Journal of Cystic Fibrosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Subtherapeutic triazole concentrations as result of a drug-drug interaction with lumacaftor/ivacaftor

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ARTICLE INFO

Keywords:
Cystic fibrosis
Triazoles
Lumacaftor/ivacaftor
Drug-drug interaction

ABSTRACT

Lumacaftor/ivacaftor (Orkambi®, LUM/IVA) is indicated for the treatment of cystic fibrosis (CF) patients aged ≥ 2 years with homozygous F580del mutation in the CFTR gene. Triazole fungal agents are used to treat fungal disease in CF. The use of triazoles is limited by pharmacokinetic challenges, such as drug-drug interactions. The most notable drug-drug interaction between triazoles and LUM/IVA is due to strong induction of CYP3A4 and UGT by LUM. In this real-world retrospective observational study, we described the effect of LUM/IVA on the trough concentration of triazoles. Concomitant use of LUM/IVA with itraconazole, posaconazole or voriconazole resulted in subtherapeutic triazole levels in 76% of the plasma samples. In comparison, in patients with triazole agents without LUM/IVA only 30.6% of the plasma samples resulted in subtherapeutic concentrations. Subtherapeutic plasma concentrations of triazoles should be considered in CF patients on LUM/IVA and further research is warranted for other dosing strategies and alternative antifungal therapy.

1. Introduction

Colonization and infection with fungal species contribute to clinical disease in Cystic Fibrosis (CF) [1,2]. Antifungals in the triazole group, including itraconazole (ITR), posaconazole (POSA), and voriconazole (VOR) are used as therapeutic agents across the spectrum of fungal disease in CF. Since the clinical effect and the occurrence of adverse events with triazoles are correlated with plasma concentrations, therapeutic drug monitoring (TDM) is indicated. The efficacy of triazoles is predicted by the ratio between the area under the concentration-time curve (AUC) and the minimal inhibitory concentration (MIC) of the causative fungal pathogen (AUC/MIC) [3]. By keeping the ITR (including OH metabolite) concentration between 2 and 4 mg/L, the POSA concentration > 1.25 mg/L, and the VOR concentration between 1 and 4 mg/L, an adequate AUC/MIC ratio can be consistently achieved. Several factors could influence the triazole plasma concentration [3–5]. Due to the metabolism of ITR, POSA and VOR, several drugs can potentially cause drug-drug interactions. ITR is a substrate for the cytochrome P (CYP)−450 enzyme CYP3A4, POSA for the enzyme uridine 5′-diphospho-glucuronosyltransferase (UGT) and VOR is a substrate for CYP3A4, CYP2C19 and CYP2C9 [4,6].

Lumacaftor/Ivacaftor (Orkambi®, LUM/IVA) is registered for the treatment of CF patients aged ≥ 2 years with homozygous F508del mutation in the Cystic fibrosis transmembrane conductance regulator (CFTR) gene. LUM is a strong inducer of CYP3A and UGT [6,7]. It is likely that strong induction of CYP3A4 and UGT by LUM will reduce the exposure of ITR, POSA and VOR. The Summaries of Product Characteristics (SPC) of LUM/IVA does not recommend concomitant use with VOR, ITR or POSA [7]. However, the information about this potential drug-drug interaction is derived from *in vitro* studies. Therefore, the objective of this study was to retrospectively assess the potential effect of the drug-drug interaction of triazole fungal therapy with LUM/IVA in adult and pediatric patients.

2. Methods

We performed a real-world retrospective cohort study between January 2017 and August 2020 in the Erasmus MC University Medical Center (Rotterdam, The Netherlands). The medical research ethics committee approved the study and waived informed consent (MEC-2020–0028). CF patients on triazole with at least one trough concentration of VOR, ITR or POS available were eligible for analysis. Patients were excluded in case of documented liver disease or concomitant use of a strong CYP inducer other than LUM/IVA. Patients were divided in

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https://doi.org/10.1016/j.jcf.2024.01.006
Received 4 July 2023; Received in revised form 27 December 2023; Accepted 15 January 2024

LUM/IVA users (study group) and non-users (control group). Data were extracted from the electronic medical record, including patient characteristics, triazole doses and plasma concentrations.

TDM of triazoles was part of regular care, in order to detect sub- or supratherapeutic plasma concentrations and adjust doses based on the findings. Trough samples were taken at steady state and analyzed using a validated ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS) method. There is a linearity between 0.05 and 5 mg/L for ITR and ITRA-OH (active hydroxyl metabolite of ITR), and between 0.1 and 10 mg/L for VOR and POS. Correction for weight-based dosing was applied to the concentration data, in order to be able to present both pediatric as adult data together. Significance was tested using a two-tailed Mann Whitney-test.

