# Cardiac toxicity associated with pharmacokinetic drug–drug interaction between crizotinib and sofosbuvir/velpatasvir: a case report

Anthia Monribot[1], Olivier Huillard[2], Nihel Khoudour[3], Laure-Hélène Préta[1], Benoit Blanchet[3], Laure Cabanes[1], Rui Batista[1], Nicolas Pallet[4], Laurent Chouchana[5], François Goldwasser[2], Philippe Sogni[6], and Audrey Thomas-Schoemann[2]

[1]Cochin Hospital, AP-HP, University of Paris
[2]Cochin Hospital, AP-HP, Université de Paris
[3]Cochin Hospital, AP-HP; CARPEM, Paris, France
[4]Hôpital Européen Georges Pompidou, AP-HP, University of Paris Descartes, INSERM U.1147
[5]Cochin Hospital, AP-HP, University of Paris,
[6]Cochin Hospital, AP-HP, Paris, France; University of Paris Descartes, Sorbonne Paris Cité

July 13, 2022

**Abstract**

This case report describes of a pharmacokinetic drug–drug interaction between crizotinib, a tyrosine kinase inhibitor, and sofosbuvir/velpatasvir, a direct-acting antiviral drug, leading to cardiac toxicity. A 75-year-old man, with no cardiovascular history but a diagnosis of metastatic non-small cell lung cancer with MET exon-14 deletion and hepatitis C virus infection genotype 1A, received both crizotinib and sofosbuvir/velpatasvir. Crizotinib was well tolerated, but 1 week after sofosbuvir/velpatasvir initiation, the patient experienced bilateral lower-limb edema and class III NYHA dyspnea. We assumed that increased exposure to crizotinib could account for this cardiac toxicity. Drug causality was probable according to the Naranjo scale. We hypothesized a reciprocal interaction between crizotinib and velpatasvir, mediated by both cytochrome 3A4 (CYP3A4) and P-glycoprotein (P-gp). Clinicians should be aware of the risk of drug–drug interactions between direct-acting antiviral agents that inhibit CYP3A4 (glecaprevir) and/or P-gp (voxilaprevir) and anticancer tyrosine kinase inhibitors that are mostly CYP3A4 and/or P-gp substrates (gefitinib, afatinib, erlotinib, crizotinib, ceritinib, lorlatinib, brigatinib, capmatinib etc.).

## Introduction

The prevalence of chronic hepatitis C virus (HCV) infection in patients with cancer ranges from 1.5% to 32% (1). The availability of highly effective direct-acting antiviral (DAA) drugs, such as sofosbuvir/velpatasvir, represents a significant progress for patients with chronic HCV infection. However, the potential for drug–drug interactions (DDIs) is major with DAA drugs, especially in patients with chronic conditions such as cancer (2).

Crizotinib is a tyrosine kinase inhibitor (TKI) targeting anaplastic lymphoma kinase (ALK), ROS1, and mesenchymal–epithelial transition (MET) prescribed for non-small cell lung cancer (NSCLC) (3). This case report highlights a pharmacokinetic DDI between crizotinib and sofosbuvir/velpatasvir associated with cardiac toxicity.

## Case report

A 75-year-old man, with no cardiovascular history and a Eastern Cooperative Oncology Group Performance Status score of 1, had a diagnosis of metastatic, synchronous NSCLC with MET exon-14 deletion. Thoracic-abdominal-pelvic computed tomography (CT) revealed pulmonary and renal metastases. Crizotinib was initiated at the recommended dose (250 mg twice a day) in March (Figure 1) (3). The diagnosis of HCV infection genotype 1A was confirmed in April (viral load 1.08 x$10^6$ IU/mL). Aspartate aminotransferase, gamma glutamyl transferase, alkaline phosphatase, bilirubin, and albumin levels; prothrombin ratio; and platelet count were within normal ranges; alanine aminotransferase level was 1.3 the upper limit of normal, and creatinine level was 111.5 µmol/L. Liver stiffness (Fibroscan) was 13.5 kPa, suggesting advanced liver disease. Hepatic steatosis was identified by ultrasonography. Therefore, after the first tumor-response evaluation showing partial tumor response and in the context of a fair cancer prognosis associated with advanced liver disease, sofosbuvir/velpatasvir (400 mg/100 mg, once daily), was started in June for 12 weeks (Figure 1) (4). The official Summary of Product Characteristics contained no information about a potential pharmacokinetic DDI (5).

