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Brief Report
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Evaluation of the drug–drug interaction between triazole antifungals and cystic fibrosis transmembrane conductance regulator modulators in a real-life cohort

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Abstract

Limited data on the clinical management of drug–drug interactions between triazoles and Cystic Fibrosis transmembrane conductance regulator (CFTR) modulators are available. We retrospectively evaluated azole target attainment and dose adaptations in patients from two Dutch CF centres concomitantly receiving triazoles and CFTR modulators. In total, 21 patients with 59 triazole trough concentrations were evaluated. Subtherapeutic concentrations were frequently observed, especially for itraconazole and voriconazole. Of the investigated antifungal agents, posaconazole appears the most preferable option. Our results emphasize the importance of adequate management of this interaction and underpin the added value of therapeutic drug monitoring of triazoles in this population.

Lay summary

Fungal infections are serious complications in Cystic Fibrosis (CF) patients. We evaluated patients concomitantly receiving triazoles and CF transmembrane conductance regulator modulators: subtherapeutic triazole exposure was frequently observed. Posaconazole appears the preferable antifungal agent.

Key words: antifungal agents, therapeutic drug monitoring, CFTR modulators, pharmacology, CF.

Introduction

Fungal infections are serious complications in Cystic Fibrosis (CF) patients.[1–4] CF is a life-limiting inherited disease characterized by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene. CFTR modulators are the first class of drugs aimed to treat this underlying cause of CF.[5] Where these drugs have improved lung function and quality of life of patients with CF significantly, fungal infections remain to be associated with worsening of clinical outcomes in this population.[1–4]

Triazoles are the first-line antifungal treatment, but demonstrate significant, bi-directional, drug–drug interactions with the CFTR modulators through interference of the cytochrome *P*-450 (CYP) system as outlined in Table S1 in the Supplementary Materials.[6] Consequently, dose adjustments are recommended to prevent toxicity or inefficacy.[7–12] Limited information to substantiate these recommendations is available.

Real-world evidence to support the clinical management of these interactions is needed. Therefore, we aimed to assess the impact of concomitant administration of CFTR modulators and triazoles in a real-life cohort.

Methods

We performed a retrospective cohort study in two Dutch CF centres. Patients were included if they concomitantly received a CFTR modulator, i.e., ivacaftor, ivacaftor/lumacaftor, ivacaftor/tezacaftor, or ivacaftor/tezacaftor/elexacaftor, and a triazole, i.e., isavuconazole, itraconazole, posaconazole, or voriconazole, between 2014 and 2022 and had at least one triazole trough concentration (C_{min}) measured. The local Ethical Committees provided waivers to obtain informed consent from participants. Data were collected from the electronic patient record, including demographics, drug history, CF genetic mutation, CF related co-morbidities, indication for antifungal therapy, co-medication, and triazole C_{min}. Triazole concentrations other than C_{min} and collected before day 2 of therapy were excluded.

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Table 1. Demographic characteristics ($N = 21$).

Characteristic	Median (range)
Age (years)	26 (11–64)
Sex, female, *n* (%)	9 (43)
Weight (kg)	58 (35–80)
Height (cm)	172 (148–186)
BMI (kg/m^2)	20.2 (16.0–24.7)
CFTR genotype, *n* (%)	
dF508/dF508	19 (90)
dF508/A455E	1 (5)
dF508/S1251N	1 (5)
CF related disease, *n* (%)	
Pancreas dysfunction	18 (86)
Diabetes (CFRD)	11 (52)
Kidney disease (CFKD)	1 (5)
Liver disease (CFRLD)∗	1 (5)
Pseudomonas aeruginosa colonization	9 (43)
Administered CFTR modulator, *n* (%)	
Ivacaftor	1 (5)
Ivacaftor/lumacaftor	12 (57)
Ivacaftor/tezacaftor	12 (57)
Indication for antifungal therapy, *n* (%)	
Aspergillus bronchitis	11 (52)
Allergic broncho-pulmonary aspergillosis (ABPA)	7 (33)
Pulmonary aspergillosis	3 (14)
Identified pathogen, *n* (%)	
Aspergillus fumigatus	16 (76)
Aspergillus fumigatus and *Aspergillus flavus*	1 (5)
Aspergillus fumigatus and *Aspergillus terreus*	1 (5)
Aspergillus fumigatus and *Paecilomyces variotii*	1 (5)
None	2 (10)
Administered triazole, *n* (%)	
Itraconazole	5 (24)
Posaconazole	12 (57)
Voriconazole	6 (29)

BMI, Body Mass Index; CF, Cystic Fibrosis; CFTR, Cystic Fibrosis Transmembrane Conductance Regulator; CFRD, Cystic Fibrosis Related Diabetes; CFKD, Cystic Fibrosis Kidney Disease; CFRLD, Cystic Fibrosis Related Liver Disease; TDM, Therapeutic Drug Monitoring. ∗ = the individual with CFRLD was scored as Child-Pugh Class A and thus did not require CFTR modulator dose adjustments upfront.

