clinical cases DDIs

Date of report 04 Apr 2023

Reported case interaction between **Bictegravir** and **Clarithromycin**

Drugs suspected to be involved in the DDI

Victim
Bictegravir

Daily Dose
50 (mg)

Dose adjustment performed
No

Administration Route
Oral

Start date
Dec. 1, 2020

End date
Ongoing

Perpetrator
Clarithromycin

Daily Dose
100 (mg)

Dose adjustment performed
No

Administration Route
Oral

Start date
Nov. 20, 2021

End date
Ongoing

Complete list of drugs taken by the patient

Antiretroviral treatment

Bictegravir/Emtricitabine/Tenofovir-AF

Complete list of all comedications taken by the patient, included that involved in the DDI

Clarithromycin, Clofazimine, Bedaquiline, TMP/SMX, Gancyclovir

Clinical case description

Gender

Male

Age

37

eGFR (mL/min)

60-30

Liver function impairment

No

Description

37-year-old patient, originally from sub-Sarahan Africa. HIV infection was diagnosed many years ago, but untreated. Moderate chronic renal insufficiency due to kidney malacoplakia. Admitted to our center in November 2020 for fever, weight loss and diarrhea with a final diagnosis of disseminated Mycobacterium avium intracellulare and Mycobaterium simiae infection (both confirmed with cultures from several different sterile sites). Additionally, also confirmed disseminated CMV infection (colitis and retinitis) that was treated with gancyclovir followed by secondary prophylaxis with valgancyclovir. CD4 cell count at this time was 1 (0.5%) cells/mm^3 and HIV plasma viral load (pVL) was 2,260,000 copies/mL.
He started treatment (according to resistance profile of both mycobacteria) with bedaquiline, clofazimine and

clarythromycin, and with BIC/FTC/TAF for HIV infection within two weeks of mycobacteria treatment. Although Prot/Creat urine ratio was abnormal since the beginning, it did not worsened after ART initation.
Clinical evolution was slowly favourable. In December 2022 CD4 count was 99 (11%) cells/mm^3 and pVL was undetectable . He continued ART with BIC/FTC/TAF and also triple therapy for both mycobacteria, with good tolerance and no remarkable side effects. No toxicity due to bictegravir or TAF was observed.
Clarithromycin is a strong inhibitor of CYP3A4 and P-gp and is predicted to increase bictegravir concentrations but to a modest extent. Clofazimine is also moderate inhibitor of CYP3A4 and may increase bictegravir concentrations, but also to a modest extent. Coadministration of clarithromycin and clofazimine in this patient may have potentially increased bictegravir concentrations (without options for dose adjustment). Considering each drug individually, this increase is unlikely to be clinically significant since data from phase 2 and phase 3 studies (48 weeks of treatment), showed a good safety profile with up to a 2.4 fold increase in bictegravir AUC. However. the additive effect of these two drugs on bictegravir concentrations is unknown.
In addition, tenofovir alafenamide (the prodrug of tenofovir) is a substrate of P-gp, and inhibitors of P-gp such as clarithromycin are expected to increase the absorption of tenofovir alafenamide and thereby to increase the systemic exposure to tenofovir. The recommended daily dose of 10 mg tenofovir alafenamide with P-gp inhibitors is not possible with Bictegravir, which is only available as a fixed dose combination containing 25 mg tenofovir alafenamide. However, the patient maintained stable creatinine levels over the duration of the therapy (ongoing due to incomplete immunological recovery).

Clinical Outcome

No unwanted outcome

Editorial Comment

Clarithromycin is a strong inhibitor of CYP3A4 and P-gp and therefore, it is predicted to increase bictegravir concentrations. Clofazimine is also moderate inhibitor of CYP3A4 and may increase bictegravir concentrations. In addition, tenofovir alafenamide is a substrate of P-gp and increased absorption and, subsequently,higher plasma concentrations are expected when it is coadministered with P-gp inhibitors such as clarithromycin. Therefore, the recommended dose of tenofovir alafenamide is 10 mg when a strong inhibitor of P-gp is concomitantly used.
Bictegravir is available is only available as a fixed dose combination containing 25 mg tenofovir alafenamide.
Despite bictegravir and tenofovir alafenamide has shown a good safety profile, the fixed dose combination BIC/FTC/TAF should be used with caution when it is administered concomitantly with strong inhibitors of CYP3A4 and P-gp.
Kidney function and tubular damage markers should be monitored in high risk patients or other ART options should be also considered.

University of Liverpool Recommendation

■ Potential interaction - may require close monitoring, alteration of drug dosage or timing of administration

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