Crizotinib was well tolerated, but 1 week after sofosbuvir/velpatasvir initiation, the patient experienced bilateral lower-limb edema and class III New York Heart Association dyspnea (NYHA). Electrocardiography revealed grade 2 sinus bradycardia with normal PR interval, which is a reported toxic effect of crizotinib, with heart rate decreasing from 69 to 50 beats per min before and after sofosbuvir/velpatasvir initiation, respectively. Serum electrolyte levels were normal. Transthoracic echocardiography and chest CT scan revealed no new anomalies. After a multidisciplinary consultation (oncologist, cardiologist, pharmacist), crizotinib causality was deemed possible and was withdrawn (3,6). Plasma drug monitoring showed a 1.6-fold increase in plasma trough concentration ($C_{min}$) of crizotinib since DAA initiation and confirmed crizotinib plasma overexposure (7). In mid-July, the symptoms had resolved. Crizotinib was resumed at 200 mg twice a day and was well tolerated (Figure 1), with heart rate 62 beats per minute. Two plasma drug monitorings, performed in August and September, revealed velpatasvir plasma overexposure, $C_{min}$ 1255 and 1752 ng/mL, respectively (mean target $C_{min}$ 42 ±28 ng/mL) (8). The plasma $C_{min}$ for sofosbuvir and its major metabolite SOF-007 measured after re-initiation of crizotinib was within the normal range.

One month after sofosbuvir/velpatasvir discontinuation, crizotinib was increased to 250 mg twice a day with no toxic effects. The patient achieved sustained virologic response at 12 weeks after treatment. Cancer progression was documented 8 months after the initiation of crizotinib.

## Discussion

We report a DDI between crizotinib and sofosbuvir/velpatasvir associated with severe cardiac toxic effects leading to crizotinib discontinuation. Overexposure to crizotinib could have accounted for these effects, which was confirmed by the clinical improvement with crizotinib dose reduction (3). Drug causality was probable according to the Naranjo scale (score = 8) (9). Factors that could explain the variability in crizotinib overexposure could be the patient being slightly non-compliant (Girerd score) and pharmacogenetic analyses showing no cytochrome 3A5 (CYP3A5) and CYP3A4 functional polymorphism (10,11). The pharmacokinetics mechanism of this DDI may have been a reciprocal interaction between crizotinib and velpatasvir (Figure 2). *C* rizotinib is a CYP3A4/5 and P-glycoprotein (P-gp) moderate inhibitor *in vitro* and could lead to a supratherapeutic plasma level of velpatasvir, a substrate of CYP3A4 and P-gp (Table I) (3,12). Furthermore, velpatasvir is a P-gp weak inhibitor (Table I) (12). Velpatasvir may have increased the plasma concentration of crizotinib, a P-gp substrate (Table I) (3). We tested this hypothesis with a disproportionality analysis using VigiBase (the World Health Organization global database of individual case safety reports (*https://www.who-umc.org/vigibase/vigibase/)*) and observed a significant association between the concomitant use of crizotinib and P-gp inhibitors and cardiac arrhythmia (odds ratio of reporting 2.5, 95% confidence interval 1.2-5.2) as compared with the use of crizotinib without a P-gp inhibitor (13). This pharmacovigilance statistical approach supports a DDI between crizotinib and P-gp inhibitors resulting in higher cardiac adverse-drug-reaction reporting.

## Conclusions

DDIs may occur between DAA drugs and TKIs and may lead to severe toxic effects. Indeed, DAA drugs can inhibit CYP3A4 agents (glecaprevir, grazoprevir) and/or P-gp agents (voxilaprevir, ledipasvir) and interact with anticancer TKIs that are mostly CYP3A4 and/or P-gp substrates (gefitinib, afatinib, erlotinib, crizotinib, ceritinib, lorlatinib, brigatinib, capmatinib etc.) (14,15). Clinicians should be aware of the major consequences of DDIs and the importance of plasma drug monitoring in cancer patients receiving treatment for HCV.

**Table legends**

**Table I. Pharmacokinetic characteristics of velpatasvir, sofosbuvir and crizotinib** (3,8,12)

AUC: area under the plasma concentration-time curve from 0 to 24 hr; P-gp,' P-glycoprotein; BCRP, breast cancer resistance protein; OATP1B,' organic anion transporting polypeptide; CYP3A4/5, cytochrome P450

**Figure legends**

**Fig 1. Trough plasma concentration of crizotinib (ng/mL) during treatment from April 1 to November 6 in a 75-year-old man.**

- - - Effective crizotinib concentration, threshold value proposed for efficacy (233ng/mL) (7) ;

Trough plasma concentration of crizotinib during treatment.

