Clinical Infectious Diseases

CORRESPONDENCE

Re: Association of CMV DNAemia with Long-Term Mortality in a Randomized Trial of Preemptive Therapy (PET) and Antiviral Prophylaxis (AP) for Prevention of CMV Disease in High-Risk Donor Seropositive, Recipient Seronegative (D+R-) Liver Transplant Recipients

Tom A. Yates [1,2] *, Neil Halliday [3,4]

[1.] Institute of Health Informatics, University College London, London, UK; [2.] Division of Infection and Immunity, University College London, London, UK; [3.] Institute for Liver and Digestive Health, University College London, London, UK; [4.] Sheila Sherlock Liver Centre, Royal Free Hospital, London, UK

Dear Editor, We read with interest Kumar and colleagues' reanalysis of the CAPSIL trial.(1) The authors seek to understand whether differences in duration of cytomegalovirus (CMV) DNAemia, associated with alternative CMV prevention strategies, impact mortality in liver transplant recipients.

There are mechanistic reasons to think that cytomegalovirus (CMV) DNAemia might impact health outcomes in solid organ transplant recipients, even in the absence of CMV end organ disease.(2) DNAemia occurs earlier in those managed using preemptive therapy (PET) and, typically, on cessation in those taking antiviral prophylaxis (AP).

Landmark analyses, as used by Kumar *et al*, condition on survival to landmark time (100 days post transplant, in this study). This generates period-specific estimates of survival that are hard to interpret and cannot be generalised to the population to whom the intervention is to be offered.(3,4)

* Dr Tom Yates (t.yates@ucl.ac.uk), UCL Institute of Health Informatics, 222 Euston Road, London NW1 2DA, United Kingdom

DOI: 10.1093/cid/ciae004

The apparent better long term survival in CAPSIL participants randomised to PET(1) may be a chance finding. The association would be attenuated had the 5 PET (versus 1 AP) deaths occurring prior to 100 days been included. Between group differences appear to have been driven by, presumably unrelated, deaths from malignancy and from alcohol or opiate toxicity.

The association between peak CMV DNAemia and mortality in the CAPSIL trial population(1) is not from a randomised comparison. Expected confounders of the DNAemia – mortality association, such as age and degree of immunosuppression, were not included as covariates. In the general population, CMV viral load in blood (cell associated) increases with advancing age, doubling every 9.6 years.(5) Furthermore, CMV can reactivate in response to increases in immunosuppression, inflammatory stimuli, intercurrent illness and other physiological insults.(2) We cannot tell from these data whether CMV DNAemia caused ill health, and subsequent death, or whether ill health caused CMV reactivation. In our view, either residual confounding or reverse causation could fully explain the observed association.

We agree with Kumar and colleagues that 'a large head-to-head trial of PET vs AP that includes long-term follow-up for mortality' would be informative.(1)

Funding TAY is an NIHR Clinical Lecturer supported by the National Institute for Health Research. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Conflict of interest TAY undertakes research on CMV in solid organ transplant recipients but, beyond this, has no conflicts of interests to declare. TAY is also organizing a meeting on the indirect effects of CMV; this meeting will be hosted and funded by the Royal Society. TAY also sits on the board for iHOST, an NIHR study seeking to improve inpatient opiate substitution treatment for people who inject drugs; and receipt of equipment, materials, drugs, medical writing, gifts or other services from Sanofi (TAY worked on a trial of rifapentine and Sanofi provided the drug. Sanofi are developing CMV vaccines. TAY did not benefit financially from this relationship), RECOVERY Trial (TAY was an Associate Principle Investigator on the RECOVERY trial – manufacturers of medications tested in this platform trial donated the drugs. TAY did not benefit financially from his involvement in the study), GSK (In 2009-11, TAY worked on a study where the lab assays were funded by GSK. GSK are developing CMV vaccines. TAY did not benefit financially from his involvement in the study) and Pasante (In 2009, TAY worked on a study of point of care HIV testing. Pasante provided the tests used in this study. TAY did not benefit financially from his involvement in the study). NH reports payment for educational lecture from Dr. Falk Pharma and for educational discussion group from Advanza Pharma. NH has no other relevant conflicts of interest.

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