 showed values within normal ranges and remained stable to week 24. In patient 2, FE started to increase from week 16 above 200 µg/g with stable values over the course of time. Pancreatic substitution therapy could also be successfully terminated at 7 months and vitamin substitution therapy 3 months later. Reference data for growth are available from 3 months upwards. However, z-scores for weight and length show negative values throughout the period.⁵

In both patients, no side effects were observed in the laboratory analysis.

Changes in sweat chloride, LCI_{2.5%}, and FE are shown in Figure 1, and changes in anthropometry are listed in Table 1.

4 | DISCUSSIONS AND CONCLUSIONS

Results in these cases underline safety and efficacy of treatment with IVA in infants <12 months of age. Therapy

with IVA 50 mg every 12 h was generally safe and well tolerated in both subjects. Reports of high plasma concentration with an area under the curve above the 95th percentile, as seen in one infant 3 months of age who received IVA 25 mg twice daily, are recently published.⁴ However, information about plasma drug concentrations and pharmacokinetic data of our cohort is not available yet. Compared to Davies et al., who administered IVA doses according to age and weight (4 to <6 months and 5 to <7 kg 25 mg IVA every 12 h) we started and continued therapy with IVA 50 mg in patient 2 with 2 months of age and initially 4.3 kg without any clinical or laboratory abnormalities to the present day.⁴

Clinical findings are similar to study results of children who were 4 to <24 months of age.^{3,4} Remarkable improvement of CFTR function, seen in sweat chloride, a well-defined biomarker for CFTR activity, was observed. Mean absolute changes in sweat chloride by 69.5 mmol/l from baseline until month 24 are comparable to 73.5 mmol/l in 12 to <24 months and 55.7 mmol/l in 4 to <12 months (until week 24). Sweat chloride concentration at week 24 in our cohort with 15 and 24 mmol/l is lower compared to mean concentration of 41.3 mmol/l in 4 to <12 months at week 24.⁴

Although LCI was measured in only one child in 4 to <12 months in the ARRIVAL study since LCI measurements were optional, MBW measurements were routinely performed in both of our patients with normalization of values during IVA therapy.³

As reported in previous studies in preschool children, improvements in concentrations of FE were seen.^{1,2} In the ARRIVAL study, six out of nine children with FE concentrations less than 200 µg/g at baseline achieved values greater than 200 µg/g at week 24.³ In 4 to <12 months, 7 out of 11 children had regained pancreatic sufficiency. Both of our patients reached values above 200 µg/g and, therefore, were able to successfully terminate pancreatic substitution.

Although previous studies showed normal growth velocity maintained throughout the 24-week study period, z-scores for weight and length in our patients showed negative values at baseline with delayed response in patient 1

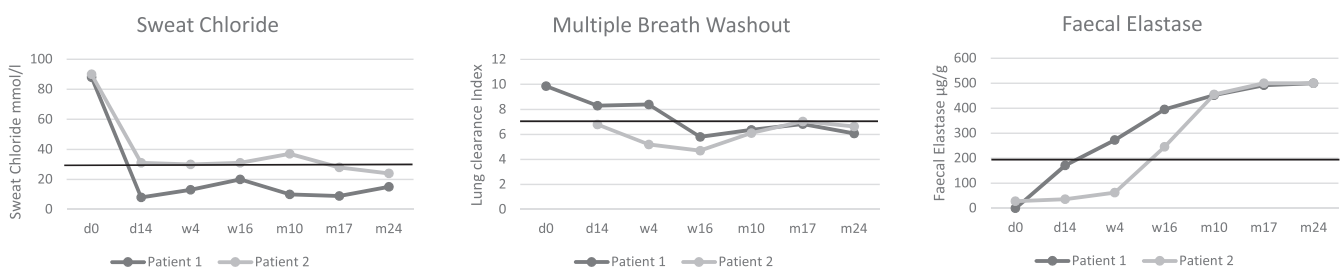


FIGURE 1 Changes in sweat chloride, LCI and FE during the 2 years observational period

TABLE 1 Changes in z-scores of weight and length (no reference data for infants <3 months of age)

	Patient 1						Patient 2							
	D 0	D 14	W 4	W 16	M 10	M 17	M 24	D 0	D 14	W 4	W 16	M 10	M 17	M 24
Weight z-scores	-1.28	-0.90	-1.05	-1.24	-1.09	-0.65	-0.51				-1.33	-1.66	-1.51	-2.04
Length z-scores	-0.99	-1.45	-0.84	-1.28	-1.08	-1.39	-0.47				-0.97	-0.39	-0.31	-0.49

and marginal difference in patient 2, respectively. Causes for reduced effect of IVA on growth in patient 2 are not clear, presumably caused by a lack of tapping full potential of dietary supplements or low-sodium status, since fractional Na⁺ excretion in the urine showed alternating but mostly low values underneath 20 mmol/l during the observational period compared to patient 1.⁶

There was no chronic colonization with *S. aureus* or *Pseudomonas aeruginosa* during the observational period in both patients.

In this study, we compared effects of IVA in two patients with different genetic statuses: patient 1 presenting with S549N, a non-G551D gating variant, patient 2 with G551D, the most common CFTR gating mutation. Reduction in sweat chloride and improvement of FE in patient 1 start earlier in therapy and seem to have a stronger instant effect, whereas impact of IVA in patient 2 is delayed. Also, effect on growth velocity is more present in patient 1. These results come along with *in vitro* data of the effects of IVA on CFTR channel opening probability and chloride transport showing greater effects on S549N than G551D-CFTR mutations.⁷

In conclusion, IVA seems to be safe and efficacious for infants <12 months of age. The results underline the early and sustainable effect of IVA, indicated especially by sweat chloride, LCI_{2.5%}, and exocrine pancreas function. Highly efficient modulators are able to maintain pancreatic function, especially when therapy is started early in life, and therefore, pancreatic substitution therapy can be successfully terminated. In CF, adequate nutrition contributes to good long-term prognosis, and therefore, internationally anthropometric targets have been defined.⁸ In the spirit of normalization of sweat chloride and exocrine pancreatic function, anthropometric targets could be aligned with those of non-CF patients. CFTR modulation with the highly effective CFTR modulator IVA is clearly disease modifying. Therefore, not only the classical anthropometric targets in this patient group could be reconsidered but also therapy recommendations, such as respiratory therapy, regarding normal CFTR function.

Further investigations on infants <12 months of age and assessments of long-term outcomes have to be performed.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interests.

AUTHOR CONTRIBUTIONS

Teresa Fuchs contributed to Writing—original draft, conceptualization, and resources. Dorothea Appelt contributed to resources and writing—review and editing. Katharina Niedermayr contributed to resources and writing—review and editing. Helmut Ellemunter contributed to writing—review and editing, and supervision.

ETHICAL APPROVAL

Not applicable.

CONSENT


Written informed consent was obtained from the patients' legal guardians for publication of the data. Corresponding author has a copy of the written consent available for review.

DATA AVAILABILITY STATEMENT

Raw data were generated at the Medical University of Innsbruck, Cystic Fibrosis Center of Innsbruck. The data that support the findings of this study are available from the corresponding author, Teresa Fuchs, upon reasonable request.

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