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Case Report

No drug-drug interaction between tezacaftor-ivacaftor and clofazimine: A case report

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ABSTRACT

In this case report the potential drug-drug interaction between cytochrome P450 (CYP) 3A4 substrates tezacaftor-ivacaftor and CYP3A4/5 inhibitor clofazimine is investigated in a patient with cystic fibrosis. Exposure to tezacaftor, ivacaftor and its metabolites was assessed by determination of the area under the plasma concentration versus time curve ($AUC_{0\text{-}24\ h}$ for tezacaftor and $AUC_{0\text{-}12\ h}$ for ivacaftor and its metabolite) before start of clofazimine and 8 and 115 days after start of clofazimine. The AUC-ratio at day 115 and pre-start was 1.09, 1.45 and 0.747 for ivacaftor, hydroxymethyl ivacaftor and tezacaftor, respectively. This case suggests that clofazimine exhibits no clinically relevant increase in exposure to tezacaftor and ivacaftor.

1. Introduction

Clofazimine is an antimycobacterial drug which is used for the treatment of non-tuberculous mycobacterium (NTM). In August 2019 clofazimine got a positive opinion for orphan designation for the treatment of NTM lung disease by the European Medicines Agency. *In vitro* clofazimine has been characterized as an inhibitor of cytochrome P450 (CYP)3A4/5, 2C8 and 2D6. In previously performed static and physiologically based pharmacokinetic (PBPK) modeling prediction studies an interaction between clofazimine and midazolam, a probe substrate for CYP3A4, was characterized. Midazolam area under the plasma concentration versus time curve (AUC) was increased with a factor 5.59 and 2.69 for static and PBPK modeling, respectively, when coadministered with 100 mg clofazimine [1]. At the moment of writing this report there are limited *in vivo* data available describing the interaction profile of clofazimine [2].

Tezacaftor-ivacaftor, a combination drug for the treatment of CF, are both substrates of CYP3A4 and CYP3A5. In the prescribing information of tezacaftor-ivacaftor dose reductions are recommended when patients are starting with a moderate to strong inhibitor of CYP3A4 [3]. Based on these data an increase in AUC of tezacaftor-ivacaftor after initiation with clofazimine was expected.

In this case study the interaction between tezacaftor-ivacaftor and clofazimine was evaluated in a patient with CF.

2. Case report

A 16-year-old girl with cystic fibrosis (CF) was initiated on clofazimine 100 mg once daily for approximately one year, as part of a quadruple therapy regimen including also ethambutol, azithromycin and amikacin to treat NTM. As chronic CF medication tezacaftor-ivacaftor was used in a regular dose of 100-150 mg, respectively, once daily in the morning, combined with ivacaftor 150 mg monotherapy once daily in the evening. Her medication profile was thoroughly screened before start of the NTM medication on drug-drug interactions. Since there were no *in vivo* data available describing the potential drug-drug interaction between clofazimine and CYP3A4 substrates, no immediate dose adjustments in tezacaftor-ivacaftor were made at the start of clofazimine. The patient was admitted to the hospital before the initiation of her NTM treatment. Blood samples were taken just before administration of tezacaftor-ivacaftor (time = 0) and 2, 4 and 6 h after administration. Similar PK curves were obtained at 8 and 115 days after start of clofazimine. Ivacaftor, hydroxymethyl ivacaftor, ivacaftor carboxylate and tezacaftor were quantified in plasma with a validated liquid chromatography-tandem mass spectrometry method

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Table 1
Area under the curve (AUC) of ivacaftor, hydroxymethyl ivacaftor, ivacaftor carboxylate and tezacaftor before start of clofazimine (day 0), and at day 8 and day 115 after start of clofazimine.

	Day 0 AUC^ (mg*h/L)	Day 8 AUC^ (mg*h/L)	AUC-ratio *	Day 115 AUC^ (mg*h/L)	AUC-ratio *
Ivacaftor	11.1	16.2	1.46	12.2	1.09
Hydroxymethyl ivacaftor	19.6	33.1	1.69	28.5	1.45
Ivacaftor carboxylate #	8.56	14.4	1.68	22.3	2.61
Tezacaftor	75.4	75.5	1.00	56.3	0.747

*AUC-ratio = $AUC_{\text{after start clofazimine (day 8 or 115)}}/AUC_{\text{before start clofazimine (day 0)}}$
^$AUC_{0\text{-}24h}$ for tezacaftor by a dose of 100 mg once daily, and $AUC_{0\text{-}12h}$ for ivacaftor and its metabolites by a dose of 150 mg twice daily.
ivacaftor carboxylate is a non-active metabolite of ivacaftor

[4]. $AUC_{0\text{-}24h}$ for tezacaftor and $AUC_{0\text{-}12h}$ for ivacaftor were determined by the linear-log trapezoidal method. At day 8, the AUC-ratio (AUC(day 8)/AUC(day 0)) was 1.46, 1.69, 1.68 and 1.00 for ivacaftor, hydroxymethyl ivacaftor, ivacaftor carboxylate and tezacaftor, respectively. The AUC-ratio at day 115 was 1.09, 1.45, 2.61 and 0.747 for ivacaftor, hydroxymethyl ivacaftor, ivacaftor carboxylate and tezacaftor, respectively (Table 1). No tezacaftor-ivacaftor dose adjustments were made based on these results.

