LETTER TO THE EDITORS

Baseline anti-CMV cellular immunity is similar between patients with a kidney transplant or receiving hemodialysis

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Cytomegalovirus (CMV) is a frequent opportunistic viral infection after solid-organ transplantation. CMV infection and disease are associated with significant morbidity and mortality after kidney transplantation. CMV monitoring and risk stratification remain important goals for all transplantation teams [1]. The current management of anti-CMV prophylaxis by clinicians is largely based on humoral immunity. CMV-seronegative recipients that receive a kidney from a CMV seropositive donor (D+/R−) are reported to have the highest risk of CMV infection and CMV disease [2]. The current guidelines for a preventive approach recommend maintaining anti-CMV prophylaxis for up to 200 days in this high-risk group [3]. However, several studies have highlighted the essential role of cellular immunity to control CMV infection. Anti-CMV cellular immunity may be assessed using Quantiferon-CMV (QF-CMV), which quantifies interferon gamma (IFN-γ) production by $CD8^+$ T cells following CMV antigen stimulation. QF-CMV has shown some ability to predict the risk of CMV infection at post-transplantation. However, no study has compared baseline QF-CMV anti-CMV cellular immunity between kidney transplant patients and hemodialysis patients who are kidney transplant candidates and compared these data with those from healthy volunteers.

In this study, we prospectively assessed the results for QF-CMV in kidney transplant (KT) patients, chronic hemodialysis (HD) kidney transplant candidates, and healthy controls (HC) in a department that specializes in kidney transplantation, at the University Hospital of Grenoble, France (NCT03916497, ClinicalTrials.gouv).

QF-CMV assay was blinded regarding patients' category and performed by the immunology department using the anti-CMV Quantiferon assay (QuantiFERON®-CMV—QIAGEN®, GmbH, Hilden, