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### ► To cite this version:

Sébastien Lalanne, Caroline Jezequel, Camille Tron, Marie-Clémence Verdier, Marion Mercerolle, et al.. TDM-guided Crushed Sofosbuvir-velpatasvir Treatment: A case study. Therapeutic Drug Monitoring, 2020, 42 (2), pp.163-164. 10.1097/FTD.0000000000000718 . hal-02440785

**HAL Id: hal-02440785**

**<https://univ-rennes.hal.science/hal-02440785>**

Submitted on 12 Feb 2020

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## TDM-guided Crushed Sofosbuvir-velpatasvir Treatment: A case study

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Disclosure: The authors report no conflicts of interest related to this work.

## Abstract

Herein, the authors report the case of a patient diagnosed with hepatitis C virus who was treated with sofosbuvir-velpatasvir (400/100 mg). As the patient was unable to swallow whole tablets, therapeutic drug monitoring was performed to evaluate the effect of crushing sofosbuvir-velpatasvir tablets on drug absorption and global exposure.

Keywords: Sofosbuvir, velpatasvir, crushing, pharmacokinetics, exposure

## CLINICIAN

The patient was a 70-year-old woman with a history of rectal cancer in 2009 and a right oropharyngectomy owing to carcinoma in 2016. She had been a heavy smoker with excessive alcohol intake for several years. A CT-scan performed in February 2019 as part of the oropharyngeal carcinoma follow-up revealed 2 liver tumors (20 mm each) in the right lobe of the liver. Liver enzymes were moderately increased: aspartate aminotransferase (AST) = 87 IU/L (N < 31); alanine aminotransferase (ALT) = 67 IU/L (N < 34);  $\gamma$ -glutamyltransferase (GGT) = 152 IU/L (N < 38). Albumin (42 g/L), total bilirubin (6  $\mu$ mol/L), and prothrombin index were normal. Alpha-fetoprotein was dramatically increased up to 14,207 g/L (N < 10), and the biopsy of the tumor and non-tumorous liver confirmed the diagnosis of bifocal hepatocellular carcinoma (HCC) developed on a non-cirrhotic METAVIR F3 fibrotic liver.[1] Hepatitis B and human immunodeficiency virus serology were negative. Hepatitis C virus (HCV) serology was positive, and active replication was confirmed by HCV RNA detection with a high viral load of 6.8 log IU/mL and genotype 1b virus infection. She underwent satisfactory surgical resection of the HCC tumors in May 2019.

The multidisciplinary team evaluating the HCV cases in the institution proposed a treatment with a direct-acting antiviral (DAA) agent comprising glecaprevir and pibrentasvir (Maviret, AbbVie) [2] for 8 weeks. This combination was selected for its high efficacy and short treatment duration. However, owing to previous oropharyngectomy, the patient was not able to swallow tablets.

### **TDM CONSULTANT**

Glecaprevir–pibrentasvir is a fixed-dose combination tablet indicated in the treatment of HCV with a pangenotypic activity at the dosage of 300/120 mg per day (3 tablets of 100/40 mg simultaneously). The drug is a combination of a NS5A (a protein responsible for regulation of the viral replicative complex and involved in assembly and release of viral particles) inhibitor (pibrentasvir) and a NS3/4A protease inhibitor (glecaprevir), which, as clearly stated in the summary of product characteristics (SmPC), should be taken with food and should not be chewed or crushed. The drug is formulated as a bilayer tablet; therefore, crushing can lead to unintended variations in bioavailability with a decrease in area under the curve (AUC) of 27–61% for glecaprevir and an increase in AUC of 21–83% for pibrentasvir compared to the exposure from whole tablets.[2,3] No other formulation such as an oral solution or dispersible tablet is available; therefore, the drug cannot be given to the patient.

