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Original Article

Immunogenic adverse events to CFTR modulators – An international survey☆

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ABSTRACT

Background: CFTR modulator therapy has unprecedented positive effects on people with CF (pwCF). However, immunogenic reactions to CFTR modulator therapy may lead to drug discontinuation. We aimed to identify pwCF, intolerant to CFTR modulator therapy due to suspected immunogenic adverse events (iAE).
Methods: This survey assessed the types of reaction (e.g. rash, liver injury, drug fever) including reactions after re-exposure and was completed by ECFS CTN Centers.
Results: Response rate to the survey was 74 %. 89 CF centers treating approximately 12000 to 17500 pwCF in 28 countries participated and 75 (84 %) CF centers reported discontinuation of CFTR modulator therapy. 37 (41.1 %) of CF centers reported iAE affecting 200 (1.1 – 1.7 %) pwCF. Detailed information about iAEs was provided for 41 of 200 (20.5 % of affected) pwCF. Of the iAEs reported in detail 33/41 (80.5 %) were associated with elexacaftor/tezacaftor/ivacaftor modulator therapy, 6 (14.6 %) with lumacaftor/ivacaftor and 2 (4.9 %) with tezacaftor/ivacaftor. 72 % of pwCF with iAE were re-exposed to CFTR modulator therapy. 32 % of re-exposed pwCF reported a second iAE. Rash and elevated liver enzymes were most frequently reported iAEs.
Conclusions: iAE were mostly transient. Drug allergy to CFTR modulator therapy was rare, but highly relevant for individual pwCF.

1. Introduction

Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy has been approved in an increasing number of countries for the treatment of cystic fibrosis (CF). Ivacaftor and fixed formulations Lumacaftor/Ivacaftor (LI), Tezacaftor/Ivacaftor (TI) and Elexacaftor/Tezacaftor/Ivacaftor (ETI) are available. CFTR modulator therapy is a life-long transformative treatment which is associated with improved quality of life and increased life expectancy. CFTR modulator therapy is mostly well-tolerated, although several cases of CFTR modulator therapy related drug allergy were observed, which in part led to permanent discontinuation of the respective CFTR modulator therapy [2–6].

The incidence and prevalence of drug allergy is known to be higher in people with CF (pwCF) [7,8], especially for beta-lactam antibiotics. In clinical studies for ETI, rash was observed in 4 to 10.9 % and 4 to 6.5 % for the control group [9,10]. In the open label extension study, rash was reported in 16.5 %, leading to discontinuation of ETI in 1.2 % of the

☆ This data has been presented at the 46th European Cystic Fibrosis Conference in Vienna, Austria [1]

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study participants [11]. Elevated liver enzymes were reported for 4 to 10.9 % for ETI and 2 to 4 % for the control group [9,10] and observed in 11.3 % percent of the study participants over a period of 3 years in the open label extension study, leading to discontinuation of ETI in 1.6 % of patients. In addition, several case studies report suspected immunogenic adverse events (iAE) after initiation of CFTR modulator therapy with ETI and LI, rarely leading to discontinuation [4,5,12,13]. The aim of this study was to identify pwCF, intolerant to CFTR modulator therapy due to suspected immunogenic adverse events and to provide information about the frequency and severity of iAE on a large CF population basis

