Reviewer’s report

Title: Emerging (val)ganciclovir resistance during treatment of congenital CMV infection: a case report and review of the literature

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Reviewer: Mark R. Schleiss

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In this interesting case report by Morillo-Gutierrez and colleagues, a case of ganciclovir resistance in an infant with congenital CMV infection is described. This is not a novel observation, but it does add to the information available about emergence of resistance on therapy. Insofar as valganciclovir is being increasingly prescribed for congenital CMV infection for six months' therapy duration, it is important to publish and disseminate this information.

The paper is well-written and the information clear. No revisions are required, however a couple of suggestions are provided for the authors' consideration:

1. The authors advocate for monitoring of drug levels for infants on valganciclovir therapy. Such levels are not always readily available to clinicians. How often do the authors suggest such monitoring, and do they recommend peaks, troughs, or both? What is the proper timing for obtaining peak levels?

2. A common question that arises in this context is the question of the risk of emergence of an antiviral resistance mutation. It seems to be unusual in clinical practice, but do the authors have information on the percentage of emergent strains that are observed in infants on a six-month regimen? Reports and reviews by Limaye (http://dx.doi.org/10.1016/S0140-6736(00)02607-6) and Drew (https://doi.org/10.1086/314747) suggest that long-term therapy is associated with a risk in the range of 5-10% for emergence of resistance. This work might be cited.

3. The authors suggest that emergence of resistance is driven by a combination of high viral load at the initiation of therapy and sub-optimal therapeutic levels of antiviral drug. These may well be the driving forces behind emergence of resistance, but how well validated are these hypotheses? Other authors suggest it's duration of therapy that is the key issue with respect to emergence of resistance. Are there any experimental data, either from mathematical modeling from the work of Vince Emery (e.g., 10.1073/pnas.140123497) or animal model studies, that shed light on this issue? This work might be cited. If high viral load at initiation of therapy is a clear risk factor for resistance emergence, that would be important information for clinicians to have access to.
4. The authors performed pyrosequencing of plasma, it appears, to map the UL97 mutation. When the retrospective analysis was conducted (...the retrospective analysis of a sample when the patient was 2 months of age identified no known CMV resistance mutations), was this also pyrosequencing on archived plasma samples? How homogeneous were the mutations when identified, in other words, what percentage of circulating virus carried the UL97 mutation?

5. After cessation of therapy, viral infection was eventually controlled, presumably due to development of a T-cell response and, possibly, high avidity antibody. Were the authors able to go back later, months after therapy was discontinued, to examine the prevalent strain of virus presumably being shed by the infant? One would presume that the infant would have viruria for months, even years, and it would be of interest to examine whether long-term colonization persisted with the UL97 mutant or if the colonizing strain reverted to wild-type.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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