Reviewer's report

Title: Fast selection of maribavir resistant cytomegalovirus in a bone marrow transplant recipient

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Reviewer: Klaus Hamprecht

Reviewer's report:

To the authors

Schubert et al., submitted a manuscript entitled
Fast selection of maribavir resistant cytomegalovirus in a bone marrow transplant recipient
to BMC Infectious Disease.

This interesting case report presents sequential genotypic data on the emergence of a GCV/PFA/maribavir drug resistance in a 13-year-old-HCMV seropositive girl, receiving a bone marrow transplant from an unrelated seronegative donor. Very early, during T-cell reconstitution, PFA lead 5 weeks after Tx to oro-genital lesions and was replaced by a combined GCV/PFA treatment. At week +19 CD34+ stem cells were additionally transfused. HCMV UL97 genotyping revealed M460V mutation conferring GCV resistance. Also CDV, ribavirin and leflunomid and maribavir were given simultaneously after termination of an intermittend short-term PFA treatment. Beside well-known UL97 mutations like L595S and M460V, also known UL54 mutations like T700A and A809V emerged in a minority of viral populations. Interestingly, also the the maribavir-associated UL97 H411Y mutation arised. This report also shows impressively, that PFA related serious side effects beside nephrotoxicity may arise very rapidly.

For the interested reader some optimization for better understanding the relation between antiviral therapy and virological findings would be helpful. Drug resistance screening is performed with adequate methods and cloning of viral variants showed that different viral strains were expressing individual mutations.

Some minor open questions remain, reflecting the clinical status and the outcome of the patient as well as the interesting discussion about the impact of the individual UL97/UL54 mutations on the emergence of the therapy failure.

1.) For strict exclusion of any confusion about the title, the authors should cite that Strasfeld et al.,2010 first reported on the same genotypic MBV resistance (T409M, H411Y) in a clinical isolate from an HTX recipient. In context of BMT the statement is correct.

Background, page 5, last sentence in the first section:
“To our knowledge no other cases of genotypic MBV resistance in treated patients have been published so far”

Please see also: Hakki, Chou, 2011, Curr Opin Infect Dis 24:

2.) Was the virological analysis performed retrospectively? What was the outcome of the patient? Did she really receive a BMT in 2010 or SCT? Did the girl suffer from organ disease under peak viral loads for HCMV and ADV prior to MBV administration? (case presentation page 6, Fig 1)?

3.) Clinical data should also be implemented into Fig 1. (infusion of CD34+ and ADV-spec T cells). What was the therapeutical rationale for giving ribavirin, which has no evident anti ADV potential in vivo?

4.) Did the authors identify ADV species and subtype responsible for disseminated ADV infection?

5.) In the abstract and on page 8, beside UL97 H411Y, also T409M and H411N are given, but in the Fig only T409A and no T409M.

6.) The interference of the UL54 mutations T700A and A809V with GCV/PFA and/or CDV drug resistance with UL97 L595S and M460V and H411Y should be discussed. What is known about contribution to antiviral hyper/hyposensitivity like interference of MBV H411Y and M460V?

7.) How the authors did estimate the individual ratios between wildtype and mutant strains? (Page 7, section 3)

8.) Did the authors try to receive a viral isolate, because plaque purification could confirm the findings of UL97 cloning for direct sequencing?

**Level of interest**: An article of outstanding merit and interest in its field

**Quality of written English**: Acceptable

**Statistical review**: No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests**:

I declare that I have no competing interests