**Plasma Venetoclax Concentrations in Patients with Acute Myeloid Leukemia (AML) Treated with Cytochrome P450 3A4 (CYP3A4) Inhibitors**

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**Background.** Venetoclax (VEN), used in patients with acute myeloid leukemia (AML), is primarily metabolized by cytochrome P450 3A4 (CYP3A4). Patients with AML simultaneously administered CYP3A4 inhibitors require a more appropriate management of drug-drug interactions (DDIs). Here, we present the case of two patients with AML: a 54-year-old male (Case 1) and a 22-year-old female (Case 2), who were administered VEN in conjunction with CYP3A4 inhibitors, including posaconazole (PSCZ), cyclosporine A (CyA), or danazol (DA). Additionally, *in vitro* assays were conducted for reverse translational studies to analyze the extent of CYP3A4 inhibition.

**Methods.** Both cases were administrated VEN with CYP3A4 inhibitors according to VENECLEXTA® prescribing information. Residual samples at each point were used to quantify plasma VEN concentrations through liquid chromatography-mass spectrometry (LC-MS/MS). Quantification of plasma PSCZ concentrations was performed through LC-MS/MS. Additionally, the extent of CYP3A4 inhibition was evaluated through the midazolam 1′-hydroxylation assay and VEN disappearance assay using recombinant CYP3A4 protein *in vitro*.

**Results.** In Case 1, the co-administration with PSCZ resulted in plasma VEN concentrations consistently regulated. However, altering VEN dosage concurrently with the discontinuation of PSCZ at the same time may lead to an increase in plasma VEN concentration. In Case 2, co-administration with two moderate CYP3A4 inhibitors (CyA and DA) resulted in plasma VEN concentrations elevated approximately seven-fold (> 14,000 ng/mL) compared to previously reported levels. The increase in concentration due to the inhibitory effects of the two CYP3A4 inhibitors was also investigated. Plasma VEN concentrations were relatively elevated at the time of PSCZ discontinuation in Case 1, suggesting that the adjustment of VEN dosage might be better conducted by considering remaining PSCZ in patients. In contrast, CYP3A4 inhibition caused by two moderate inhibitors should be considered for more appropriate plasma VEN concentration management based on Case 2 and the results of the *in vitro* experiments.

**Conclusion.** While prioritizing therapeutic efficacy for patients is one of the paramount factors, it is also imperative to conduct frequent plasma VEN concentration monitoring and make necessary dosage adjustments in response to DDIs. Such measures would be helpful for optimizing chemotherapy regimens and ensuring patient safety.

**Keywords.** CYP3A4, DDIs, Venetoclax.