To evaluate the effect of CFTR modulators on triazole exposure, we identified the number of individuals with C_{min} within the therapeutic range. Therapeutic ranges for itraconazole, posaconazole, and voriconazole were defined as 1.0–4.0 mg/l, ≥1.0 mg/l, and 1.5–5.0 mg/l, respectively.[13] Additionally, we identified the number of triazole dose adjustments.

To evaluate the effect of triazoles on CFTR modulators, we assessed the number of individuals where the Summary of Product Characteristics (SmPC) recommendations for CFTR modulator dose adjustments to prevent supratherapeutic exposure, caused by the drug–drug interaction with the triazole, was needed.[7–9] For individuals where these recommendations were not correctly applied, an assessment of signs of toxicity was performed by evaluating clinical records and liver function parameters.

Results

In total, 21 CF patients with 59 triazole (9 itraconazole, 38 posaconazole, and 12 voriconazole) C_{min} were evaluated. Demographics are presented in Table 1.

Figure 1 shows the triazole C_{min} per individual and percentages of within-target and outside-target C_{min} per CFTR modulator-triazole combination. Data from the only individual receiving ivacaftor monotherapy are not shown: two within-target posaconazole C_{min} (1.8 and 2.7 mg/l) were measured during concomitant intake.

Overall, target attainment was highest for posaconazole (50–90.9%), and much lower for itraconazole and voriconazole (0–33.3%). As indicated by the up-pointing triangles, seven individuals received at least one higher, i.e., above registered, triazole dose: 4 individuals following a below-target C_{min}, the other 3 individuals from start of therapy. For 4 out of 4 (100%) individuals, the follow-up C_{min} was still below target. For 2/3 (67%) individuals, the dose increase from start of therapy did result in a within-target C_{min}, for the other individual (33%) the follow-up C_{min} was still below target. As indicated by the down-pointing triangles, only one individual received a lower triazole dose once, resulting in a below-target posaconazole C_{min}. For this individual, increasing the dose to the registered dose resulted in a within-target C_{min}.

The recommended CFTR modulator dose adjustments were not effectuated in seven individuals. The recommended ivacaftor/lumacaftor dose reduction in the first week of treatment for individuals already treated with a strong CYP3A4 inhibitor (e.g., itraconazole, posaconazole, and voriconazole) was not performed in two of three individuals already receiving a triazole. The recommended ivacaftor/tezacaftor dose reduction from the first day of co-administration was not performed in three individuals, but later: namely after 2, 9, and 12 days of co-administration, respectively. In two individuals, the recommended ivacaftor/tezacaftor dose reduction was not performed at all, where co-administration was for 52 and 63 days. For all individuals described above, the toxicity assessment did not result in any major signs of toxicity. By chance, we observed that in three individuals ivacaftor/lumacaftor was stopped when a triazole was initiated and restarted after triazole discontinuation. The exact reason for discontinuation could not be retrospectively retrieved.

Discussion

In this retrospective evaluation of the drug–drug interaction between CFTR modulators and triazoles in a real-life cohort, subtherapeutic triazole concentrations were frequently observed. Furthermore, our findings show that dose adaptations to anticipate on this bi-directional interaction were often required.

Triazole targets were frequently not attained in our cohort, as expected by the CYP-mediated biotransformation interference of these drugs by the concomitantly administered CFTR modulators.[8,9] Our findings are thereby in line with two previous cases.[14] Although subtherapeutic triazole exposure in CF patients was already observed before CFTR modulator combinations became available,[15] where pharmacokinetic variability is likely caused by common CF-related diseases such as pancreatic insufficiency and hepatobiliary dysfunction,[16] this issue seems even more pronounced when combined with these drugs. As the percentages of within-target triazole C_{min} in our study were highest for posaconazole, this might be the most preferable option of the three evaluated triazoles in patients using CFTR modulator therapy.