3. Results

In total, 19 patients were identified with triazoles and concomitant LUM/IVA (8 with ITR, 3 with POSA and 8 with VOR). In total, we collected 42, 10 and 25 trough samples for ITR, POSA and VOR, respectively. Furthermore, for 32 CF patients not using LUM/IVA 50 VOR, 40 ITR and 18 POSA trough levels were available and used as control. Patients' characteristics are summarized in Table 1. All POSA patients used tablets. For ITR most patients used oral liquid, 5 patients (partly) used capsules of which 3 combined this with a proton pump inhibitor (2 control group, 1 LUM/IVA and control group).

Combination of LUM/IVA with ITR, POSA, or VOR resulted in significant lower plasma concentrations when compared with concentrations in patients that did not use LUM/IVA (Fig. 1). At the first TDM sample only limited patients were on target when using LUM/IVA vs control (ITR: 0/5 vs 4/12, POSA: 0/3 vs 5/5, VOR: 2/8 vs 9/15). As a result, doses administered to LUM/IVA users were increased in dose and/or frequency, resulting in higher daily doses in LUM/IVA users compared to control patients (Table 1). The median (range) of the total daily dose was 12.3 (6.8–16.3) mg/kg/day for ITR, 16.4 mg/kg/day ($n = 1$) for POS and 21.4 (5.5–43.9) mg/kg/day for VOR patients reaching the target concentrations and 6.8 (3.0–24.0) mg/kg/day for ITR, 6.0 (4.3–16.6) mg/kg/day for POS and 13.2 (5.5–23.2) mg/kg/day for VOR patients not reaching the target concentrations. Despite, these higher doses based on TDM still result in subtherapeutic concentrations in 76.1% of all the triazole samples: 78.6% for ITR, 88.9% for POSA and 68.0% for VOR. In the control patients, subtherapeutic levels were measured in 30.6% of the samples: 45% for ITR, 5.6% for POSA and 28% for VOR.

Table 1
Patient characteristics and clinical data of triazole agents.

	Triazole with LUMA/IVA ($n = 19$)	Triazole without LUMA/IVA ($n = 32$)
Gender (male/female)		
Voriconazole	(4/4)	(10/5)
Itraconazole	(3/2)	(9/3)
Posaconazole	(1/2)	(1/4)
Age (years)		
Voriconazole	11.7 (4.3–21.9)	21.9 (4.3–58.2)
Itraconazole	21.6 (10.2–28.9)	22.2 (8.3–47.4)
Posaconazole	21.5 (11.2–24.0)	28.6 (16.4–57.6)
Weight (kg)		
Voriconazole	39.7 (15.0–73.4)	60.0 (15.5–82.0)
Itraconazole	54.0 (31.2–60.0)	60.6 (29.9–67.0)
Posaconazole	50.0 (35.6–70.0)	56.9 (50.0–63.6)
Daily dose (mg)		
Voriconazole	300 (150–1000)	225 (100–400)
Itraconazole	250 (100–600)	200 (50–400)
Posaconazole	300 (200–400)	300 (200–500)
Daily dose (mg/kg)		
Voriconazole	17.8 (5.4–43.9)	8.3 (2.8–19.9)
Itraconazole	7.1 (3.0–24)	5.1 (1.7–12.5)
Posaconazole	7.2 (4.3–16.6)	2.9 (0.2–4.4)
Trough concentrations (mg/L), with desired concentrations		
Voriconazole (1–4 mg/L)	0.4 (<0.1–7.8)	1.9 (<0.1–5.6)
Itraconazole (sum, 2–4 mg/L)	1.19 (<0.1–4.69)	2.17 (<0.1–7.14)
Posaconazole (>1,25 mg/L)	0.6 (0.1–1.7)	2.9 (0.2–4.4)

Continuous variables will be presented as median and range and categorical variables will be given as counts with a percentage. LUMA/IVA, lumacaftor/Ivacaftor.

4. Discussion

In this real-world retrospective cohort study, we studied the impact on triazole exposure of the potential drug-drug interaction between LUM/IVA by assessing plasma concentrations of VOR, ITR and POSA with and without concomitant use of LUM/IVA in people with CF. We found that concomitant use with LUM/IVA resulted in significant lower trough concentrations of the triazoles, when compared with triazole use by patients without LUM/IVA. This effect was independent of the formulation used.

Although the reported drug-drug interaction is part of the SPC of LUM/IVA, this information has scarcely been described in real-world clinical care patients [7]. Only one case-report describes the subtherapeutic concentrations of POSA and VOR after initiation of LUM/IVA [8].