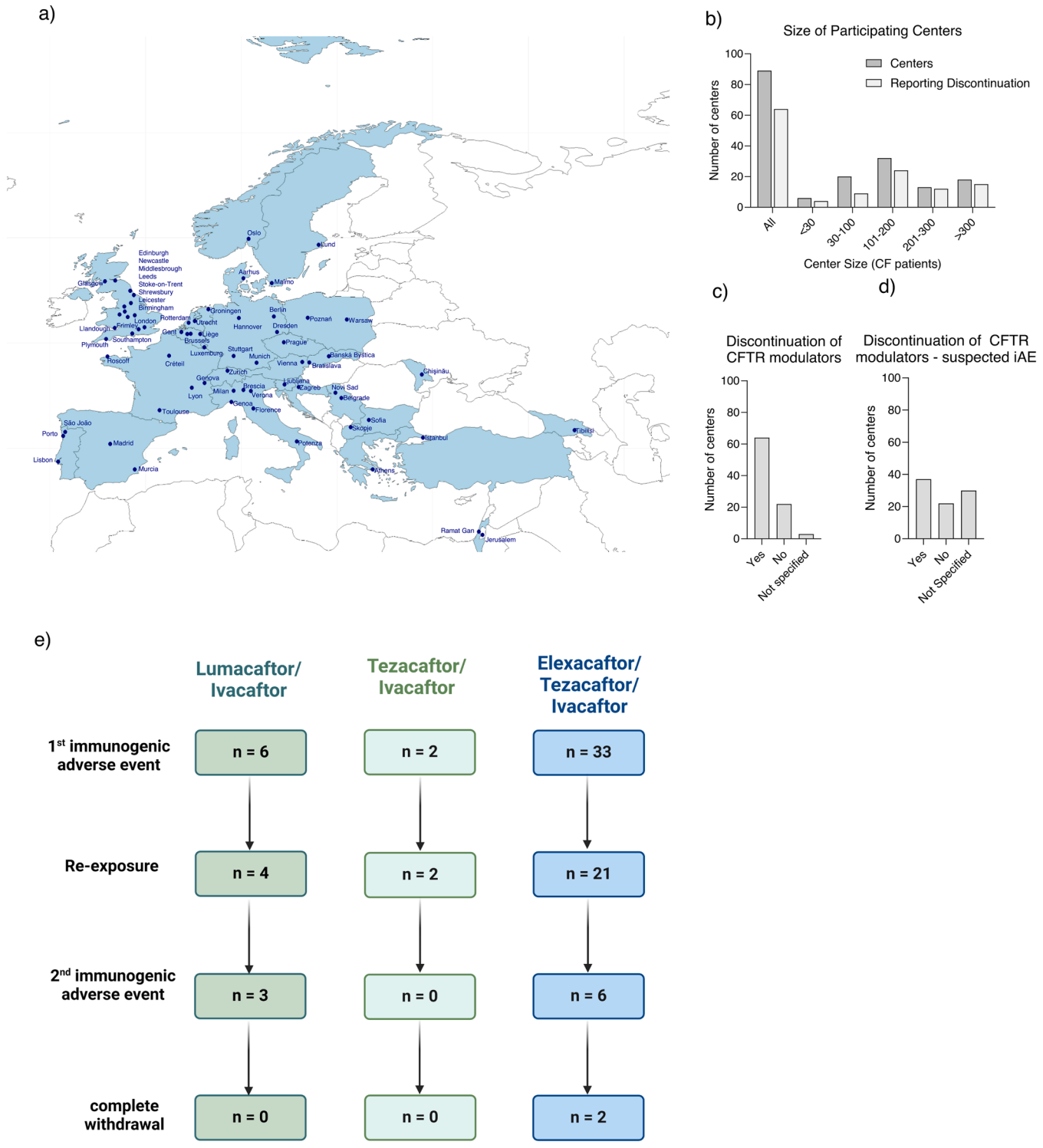

Fig. 1. Participating Centers and Discontinuation of different CFTR modulators. (a) Map of Europe showing the individual CF center locations and countries that participated in the survey. Maps were plotted with R in R Studio using the packages "ggplot2" and "maps". (**b**) Showing the participating centers according to size. (**c**) Showing number of Centers reporting Discontinuation of CFTR modulators. (**d**) Showing discontinuation of CFTR modulators due to suspected immunogenic reactions. (**e**) Flowchart showing the number of patients on Lumacaftor/Ivacaftor, Tezacaftor/Ivacaftor and Elexacaftor/Tezacaftor/Ivacaftor with suspected immunogenic adverse events, number of re-exposed and pwCF with a second reaction (Created with Biorender).