While it is not recommended to adjust doses of CYP3A4 substrates when co-administered with ivacaftor/tezacaftor,[9,17] itraconazole and voriconazole C_{min} were almost all below target. In one of the individuals with a below-target C_{min}, a dose escalation was performed but without the desired effect. In fact, none of the itraconazole or voriconazole dose increases

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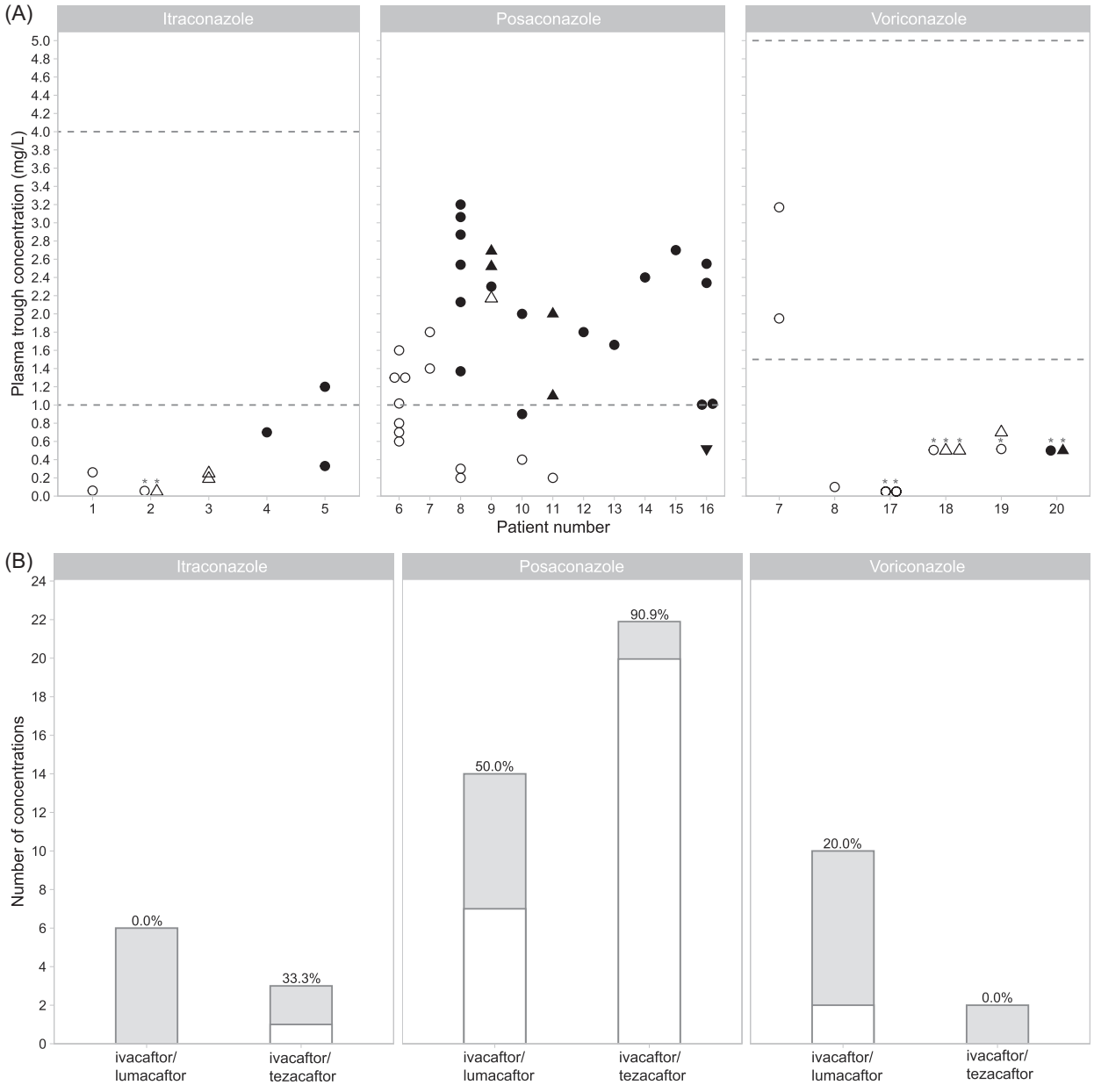

