PKP-013

# Drug Interactions with azole antifungals in patients treated with hematopoietic stem cells

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## INTRODUCTION

Recipients of haematopoietic stem cells are at high risk of developing invasive fungal disease (IFD) which is the leading cause of morbidity and mortality in these immunocompromised patients.

Fluconazole and voriconazole are recommended as the firstline agents for IFD in the department of Haematology at the National Centre for Bone Marrow Transplants, Tunisia.

These two drugs are metabolised by cytochrome P450 (CYP) enzymes; they can also be inhibitors of these enzymes. Therefore, they are source of many drug interactions with drugs metabolised by these enzymes.

## OBJECTIVE

The objective of this study is to analyse the drug interactions in hematopoietic stem cell transplant (HSCT) recipients receiving azole antifungal drugs (voriconazole and fluconazole) and investigate the impact of such interactions.

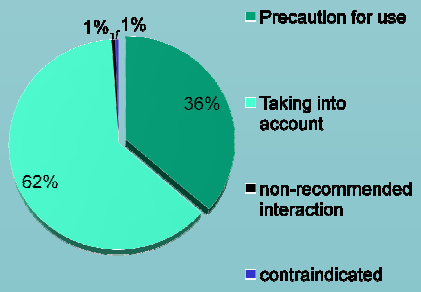
## MATERIAL & METHODS

A retrospective study was performed on 1067 daily drug prescriptions of 38 patients (61% men and 39% women) treated with hematopoietic stem cells who were hospitalized during 2012 in the haematology and transplants service.

## RESULTS & DISCUSSION

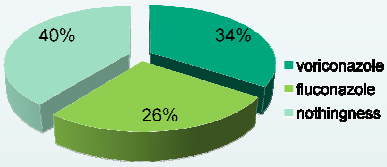
❖The average number of drugs per prescription was 5 drugs, with a minimum of 3 and a maximum of 17.
❖The average number of interactions was 2 per prescription, ranging from 2 to 18 interactions.

**Drug Interactions**

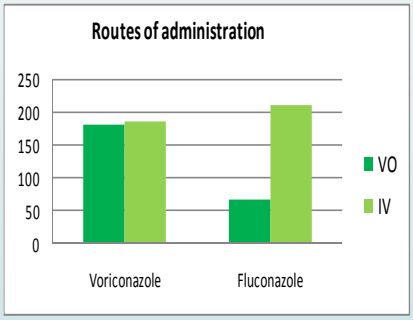



❖ 60% of prescriptions collected contained an azole antifungal.
❖ 74% of prescriptions containing an antifungal azole had at least one interaction with this antifungal drug.

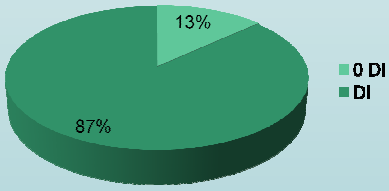
**Azole prescribed**




**Routes of administration**




**Drug Interactions (DI)**




❖In one patient (or 2.63%), an association was noted contraindicated. This interaction involved the co-prescription of voriconazole and rifampicin (an enzyme inducer responsible for the decrease in the concentration of voriconazole in the blood of more than 95%): the peak and the residual rate of Voriconazole was below the threshold detection.

❖Also a non-recommended interaction was observed in another patient between voriconazole and sirolimus.

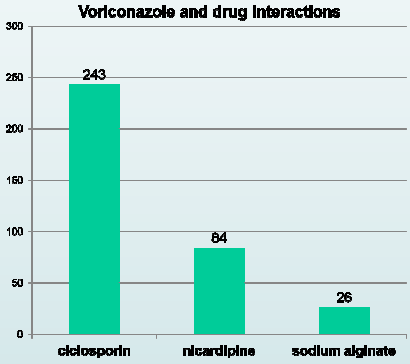
❖The majority of interactions were classed as precautions for use (3rd level of risk):

•Voriconazole : ciclosporin, nicardipine and sodium alginate
•Fluconazole: ciclosporin, acenocoumarol and sodium alginate

❖We assessed the effects of azole antifungals administration on the concentration of calcineurin inhibitors, namely ciclosporin, in the recipients of hematopoietic stem cell transplants and revealed a notably wide inter-individual variability in the magnitude of the drug interaction.

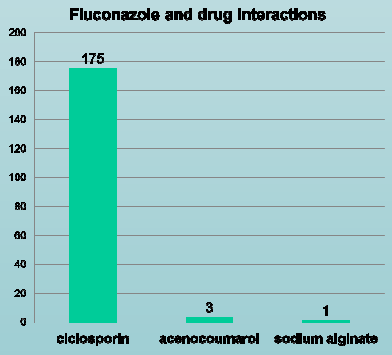
❖Azole, by their enzymatic inhibition of CYP3A4, increase plasma concentrations of ciclosporin and thus the risk of nephrotoxicity: the concentration of ciclosporin increased by 60% on average.
❖There is a risk of hypotension when association between voriconazole and nicardipine.

**Voriconazole and drug interactions**




❖Fluconazole induced increase in INR value (1.23 to3, 42) which can cause a bleeding risk.
❖Sodium alginate decreases absorption of the antifungal administered simultaneously. To avoid this risk, sodium alginate must be taken away at least two hours of the azole antifungal.

**Fluconazole and drug interactions**




## CONCLUSION

❖Polypharmacy in patients treated with hematopoietic stem cells requires a certain level of vigilance to prevent the adverse effects and the occurrence of iatrogenic events.

❖Understanding the mechanisms of drug interactions allows clinicians to avoid certain interactions and to develop a possible strategy to minimise iatrogenic events. This is facilitated by the establishment of a computerised system in the service to prevent iatrogenic drug and ensure patient safety.