2. Material and methods

2.1. Study design and distribution

To assess the frequency of iAE to CFTR modulator therapy we designed a survey to help identify people with suspected drug allergy to modulator therapy. The survey included questions about CFTR modulator use and center size, number of pwCF who discontinued CFTR modulator therapy due to suspected immunogenic adverse event. iAE were defined as rash (localised, generalised, with/without mucosal involvement, hives, blisters), swelling (localised, generalised, mucosal involvement, joints, face), liver injury (elevated liver function tests: transaminases, bilirubin or clinical jaundice without different explanation), bronchial spasm or other possibly immunogenic events. Caregivers were asked to exclude isolated pulmonary obstruction AE to LI, as this is a very common and thoroughly reported non-allergic adverse event [14]. Drug allergy was defined as persistent iAEs or recurrent iAEs. The survey was distributed via the European Cystic Fibrosis Society (ECFS) clinical trial network (CTN) mailing list. Survey: https://southampton.qualtrics.com/jfe/form/SV_d57cfgLi9XPrL94. Data was collected from October 2022 until December 2022.

2.2. Exclusion criteria

Data from participating CF centers that failed to provide a center name, contact person or location were excluded. In addition, multiple entries from the same IP address were carefully checked and excluded if not reasonable.

2.3. Data analysis

Data were processed in Microsoft Excel (2021) and R in R Studio. Maps were plotted with R in R Studio using the packages "ggplot2" and "maps". Point prevalence was calculated based on the center size reported by the individual centers (categories: <30; 30 −100; 101–200; 201–300; <300 patients). The lowest number and highest number of treated pwCF covered by this survey was calculated using those categories. This also includes pwCF that were not eligible for CFTR modulator treatment which other studies have reported to be around 10 % of all pwCF [15–17]. The point prevalence of iAE was calculated using all reported patients with iAE ($n = 200$) and the estimated cohort of pwCF (lowest to highest). As detailed information was not provided for all patients with iAE, we provide the detailed analysis of frequency and type of reaction for the subgroup of patients with detailed information ($n = 41$). Percentages were calculated as indicated in the respective results.

3. Results

The survey was distributed via the ECFS-CTN mailing list and response rate was 74 %. Physicians from 89 CF-centers in 28 countries completed the survey, with 97 % of participants being from Europe (Fig. 1a). Reported center size ranged from treating <30 to treating >300 pwCF (Fig. 1b). The majority of centers treated 101–200 patients. The approximate total number of treated pwCF was 12,000 to 17,500. 76 % of centers ($n = 64$) reported discontinuation of CFTR modulator therapy in at least one patient (Fig. 1c). A total of 41.1 % ($n = 37$) of the CF centers reported discontinuation of CFTR modulator treatment for >7 days due to suspected iAE (Fig. 1d). This included 200 individuals (1.1 – 1.7 %) being discontinued from CFTR modulator treatment. Detailed information about iAE was provided for 41 of these 200 (20.5 %) pwCF (Table 1).

3.1. Discontinuation of CFTR modulator therapy due to immunogenic adverse events

For the analysis of type and properties of iAE we used the provided detailed data for 41 of the 200 affected pwCF. 51.2 % ($n = 21/41$) people were female. Of all reported iAE 80.5 % people were on ETI ($n = 33/41$), 14.6 % people on LI ($n = 6/41$) and 4.9 % people received TI (2/41) (Table 1). iAE leading to discontinuation occurred later than 24 h after initiation of CFTR modulator therapy in 97.5 % pwCF ($n = 40/41$), and for 75 % pwCF ($n = 30/41$) later than 8 days after initiation. A total of 60 % ($n = 26/41$) had to temporarily pause while 40 % ($n = 14/41$) discontinued CFTR modulator therapy. The most common iAE for all modulators was rash; this included 44 % ($n = 18/41$) of all pwCF with iAE. The majority (68.5 %) of pwCF that reacted with rash were on ETI ($n = 14$). In 72 % ($n = 13/18$) the rash was generalised and either maculopapular ($n = 14/18$) or with hives ($n = 7/18$). Blisters were not reported. The second most frequent iAE were elevated liver function tests and bilirubin levels. Elevated liver enzymes were reported for one-third (36.5 %; $n = 15/41$) of pwCF with iAE (Table 1). In most pwCF liver enzymes normalized within 8–30 days after discontinuation.

Table 1
Discontinuation of CFTR modulator therapy and type of reaction.