3. Discussion

In this case report no clinical significant increase in exposure of tezacaftor-ivacaftor at day 8 and day 115 was seen after the start with clofazimine therapy.

In order to calculate the AUC, blood samples were taken just before administration of tezacaftor-ivacaftor (time = 0) and 2, 4 and 6 h after administration. The maximum plasma concentration (C_{max}) of tezacaftor and ivacaftor are reached after 4 and 6 h, respectively. Steady state plasma concentrations (C_{ss}) of tezacaftor and ivacaftor are reached within 8 days [3]. Inhibition of CYP enzymes is immediate and is normally dependent on the dose of the inhibitory drug. Since clofazimine has a very long elimination half-life of 25 days, C_{ss} is reached after approximately 3-4 months [5]. Therefore, blood samples were not only taken at day 8, but also on day 115 days after start of clofazimine when (higher) steady-state levels are present.

The observed AUCs of ivacaftor and tezacaftor in this patient before start of clofazimine correspond to the AUCs reported in the registration documents. Mean AUC (SD) at C_{ss} in the registration documents are $AUC_{0\text{-}24h}$ 97.1 (35.8) mg•h/L and $AUC_{0\text{-}12h}$ 11.4 (5.5) mg•h/L for tezacaftor and ivacaftor, respectively [3].

Maartens et al. studied the effect of clofazimine on bedaquiline exposure in a group of tuberculosis patients. The difference in exposure of bedaquiline in patients treated with and without clofazimine was -9.1% (90% CI -22.8 to +7.1; p=0.19). This study was however not designed to examine this DDI in particular and the confidence interval of the interaction effect were quite large, thus its clinical relevance was questioned. However, our findings support their results and in this case the patient served as its own control [2].

The difference between midazolam and tezacaftor-ivacaftor is remarkable, since other inhibitors of CYP3A4 do increase its AUC. In the study of Sangana et al. clofazimine was characterized as a moderate to strong inhibitor of CYP3A4 by *in silico* studies, with significant increases in midazolam AUC. However, in the study of Maartens et al. *in vivo* no clear inhibitory effect of clofazimine on bedaquiline exposure was seen. Therefore the CYP3A4 inhibiting potency of clofazimine *in vivo* may be questioned and further research is needed.

The AUC-ratio at day 115 and pre-start was 1.09, 1.45 and 0.747 for ivacaftor, hydroxymethyl ivacaftor and tezacaftor, respectively. These increases are not clinically relevant as registration documents define a moderate or strong inhibitor of CYP3A4 by respective AUC-ratios of 3- and 16-fold [3]. Only ivacaftor carboxylate showed an increase in AUC-ratio of 2.6 at day 115, but this is a pharmacologically non-active metabolite. Therefore, no adjustment in the dose of ivacaftor was made.

The AUC-ratio of ivacaftor metabolites increased after introduction of clofazimine. This was remarkable, since the opposite was expected when inhibiting the metabolism of ivacaftor. This phenomenon can possibly be explained by a lower clearance or inhibited metabolism of the metabolites. On the other hand, the reduction of tezacaftor with an AUC-ratio of 0.747 was also the opposite from expected when inhibiting the metabolism of tezacaftor. This reduction may be the result of a reduced bioavailability and/or an increased clearance.

Small differences were observed between the AUC-ratios at day 8 and 115. These differences are clinically not relevant and can possibly be explained by intra-individual variability in pharmacokinetics of tezacaftor-ivacaftor. For instance, both compounds are both poorly soluble, lipophilic molecules and administration with fat-containing food increases their AUC [3].

Limitations of this case report are that the patient was not genotyped for CYP3A4, however the clinical relevance of this is questioned, since the patient served as its own control. Secondly, food intake on the days of sampling was not controlled. The patient was advised to administer tezacaftor-ivacaftor with fat containing food as stated in the prescribing information [3], but on these days no restrictions were made compared to usual days. In summary, in this case report the drug-drug interaction between tezacaftor-ivacaftor and clofazimine was examined in a patient with CF treated for NTM. No clinical significant increase in exposure of tezacaftor-ivacaftor was seen after introduction of clofazimine, and no adjustments in the dose of tezacaftor-ivacaftor were made.

Patients perspective

I am a girl aged seventeen and live in the Netherlands in a village near the sea. When I was five years old I was diagnosed with Cystic Fibrosis. Last year I started the treatment with clofazimine for my NTM. I had been using tezacaftor-ivacaftor for a while and I did not have any side effects. Before the start and during the treatment with clofazimine the physicians checked the concentrations of tezacaftor-ivacaftor. For this, blood had to be taken several times, luckily I am used to this. After the start of the treatment with clofazimine I still almost had no side effects. The only side effect I had is that I get a sunburn really fast, but this also comes with a nice tan. After using clofazimine for over a year I got rid of my NTM, and I am very happy with that. I think it is special that I am the first person in whom this combination has been researched as far as my practitioners know, and hopefully other practitioners can learn something from this.

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.

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