

Manuscript: “HCV cure after DAA-related drug-induced liver injury: case report”

We appreciate and thank the reviewers for their fruitful insights and input regarding our manuscript. We also believe that this case report is of importance due to the growing use of DAAs in HCV.

We present our specific responses to the points raised by the reviewers:

Reviewer 1:

Please, there are not spaces between words in many parts of the manuscript.

Checked and corrected where applicable.

Please, page 4, line 4 – The date should be reviewed.

Date was corrected!

The detailed description of the clinical case becomes relevant, especially in the current context of the DAAs’ use in clinical practice.

The mathematical model is complex and could not be sufficient to explain the data observed in the current study. Can the authors clarify this issue?

The purpose of the mathematical modeling is to suggest possible explanations about the surprising HCV cure after such a short duration of DAA therapy. We show that both of our previously developed models (i.e., the standard biphasic model (Science 1988) and the multiscale model (PNAS 2013)) do not predict cure without assuming a lingering (3-6 weeks after treatment stopped) effect of DAA therapy, which seems unlikely. One potential explanation (among others that are noted in the Discussion section of the main manuscript) for cure after such a short duration of therapy is that the last infectious virus in the extracellular fluid was eradicated before the end of treatment. Indeed, we agree with the reviewer that the available measured viral kinetic data does not distinguish between infectious and non-infectious viruses, therefore further experiments are needed to confirm this concept. To make it clear we added a sentence on Page 7.

- **Reviewer conclusion: Accept but needs minor revision.**

Reviewer 2:

This case report is worth to be published because the history of treating chronic hepatitis C is happening right now, and very few case reports we can find in the literature regarding paritaprevir, ombitasvir, dasabuvir, ritonavir, and ribavirin therapy.

I have a question for authors regarding the Ribavirin dose that they gave: 400 mg twice daily, because in the Viekiera Pak prescribing information the recommended doses are 1000-1200 mg daily.

In elderly lightweight female patients weighing less than 65 kgs we prefer to start with a lower Ribavirin dose - 800 mg/day as per the literature and our experience

Ribavirin dosing in chronic hepatitis C: application of population pharmacokinetic-pharmacodynamic models.

Jen J, et al. Clin Pharmacol Ther. 2002.

The second issue is that the mathematical modeling is very complicated, very sophisticated, but in my opinion does not explain the sustained viral response in this case with very short duration of therapy. This phenomenon is indeed very interesting, I am very sorry that the authors do not have the RNA viral load at the end of treatment.

We agree with the reviewer that due to the lack of data it is not possible to dis/confirm our modeling predictions of why HCV was eradicated after such a short duration of DAA therapy. To address the reviewer's comment (and the other reviewer comment on the subject) we state now on Page 7 that further experimental and modelling efforts are needed to reveal the actual biological/immunological reason of HCV cure after such a short duration of DAA therapy.