Participants	Total number			
Participating CF Centers	89			
Countries	28			
Estimated number of patient base population (minimum - maximum): 12,000 – 17,500				
Suspected immunogenic adverse event	Total number n (%)	Treatment groups n (% whole population)		
		LI	TI	ETI
CF Centers (%)	37 (41.1)			
pwCF with reactions to CFTR modulator therapy	200			
pwCF with details about reactions (%)	41 (100)	6 (14.6)	2 (4.9)	33 (80.5)
Female (%)	21 (51.2)	4 (66.7)	1 (50)	16 (48.5)
Pediatric (%)	17 (41.5)	4 (66.7)	0 (0)	13 (39.4)

Type of reaction	Total number n (%)	n (% all LI)	n (% all TI)	n (% all ETI)
Rash (%)	18 (44)	2 (33.3)	–	16 (48.5)
Elevated LFTs (%)	15 (34)	3 (50)	1 (50)	11 (33.3)
Drug Fever (%)	1 (2.5)	1 (16.7)	–	–
Swelling (%)	6 (15)	2 (33.3)	–	4 (12.1)
Bronchial Spasm (%)	2 (5)	1 (16.7)	–	1 (3)

Type of reaction of people with CF (pwCF) to CFTR modulator therapy after 1st AE. Elevated liver function tests (LFT): alanine-aminotransferase (ALT) or aspartate-aminotransferase (AST) > 8 x upper limit of normal (ULN) $n = 4$ (ETI $n = 3$; LI = 1). ALT or AST >5 × ULN ≥ 2 weeks $n = 6$ (ETI $n = 4$; LI $n = 2$). ALT or AST >3 × ULN, total bilirubin >2 × ULN and/or clinical jaundice $n = 5$ (ETI $n = 4$; TI $n = 1$).

3.2. Re-exposure to CFTR modulator therapy

67 % ($n = 27/41$) of pwCF were re-exposed to their respective CFTR modulator therapy (Fig. 1e). The majority (78 %, $n = 21$) received ETI. A second iAE occurred in 6 ETI-re-exposed pwCF, leading to complete discontinuation in two pwCF (Table 2). TI-re-exposed pwCF ($n = 2$) did not experience a second reaction. 3/4 of the re-exposed pwCF on LI experienced a second iAE, which did not lead to discontinuation of CFTR modulator treatment.

In summary, one third ($n = 9$) of re-exposed patients had a second iAE to CFTR modulator therapy (Fig. 1e and Table 2). Similar to the first iAE, the second suspected iAE occurred later than 8 days after re-exposure. 78 % ($n = 7/9$) experienced the same reaction as before. Two (22 %) out of the nine individuals had to completely discontinue CFTR modulator therapy after a second iAE, both were adults and on ETI. (Table 2).

In conclusion, 14/41 pwCF on CFTR modulators (0.08 to 0.12 % of

Table 2
Patient reactions after re-exposure to CFTR modulator therapy.

Type of Reaction			Rash	Elevated LFTs	Drug Fever	Swelling	Bronchial Spasm	Reaction (1st = 2nd)	Complete Withdrawal
LI	1	F	–	yes*	–	–	–	no	no
	2	M	–	yes*[1]	–	–	–	yes	no
	3	M	–	–	–	–	–	yes	no
ETI	4	f[#]	yes	–	–	yes (eye)	–	yes	yes
	5	m	–	yes*[2]	–	–	–	yes	no
	6	f[#]	yes	–	–	–	–	No	no
	7	f	–	yes*[1]	–	–	–	yes	no
	8	m[#]	ns	ns	ns	ns	Ns	yes	yes
	9	m[#]	–	yes*[1]	–	–	–	yes	no

F = female; m = male; # = ≥ 18 years old; LFT = liver function test; ALT = alanine-aminotransferase; AST = aspartate-aminotransferase: ns = not stated; ULN = upper limit of normal; * = ALT or AST >8 × ULN, *1 = ALT or AST >5 × ULN ≥ 2 weeks, *2 = ALT or AST >3 × ULN, total bilirubin >2 × ULN and/or clinical jaundice.

the whole cohort) had to completely withdraw from modulator therapy due to iAE without a re-exposure. However, only 2/9 pwCF (0.01 to 0.02 % of the whole cohort) that were re-exposed had to withdraw from modulator therapy. Based on this limited dataset 92.6 % (25/27) of re-exposed pwCF could safely receive CFTR modulator therapy after and 7.4 % (2 out of 27 re-exposed) pwCF had to withdraw from modulators permanently.