Figure 1. Triazole plasma trough concentrations (A) and number of triazole plasma trough concentrations within and outside target (B) of patients concomitantly receiving ivacaftor/lumacaftor or ivacaftor/tezacaftor. Panel a: Open datapoints (○) indicate that the concentration was measured during concomitant intake with ivacaftor/lumacaftor; closed datapoints (●) indicate concomitant intake with ivacaftor/tezacaftor. Up-pointing triangles (△/▲) indicate the concentration is measured during an increased triazole dose, down-pointing triangles (▽/▼) indicate the concentration is measured during a decreased triazole dose. The dashed horizontal lines represent the threshold therapeutic concentrations of 1.0 and 4.0 mg/l for itraconazole, 1.0 mg/l for posaconazole, and 1.5 and 5.0 mg/l for voriconazole. Plasma trough concentrations at the lower limit of quantification are indicated with an asterisk (*). Data from the individual receiving ivacaftor monotherapy are not shown. Panel b: The percentages presented on top of each bar represent the proportion of observations within target. None of the observations were above target. White = within target, grey = below target.

during co-administration with any evaluated CFTR modulator resulted in adequate exposure. On the contrary, increasing the dose of posaconazole, notably not a CYP3A4 substrate, in two evaluated individuals resulted in adequate exposure although in general this was already more frequently observed with standard posaconazole doses. Switching antifungal agent in patients where dose escalation still results in subtherapeutic C_{min} should be considered, with posaconazole being the least affected triazole. Our findings underline the importance of therapeutic drug monitoring of triazoles in the CFTR modulator treated population.

Treatment modifications in both triazole and CFTR modulator therapy were frequently performed in our cohort, often from initiation of combination therapy onwards. In some cases, the CFTR modulator was even stopped during triazole therapy. Discontinuation of CFTR modulator therapy may enhance the chance of adequate triazole exposure, and subsequent management of the fungal disease, but poses a

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risk of decreased CF disease control. Here, it may be more appropriate to select a triazole for which adequate exposure is expected, e.g., posaconazole, without the need to discontinue CFTR modulator treatment. As co-administration may also result in supratherapeutic CFTR modulator exposure potentially resulting in toxicity, it is advised to adjust doses as recommended.

Notably, our findings may be impacted by other matters, such as CYP-polymorphism, interactions with food, and/or therapy adherence. The retrospective nature of our study did not allow us to assess the potential impact of these factors. None of the included patients were treated with isavuconazole and ivacaftor/elexacaftor/tezacaftor was not yet available at the time of this study, leaving a knowledge gap for these drugs. Isavuconazole has the most favourable drug–drug interaction profile of the triazoles, making it an antifungal agent worth evaluating. In addition to our evaluations, a comparison of triazole exposure with and without concomitant use of a CFTR modulator within an individual would be highly interesting. As triazoles affect CYP3A4-mediated metabolism of CFTR modulators as well,[7–9] CFTR modulator exposures should ideally also be evaluated in future studies to quantify these effects.

We acknowledge the changing landscape of CF therapy, where more patients receive triple CFTR modulator therapy. Nevertheless, our findings are very valuable for those individuals effectively managed with CFTR modulator therapy other than elexacaftor/tezacaftor/ivacaftor. Considering our results, a subsequent analysis of the interaction between triple CFTR modulator therapy and triazoles is considered important. Similar effects as with tezacaftor/ivacaftor may be expected.

In conclusion, our evaluations demonstrate that the drug–drug interaction between triazoles and CFTR modulators is manageable in most cases. Target attainment was most frequently observed with posaconazole. Our results underline the importance of adequate clinical management of this drug–drug interaction, and underpin the added value of triazole therapeutic drug monitoring.

Supplementary material

Supplementary material is available at *Medical Mycology* online.

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Author contributions

Anouk M.E. Jansen (Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing), Margot N. Eggermont (Data curation, Writing – review & editing), Erik B. Wilms (Writing – review & editing), Sami Aziz (Data curation, Writing – review & editing), Monique Reijers (Writing – review & editing), Jolt Roukema (Writing – review & editing), Adilia Warris (Writing – review & editing), Roger J.M. Brüggemann (Conceptualization, Methodology, Supervision, Writing – review & editing), and Renske Van Der Meer (Conceptualization, Methodology, Supervision, Writing – review & editing).

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Conflicts of interest

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