However, no clear recommendation is available for sofosbuvir–velpatasvir (Epclusa), an RNA-dependent RNA polymerase NS5B and NS5A inhibitor with pangenotypic anti-HCV activity. Indeed, SmPC does not recommend crushing these tablets because of their bitter taste, but there is a lack of information about the effect of crushing on sofosbuvir–velpatasvir pharmacokinetics. Velpatasvir is also highly sensitive to the acidic stomach environment, as underlined by the decrease in drug exposure ranging from 26% to 60% when given with

omeprazole,[4–6] and influenced by food with an increase in AUC of 20% to 30% with a high and moderate fat meal, respectively.[7] Moreover, taking the drug with an acidic beverage may enhance velpatasvir absorption.[5] We then suggested administering crushed sofosbuvir–velpatasvir with an acidic beverage during a meal and conducting therapeutic drug monitoring (TDM) of sofosbuvir and velpatasvir by monitoring peak on the first day and global exposure of the drugs by measuring steady-state trough plasma drug concentrations ( $C_{ss}$ ).

## **CLINICIAN**

Sofosbuvir–velpatasvir treatment for 12 weeks was approved by the multidisciplinary team, according to French and European guidelines for the management of patients with acute and chronic HCV infections.[8,9] In addition, TDM was planned to assess the absorption of the drugs. Blood samples were collected on the first day of treatment before DAA administration (trough concentration ( $C_{min}$ ) and 2 (C2), 3 (C3), and 4 (C4) hours after the first DAA administration. Additional trough blood samples measured at steady-state ( $C_{ss}$ ) were collected 1 week and 10 weeks after commencement of treatment.

## **TDM CONSULTANT**

Sofosbuvir and velpatasvir peak ( $C_{max}$ ) and  $C_{ss}$  are well documented, with sofosbuvir having a  $C_{max}$  of  $511 \pm 174$  ng/mL [10] and a rapid elimination (half-life elimination: 30 min), leading to a trough concentration generally below the limit of quantification of the analytical method, and velpatasvir having  $C_{max}$  and  $C_{ss}$  of  $575 \pm 213$  and  $42 \pm 28$  ng/mL respectively.[7,11] Therefore, these parameters could be easily compared to the value measured in the patient. Drug levels were determined using a liquid chromatography-tandem

mass spectrometry method validated according to the European Medicines Agency guidelines.[12]  $C_{\min}$ ,  $C_2$ ,  $C_3$ , and  $C_4$  for sofosbuvir were <20, 1,544, 1,497, and 642 ng/mL, respectively, while for velpatasvir, these were <20, 285, 966, and 1,244 ng/mL, respectively.  $C_{ss}$  at day 7 and week 10 were <20 ng/mL for sofosbuvir and 116 and 107 ng/mL for velpatasvir.

The time to reach maximal concentration ( $t_{\max}$ ) was 1 and 3 h for sofosbuvir and velpatasvir respectively.[7,11,13] The results of sofosbuvir and velpatasvir TDM were consistent with an increase in the absorption of both drugs in this patient after crushing the tablet. Sofosbuvir is rapidly metabolized, and its  $C_{ss}$  values were consistent with its pharmacokinetic parameters.[14] More importantly, velpatasvir  $C_{ss}$  values were in favor of a correct exposure to the drug ( $C_{ss}$  range 14–70 ng/mL; mean reported concentration  $\pm$  standard deviation).[11]

## CLINICIAN

The drugs seemed to be very well resorbed. When compared with usual  $C_{\max}$ , their concentrations were in favor of an increase in sofosbuvir and velpatasvir absorption when crushed. Velpatasvir  $C_{ss}$  measurements appeared to be related to a high drug exposure without any accumulation of the compound as confirmed by the very similar  $C_{ss}$  reported at week 1 and week 10. After completion of sofosbuvir–velpatasvir combination treatment, the patient reported no treatment-related adverse events. Liver parameters improved: AST, 13 IU/L; ALT, 30 IU/L; GGT, 20 IU/L; total bilirubin, 6  $\mu$ mol/L; and albumin, 47 g/L. HCV viral load decreased rapidly, became undetectable after 4 weeks of treatment, and remained undetectable after 12 weeks of treatment.

## TDM CONSULTANT

In conclusion, this report describes the first case of a successful HCV treatment in a treatment-naïve patient by using crushed sofosbuvir–velpatasvir tablets. TDM showed that, when taken with food and an acidic beverage, the absorption of both drugs increased. As velpatasvir is a low solubility drug, particularly in gastric pH above 4.5, crushing the tablet may enhance the drug solubility. TDM of velpatasvir trough  $C_{ss}$  also allowed the verification of treatment exposure during the treatment period, thereby ensuring its efficacy.

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