PRE-TRANSPLANT CELLULAR IMMUNE RESPONSE TO CMV AND OCCURRENCE OF VIREMIA IN THE FIRST YEAR POST-TRANSPLANTATION

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Objectives:

Updated International Consensus Guidelines on the Management of CMV in solid organ transplantation, published in 2013, recommend immunological monitoring of CMV, beside virological monitoring of CMV-DNAemia to evaluate the risk of CMV infection/disease. A recent study found that CMV-cellular immune response status before transplantation (evaluated by Quantiferon assay) may predict the risk of viremia at 24-month follow-up. No further studies have been performed to confirm this; moreover, no data are available about such potential for Elispot assay (also used to evaluate virus-specific cellular immune response).

To evaluate the potential for pre-transplant CMV-specific immunological status evaluated by Elispot assay to predict the risk of CMV viremia post-transplantation in renal transplant.

Methods:

We evaluated CMV-specific immunological status pre-transplant (T0) in 80 patients, subsequently subjected to kidney transplantation. Anti-CMV prophylaxis with ganciclovir was administered for 3 months in 6 patients with CMV-serological matching D+/R-. CMV-specific cellular immune status was evaluated by Elispot assay. Briefly, automated separation of CD3+ cells was performed with the RoboSepR instrument (StemCell Technologies, Vancouver, Canada) using the EasySep negative selection protocol, following the manufacturer's instruction. Separated cells were resuspended in RPMI-1640 medium (supplemented with 1% L-glutammine and 10% fetal calf serum). An aliquot of $2x10^5$ cells (100 µL/well from a $2x10^6$/mL mix) was incubated on an anti-IFN-γ antibody-coated plate (EliSPOT Interferon-γ Basis Kit; Autoimmun Diagnostika GmbH, Strassberg, Germany) with CMV-specific peptide mix (pp65 and IE-1; ELITechGroup), medium alone (negative control) or phytohemagglutinin (positive control). IFN-γ production was visualized by an enzyme-labeled detection antibody, with each spot representing a single cell secreting IFN-γ. Results were analyzed using a computer-assisted system (AID EliSPOT Reader System, Autoimmun Diagnostika). Results were expressed as spot forming units (SFU)/$2x10^5$ cells and evaluated as previously described: invalid assay >5 SFU for the negative control and <20 for the positive control; absent/weak response <20 SFU, strong response ≥20 (accordingly, non-responders and responders patients).
Occurrence of CMV-DNAemia was evaluated at 12-month follow-up by a commercially available quantitative real-time PCR assay (Elite CMV, Elitech Group) and related to immunological pre-transplant status. Anti-viral prophylaxis was administered in six D+/R- patients.

Results:

Overall, 49/80 (61.2%) patients were responders pre-transplantation, whereas 31 (38.8%) non-responders, including 9 CMV-seronegative. At 3 months, viremia occurred in 16/49 (32.7%) and 8/31 (25.8%) of responders and non-responders, respectively. Cumulative incidence of viremia at 12 months was 16/49 (32.7%) and 15/31 (48.4%) in the two groups, with a tendency to a higher rate of incidence of viremia at 12 month in non-responders vs responders pre-transplantation (Figures 1-2). Patients with at leas one episode of viremia in the first year post-transplantation presented lower level of immune response by Elispot (40.9 vs 66.2 spot forming unit/200000 peripheral blood mononuclear cells)(Figure 3). CMV-specific immunological status pre-transplant may be related to the occurrence of viremia, however only in the long-term follow-up.

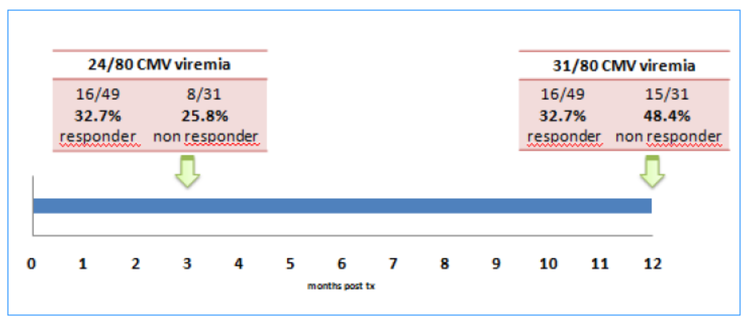

Figure 1

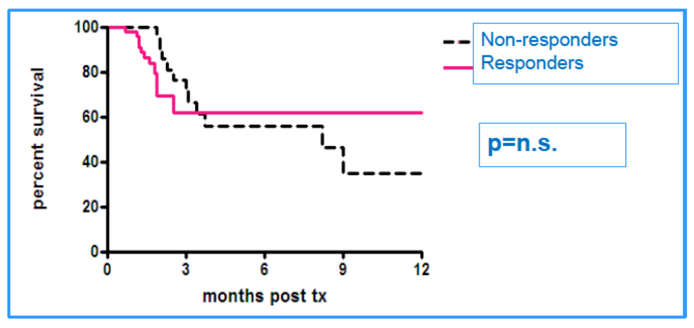

Figure 2

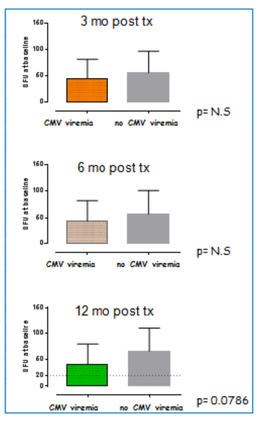

Figure 3

Conclusions:

Further studies are needed to evaluate the potential for pre-transplant evaluation of cellular immune response to CMV by Elispot assay and the risk of viral reactivation.
However, these preliminary results seems to suggest a potential role for pre-transplantation evaluation of CMV-specific cellular immune response that could provide data useful for the clinico-therapeutic management of kidney transplant patients.

References:

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