Our results have implications for the antifungal therapy in CF patients. In addition to LUM/IVA, two other CFTR modulator combinations elexacaftor/tezacaftor/ivacaftor (ETI) and tezacaftor/ivacaftor (TEZA/IVA) have now also become available. Importantly, ETI and TEZA/IVA lack the strong induction of CYP enzymes and UGT [9,10]. With the availability of ETI and TEZA/IVA, LUM/IVA is used less often in the treatment of CF [11]. However, in children <6 years and in situations where ETI and TEZA/IVA are not tolerated or commercially available, there still will be cases in which a patient with LUM/IVA needs antifungal therapy. In these cases, an alternative antifungal therapy is recommended. For example, despite limited literature, amphotericin B has been used in nebulized form to treat ABPA [12,13]. Moreover, based on the metabolism, isavuconazole (substrate for CYP3A4) will probably also be influenced by LUM. Finally, temporarily halting LUM/IVA treatment could be considered, but is not recommended when long lasting triazole treatment is needed.

Accordingly, there still will be cases in which LUM/IVA needs to be combined with triazoles. In these cases, we recommend to administer a higher starting dose and a higher maintenance dose. Plasma concentrations can further be elevated to therapeutic levels by increasing dosing frequency two times a day to three times day. In all cases, therapy should be intensively monitored by TDM. Furthermore, due to the limited literature, further research is needed on optimizing dosing strategies during triazole therapy with LUM/IVA.

Some limitations of this study should be noted. First, the retrospective design and the relatively small number of patients. However, our study is the first real-world evidence of the drug-drug interaction between LUM/IVA and VOR, POSA and ITR. Second, we did not evaluate the variable inflammation, which is known to reduce POSA and VOR metabolism and could therefore lead to supratherapeutic concentrations. However, as the few available CRP levels were low, no clinical effect was expected. Third, we did not relate the subtherapeutic triazole concentrations to the clinical efficacy. However, since triazole concentrations are correlated to clinical efficacy it is likely that low triazole concentrations resulted in suboptimal therapy.

5. Conclusions

In conclusion, in 76.1% of the analysed triazole samples from patients with CF using concomitant LUM/IVA, subtherapeutic concentrations were measured. Our results can help in more awareness of

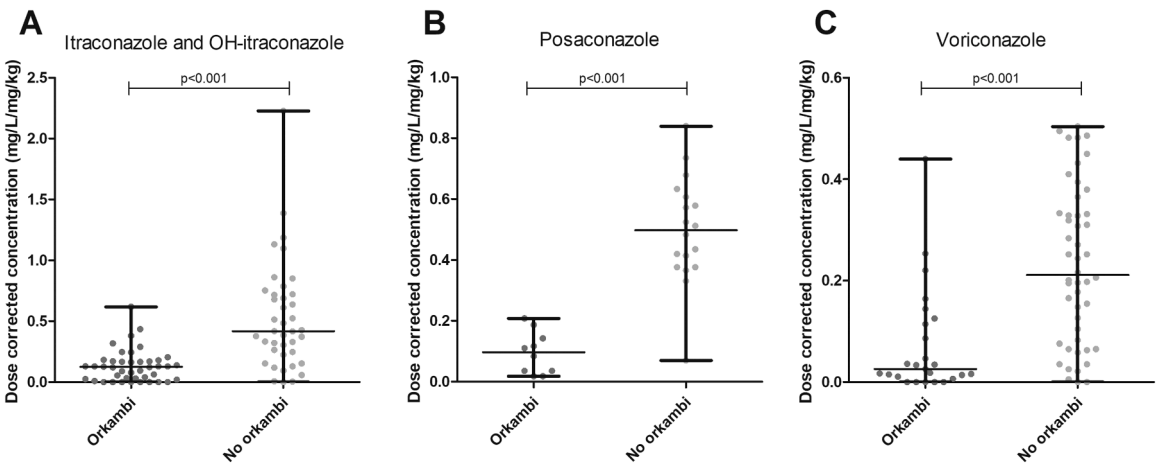

Fig. 1. Dose corrected concentrations of ITR sum (ITR plus OH-ITR), POSA and VOR with or without combination with LUM/IVA.

subtherapeutic triazole concentrations during concomitant therapy with LUM/IVA. We suggest to increase the starting and maintenance triazole dose, following by more frequently TDM. At last, more research is warranted for other dosing strategies and alternative antifungal therapy during concomitant use of LUM/IVA.

Statement of ethics

The medical research ethics committee of Erasmus MC University Medical Center, Rotterdam, the Netherlands, approved the study and waived informed consent (MEC-2020–0028).

CRediT authorship contribution statement

T.J.L. Smeets: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **H. van der Sijs:** Conceptualization, Writing – review & editing. **H.M. Janssens:** Writing – review & editing. **E.J. Ruijgrok:** Conceptualization, Writing – review & editing. **B.C.M. de Winter:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding sources

No funding was received for this research.

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