Monitoring CD4+/CD8+ CMV-Specific T-Cells Response could predict viral reactivation in renal transplantation

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OBJECTIVES

Human cytomegalovirus (CMV) infection is still a major complication after kidney transplantation. Because of T cell immunosuppression, transplant recipients are at increased risk to develop CMV infection early after transplantation. Cytotoxic CMV-specific T cells play a crucial role controlling CMV survival and replication: in particular, dominant T cell responses against immediately early-1 (IE-1) antigens and phosphoprotein 65 (pp65) seem to be essential for CMV control.

Recent relevant reports using different T cell immune monitoring tools have shown the importance of such CMV specific T cell responses for controlling CMV infection after transplantation and that monitoring CMV-specific T cell response before transplantation, particularly against the IE-1, may improve the identification of kidney allograft recipients at high-risk for CMV infection.

IN OUR PERSPECTIVE OBSERVATIONAL STUDY, WE AIMED TO EVALUATE THE CLINICAL USEFULNESS OF MONITORING CMV-SPECIFIC T CELL RESPONSES AGAINST DOMINANT CMV ANTIGENS (IE-1 AND PP65), FOR PREDICTING POST-TRANSPLANT CMV INFECTION IN THE FIRST YEAR POST TRANSPLANTATION.

METHODS

Between 2010 and 2013, 40 consecutive kidney adult renal transplant recipients, CMV seropositive and not on anti-CMV prophylaxis treatment, were enrolled.

All patients received induction immunosuppression with Anti-CD25 monoclonal Ab and maintenance immunosuppression with Tacrolimus, Mycophenolate Mofetil and Steroid.

Anti-CMV T cell immune response was assessed using IFN-g Elispot assay. CMV infection was defined as a positive CMV-DNA with no symptoms.

CMV disease included both viral syndrome and tissue invasive disease. Preemptive treatment strategy was based on gancyclovir 500 mg iv daily if CMV-DNA > 50.000 copies/ml.

RESULTS

Firstly we divided our patients according to transplantation age. Patients with transplantation age ≤ 6 months (group A) did not show any significant difference for age, gender, DGF and acute rejections incidence, eGFR and proportion of seropositive donors, compared to recipients with transplantation age between 6 and 12 months (group B). As reported in Table 1 significant differences between the two groups were observed in: i) proportion of viremia; ii) number of spots after stimulation with the pp65 antigen.

Independently from transplantation age, at Elispot dosage time, viremic patients did not present any significant differences in T-cells response after stimulation with pp65, while the number of spots using IE1 was greater in viremic patients than in not viremic patients ($p<0.03$).

Only three patients developed a viral load greater than 50,000 copies/ml, requiring antiviral treatment. These patients, after stimulation with IE1, showed a number of spots lower than patients who developed low loads viremia (3 ± 1.6 vs 27 ± 15.3, $p<0.01$) and similar to non-viremic patients (3 ± 1.6 vs 2.3 ± 1.1).

Table 1. CMV viremia and Elispot values by Transplantation Age.

	Group A (n=19)	Group B (n=21)
CMV DNA > 650 copies/ml	8	5 *
CMV DNA > 50,000 copies/ml	3	0 *
CMV Disease	0	0
T-Cells anti pp65 (spots/2×10^5)	6 ± 4.9	95 ± 28 *
T-Cells anti IE-1 (spots/2×10^5)	14 ± 6.2	21 ± 15.3

* Difference between groups $p < 0.05$

CONCLUSIONS

THE HIGH LEVELS OF CD4+/CD8+ CMV-SPECIFIC T-CELLS OBSERVED 6 MONTHS AFTER TRANSPLANTATION, ASSOCIATED WITH A LOWER INCIDENCE OF VIRAL REACTIVATION, INDICATE THE NEED OF AT LEAST 6 MONTHS FOR THE RECONSTITUTION OF CMV-SPECIFIC IMMUNITY.

MONITORING IE-1 CMV-SPECIFIC T-CELL FREQUENCIES AFTER TRANSPLANTATION WOULD HELP TRANSPLANT PHYSICIANS TO GUIDE PREEMPTIVE ANTIVIRAL TREATMENT.

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