4. Discussion

This is the first real-world survey-based study collecting data about drug allergy associated with CFTR modulator therapy. Our data suggests that drug allergy to CFTR modulator therapy is very rare and demonstrates that iAE mainly appear as non-immediate reactions with mild rashes. One-third of pwCF with iAE to CFTR modulator therapy had a second reaction after re-exposure. Based on the group that was re-exposed to CFTR modulator therapy, one could speculate that two-thirds of non-re-exposed pwCF could safely receive CFTR modulator therapy, but did not at the time of the survey.

Most reported iAE occurred later than a week after initiation, supporting delayed-type drug allergy as underlying mechanism [4,5]. To date, validated *in-vitro* tests, which predict the risk of repeated reactions to CFTR modulator therapy are lacking. Of note, in several independent cases, lumacaftor- and ivacaftor-specific T-lymphocytes were detected [4,5,18].

Rash was the most common iAE after initiation and upon re-exposure to CFTR modulator therapy. In contrast to previously published data, our data suggests a gender balanced prevalence of rash [4,9,10,12,13,19]. Importantly, no severe rashes e.g. blistering of the skin were reported [20]. Elevated liver function tests, as described before, were commonly reported in our survey [21–23]. After discontinuation of CFTR modulator therapy, liver enzymes normalized within weeks to months. However, immunogenic drug induced liver injury is most likely just one mechanism among others for liver injury. Infections with hepatotropic viruses, direct hepatotoxicity and underlying CF liver disease should be considered as well [22,24].

This is the first multinational study on drug allergy to CFTR modulator therapy, however it comes with limitations due to the survey-based approach of data collection. As the study was distributed through the ECFS-CTN, centers outside of ECFS-CTN may not have known about this project. This data may include bias of healthcare professionals that are treating pwCF with suspected drug allergy. Due to the nature of a survey study, the definition of iAE including liver injury and the definition if the whole sample size is not precise.

5. Conclusions

Rashes and liver injury associated with CFTR modulator therapy are mostly transient. Therefore, re-exposure or even treat-through approaches are reasonable due to the high rate of tolerance. Manifest drug allergy against CFTR modulator therapy is rare - complete withdrawal even more rare, however highly relevant for individual affected pwCF. For those with proven drug allergy and complete withdrawal from CFTR modulator therapy, specific immune mechanisms need to be characterised to enable individualised diagnostic and management approaches. The "Allergies related to CF" (ART-CF) project aims to investigate the epidemiology, chemical and immunological basis of allergic reactions to CFTR modulator therapy.

CRediT authorship contribution statement

Ruth Maria Urbantat: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Laura Behan:** Methodology, Data curation, Writing – review & editing. **Sebastian Wisniewski:** Data curation, Writing – review & editing. **Joshua Gardner:** Conceptualization, Writing – review & editing. **Mirjam Stahl:** Writing – review & editing. **Marcus A. Mall:** Writing – review & editing. **Daniel Peckham:** Conceptualization, Writing – review & editing. **Dean Naisbitt:** Conceptualization, Writing – review & editing. **Jobst F. Roehmel:** Conceptualization, Methodology, Writing – review & editing.

Questionnaire URL

https://southampton.qualtrics.com/jfe/form/SV_d57cfgLi9XPrL94.

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Declaration of competing interest

R.M.U. is participant of the Berlin Institute of Health (BIH)-Charité Junior Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin and the BIH. M.S. is participant of the Berlin Institute of Health (BIH)-Charité Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin and the BIH. M.S. reports an Independent Research Innovation Award and honoraria for lectures and participation in advisory boards, all by Vertex Pharmaceuticals Incorporated, outside of the submitted work. She is Chairman of the German CF Research Council (FGM), Treasurer of the German Society of Paediatric Pulmonology (GPP), and was Secretary of the Group CF of the Paediatric Assembly of the ERS. M.A.M. reports grants from Vertex Pharmaceuticals; fees for advisory board participation or consulting from Boehringer Ingelheim, Enterprise Therapeutics, Kither Biotech,

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