Recently, Canini et al. [1] have described for the first time an interesting pharmacokinetic/viral kinetic (PK/VK) model to assess the clinical effectiveness of danoprevir in treating chronic HCV patients in a short-duration treatment with different doses/ regimens of danoprevir lasting for 14 days. Therefore, the conceptual thinking and development of the PK/VK model should be commended because of the immense value such a model would provide in understanding the dosing/ regimen considerations for treating HCV patients as well as on the utility of such models to optimize the therapy on an individual basis.

The intent of the report is not to question the assumptions of the PK/VK model but only to highlight certain key observations that may aid in better understanding of the developed PK/VK model.

a) The cursory examination of the tabulated data on the average effectiveness of danoprevir during the course of the treatment suggested almost equal performance of the PK/VK model versus time varying drug efficacy (VE; viral load) model for the various parameters; it was also confirmed by the rigorous statistical analyses [1]. While this may lead to questioning the true value of a more rigorous PK/VK model relative to that of the VE model; the evaluation of predicted first-phase log decline for both PK/VK and VE models sets apart the two models. With the exception of cohort 2 (100 mg, 3 times daily), all remaining cohorts showed differential values between the two models in the first-phase log decline suggesting that the PK/VK model was more conservative as compared with the VE model. Furthermore, the examination of cohort 5 (300 mg, twice daily non-responder) suggested that the VE model predicted the first-phase log decline which was much higher than that of the PK/VK model. On a speculative note, this may imply that the VE model may be prone to false-positive observations as compared with the PK/VK model. Perhaps, the quantum of first-phase log decline may be an important consideration in managing the treatment of HCV with danoprevir and may be used as a guiding principle to differentiate the responder versus non-responder to the drug therapy.

b) It may be worthwhile to ask the question of whether increasing the frequency of dosing of danoprevir changed the cohort 5 patients from non-responders to being responders.

c) Because the effectiveness of danoprevir therapy is achieved rapidly with a major contribution coming from the first-phase log decline of the viral load after danoprevir dosing, it would have been important to perhaps test the PK/VK model using the first day PK data of danoprevir. Although it is not expected that the combination of the first and last day PK data of danoprevir would drastically change the model as compared with the modelling with first day PK data, such information would have been useful in designing a limited sampling strategy protocol for danoprevir which may include a few PK samples on day 1 of danoprevir dosing in HCV patients.

d) As well articulated by the authors, the problematic area is to decipher the almost flat decline of the viral load in the second phase during the treatment with danoprevir in the majority of the patients regardless of the PK/VK versus VE models. Because of treatment-resistant viral strains still in the system it may be difficult to achieve very high cure rates despite the initial rapid decline of the viral load when the therapy was initiated. Hence, the initial rapid decline phase of the viral load may be a key area for differentiating between the PK/VK versus VE models to understand the robustness of the effectiveness of danoprevir.

In summary, the proposed PK/VK model has clarified the effectiveness of danoprevir in a much more robust manner as compared with VE model alone [1]. Although the VE model appears to serve the purpose as enumerated by the modelling exercise, it may be necessary to input the PK component for a rigorous assessment of the viral load data during danoprevir therapy in chronic HCV patients. It is the opinion of the author that development of a limited sampling
strategy to assess danoprevir PK on day 1 may further aid in fine-tuning the PK/VK model from a clinical utility perspective.

Disclosure statement

The author declares no competing interests.

References


Authors’ reply

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We thank Nuggehally R Srinivas for his interest in our work [1]. The author questioned one of our conclusions regarding the use of a viral kinetic (VK) model with a time varying drug efficacy (VE model) to model the effectiveness of danoprevir in chronically HCV-infected patients. The VE model is a simple phenomenological model for drug effectiveness that can be used in the absence of pharmacokinetic (PK) data. We agree with the author that a model that includes PK information, a PK/VK model, is more informative and should therefore be used preferentially when PK data are available. However, such data are not always available, particularly in large trials where collecting frequent samples for PK analysis is not done routinely.

The VE model has been previously used to study the effects of various treatments for HCV infection [2–4] and in [1] we compared the predictions of the VE model with that of a PK/VK model for different dosing regimes of danoprevir as PK information was available. We showed that on average the VE model performed well, especially after the first day of therapy. However, we agree with the author that the VE and PK/VK predictions can differ substantially immediately after the start of therapy, that is, during the first phase of decline. We found this to be particularly true when danoprevir was administered twice daily (cohorts 1, 3 and 5). Figure 1 shows that the VE model underestimates the first-phase decline for cohort 1 (100 mg twice daily) and over estimates it for cohorts 3 and 5 (200 mg and 300 mg twice daily, respectively). The better performances of the VE model with three times daily dosing, cohorts 2 and 4, than in the twice daily cohorts probably reflects the fact that the drug concentration does not fluctuate as much when danoprevir is more frequently administered.

The author’s point b, concerns cohort 5, in which non-responders to previous pegylated interferon (PEG-IFN)-α/ribavirin (RBV) were treated with 300 mg twice daily of danoprevir. The author asked if increasing the frequency of dosing of danoprevir could change the patients from non-responders to responders. As their status was defined prior to their inclusion in this clinical trial based on their response to PEG-IFN/RBV, this would not be possible.

The author’s point c concerned the possibility of using only the first day of PK data in our analysis. We admit that frequent PK data taken during the first day of treatment and possibly during the steady state would have allowed us to develop a more refined PK model. For example, danoprevir absorption might have been described more thoroughly. We agree with the author that a detailed PK model might permit one to design a limited sampling strategy that could be used in other danoprevir studies; however, this is beyond the purpose of our present work. Moreover, considering the quality of the fits that we obtained, we do not expect that adding frequent sampling during the first day of treatment would considerably modify our model or the conclusions that we have drawn.

To conclude, whereas there is no doubt that an accurate PK/VK model is valuable to deduce both the mode of action and effectiveness of an antiviral, in practice, PK samples are not always available. It is therefore important to develop and assess alternative models, such as the VE model, to describe VK under treatment.

Disclosure statement

ASP has received research funding from Roche and has consulted for Gilead, Bristol–Myers Squibb, Santaris and Achillion on HCV-related matters. JG has consulted for Gilead on HCV related matters. LC has no competing interests.

References

Figure 1. Comparison of the average viral load decline predicted by the PK/VK model and VE model for each cohort

Pharmacokinetic/viral kinetic model (PK/VK) is shown in black and the time varying drug efficacy model (VE) is shown in red.


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