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

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Background

The cystic fibrosis transmembrane conductance regulator (CFTR) modulating drug lumacaftor/ivacaftor is indicated for the treatment of cystic fibrosis (CF) patients aged ≥ 2 years with homozygous F580del mutation in the CFTR gene. In CF patients, the thickened mucus and increasing destruction of airway mucosa lead to a chronic colonization of bacteria and fungi. Triazoles, including itraconazole, isavuconazole, voriconazole, and posaconazole, are used as therapeutic agents across the spectrum of CF fungal disease. However, this class is limited by pharmacokinetic challenges that may contribute to subtherapeutic drug levels. Knowledge of drug-drug interactions between triazoles and CFTR modulators are of specific interest for the treatment of fungal infections in CF patients. It is likely that strong induction of CYP3A4 by lumacaftor/ivacaftor will reduce the concentrations of triazole antifungals. Literature regarding drug-drug interactions between triazole agents and lumacaftor/ivacaftor is limited. We found one previous case report that describes a patient with both subtherapeutic serum levels of voriconazole and posaconazole.

Methods

Data of concomitant use of lumacaftor/ivacaftor and triazoles from January 2017 to March 2020 from 321 paediatric and adult CF patients from the Erasmus MC University Medical Center (Rotterdam, The Netherlands) were extracted from the electronic health record. In clinical practice, therapeutic drug monitoring (TDM) is standard care during treatment with triazole antifungal therapy. Besides concentrations of triazole agents, clinical information was collected.

Results

This retrospective cohort describes 15 patients with concomitant use of lumacaftor/ivacaftor and triazole antifungal therapy. 8 Patients used voriconazole, 6 itraconazole and 3 posaconazole and 25, 35 and 8 serum samples were obtained respectively. Concomitant use resulted for 68,0% (17/25), 100% (8/8) and 68,6% (24/35) in subtherapeutic serum levels of voriconazole, posaconazole and itraconazole, despite frequent dose-adjustments following TDM.

Conclusions

When combining lumacaftor/ivacaftor with voriconazole, itraconazole and posaconazole, 68,0%, 68,6% and 100% respectively of the measured serum samples resulted in subtherapeutic levels of the triazoles. Subtherapeutic triazole concentrations should be considered during concomitant treatment with lumacaftor/ivacaftor. Whenever possible, we would advise temporarily withdrawing of lumacaftor/ivacaftor before triazole initiation, or increase the dose in advance.

Key words: Triazole antifungal, pharmacokinetic interaction, lumacaftor/ivacaftor, Therapeutic Drug Monitoring