**Fig 2. The pharmacokinetic mechanism of the drug–drug interaction between crizotinib and sofosbuvir/velpatasvir.**

**Acknowledgments**

This case has been reported to the French pharmacovigilance system (no. PV20190502). The information in VigiBase comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information does not represent the opinion of the Uppsala Monitoring Centre or WHO and only reflects the authors' opinion.

**Informed Consent**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**Conflict of interest**

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

**References**

1. Torres HA, Shigle TL, Hammoudi N, Link JT, Samaniego F, Kaseb A, et al. The oncologic burden of hepatitis C virus infection: A clinical perspective. CA: a cancer journal for clinicians. 2017;67(5):411–31.

2. Garrison KL, German P, Mogalian E, Mathias A. The Drug-Drug Interaction Potential of Antiviral Agents for the Treatment of Chronic Hepatitis C Infection. Drug Metabolism and Disposition. 2018;46(8):1212–25.

3. Hamilton G, Rath B, Burghuber O. Pharmacokinetics of crizotinib in NSCLC patients. Expert Opinion on Drug Metabolism & Toxicology. 2015;11(5):835–42.

4. Drilon A, Clark JW, Weiss J, Ou S-HI, Camidge DR, Solomon BJ, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. Nature Medicine. 2020;26(1):47–51.

5. Pfizer. Xalkori (crizotinib) 250 mg, hard capsules, Summary of product characteristics (SmPC). Pfizer Europe MA EEIG, Belgium (2012 rev 23/10/2018).

6. Tartarone A, Gallucci G, Lazzari C, Lerose R, Lombardi L, Aieta M. Crizotinib-induced cardiotoxicity: the importance of a proactive monitoring and management. Future Oncology. 2015;11(14):2043–8.

7. Yu H, Steeghs N, Nijenhuis CM, Schellens JHM, Beijnen JH, Huitema ADR. Practical Guidelines for Therapeutic Drug Monitoring of Anticancer Tyrosine Kinase Inhibitors: Focus on the Pharmacokinetic Targets. Clinical Pharmacokinetics. 2014;53(4):305–25.

8. Smolders EJ, Jansen AME, ter Horst PGJ, Rockstroh J, Back DJ, Burger DM. Viral Hepatitis C Therapy: Pharmacokinetic and Pharmacodynamic Considerations: A 2019 Update. Clin Pharmacokinet. 2019 Oct;58(10):1237–63.

9. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology and Therapeutics. 1981;30(2):239–45.

10. Hodges LM, Markova SM, Chinn LW, Gow JM, Kroetz DL, Klein TE, et al. Very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein). Pharmacogenetics and Genomics. 2011;21(3):152–61.

11. Girerd X, Hanon O, Anagnostopoulos K, Ciupek C, Mourad JJ, Consoli S. Assessment of antihypertensive compliance using a self-administered questionnaire: development and use in a hypertension clinic. Presse Med. 2001 Jun 16;30(21):1044–8.

12. Mogalian E, German P, Kearney BP, Yang CY, Brainard D, McNally J, et al. Use of Multiple Probes to Assess Transporter- and Cytochrome P450-Mediated Drug–Drug Interaction Potential of the Pangenotypic HCV NS5A Inhibitor Velpatasvir. Clinical Pharmacokinetics. 2016;55(5):605–13.

13. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiology and Drug Safety. 2004;13(8):519–23.

14. Mir O, Blanchet B, Goldwasser F. Drug-Induced Effects on Erlotinib Metabolism. New England Journal of Medicine. 2011;365(4):379–80.

15. Hong J, Wright RC, Partovi N, Yoshida EM, Hussaini T. Review of Clinically Relevant Drug Interactions with Next Generation Hepatitis C Direct-acting Antiviral Agents. Journal of Clinical and Translational Hepatology. 2020 Sep 28;8(3):1–14.

**Hosted file**

`Figure_1_legends .docx` available at https://authorea.com/users/494905/articles/576810-cardiac-toxicity-associated-with-pharmacokinetic-drug-drug-interaction-between-crizotinib-and-sofosbuvir-velpatasvir-a-case-report

**Hosted file**

`Figure_2_legends.docx` available at https://authorea.com/users/494905/articles/576810-cardiac-toxicity-associated-with-pharmacokinetic-drug-drug-interaction-between-crizotinib-and-sofosbuvir-velpatasvir-a-case-report

**Hosted file**

`Table_I_legends .docx` available at https://authorea.com/users/494905/articles/576810-cardiac-toxicity-associated-with-pharmacokinetic-drug-drug-interaction-between-crizotinib-and-sofosbuvir-velpatasvir-a-case-report