Review of: "Novel Derivatives of BCV and (S)-HPMPA Inhibit Orthopoxviruses and Human Adenoviruses More Potently Than BCV"

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Potential competing interests: No potential competing interests to declare.

- The introduction shows poor bioavailability as a limitation, but the pharmacokinetic data does not reveal the enhancement in bioavailability. Since a comparison of absolute bioavailability (Oral AUC/IV AUC) of BCV/cidofovir from the BCV formate may be necessary to justify this, this aspect should be moderated.
- The enhancement in antiviral activity in vitro is due to the enhanced availability of the drug/metabolite or that the prodrugs are themselves active.
- What was the dose (mg/kg) of administration to mice and how was it rationalised?
- “BCV formate also displayed better protection, but its efficacy did not significantly differ from those of the vehicle and BCV”. This shows that there are no significant differences in the efficacy of BCV and BCV formate compared to the vehicle against vaccinia. Considering that BCV is the approved prodrug, and the effect of cidofovir is already reported against vaccinia infection in mice, prior literature (for example https://doi.org/10.1016/S0166-3542(01)00159-0) should be discussed to justify the findings. Also, the advantage of BCV-formate over BCV is not visible.
- “Bottlenecks, such as toxicity, poor oral bioavailability, and limited translatability, restrain NAs from being applied to more viral diseases”. This manuscript does not seem to address these issues. Nonetheless, the findings of this work are interesting, considering the development and evaluation of ODE-(S)-HPMPA formate and HDP-(S)-HPMPA formate as new antivirals. So, the title, introduction, and discussion parts should be aligned accordingly.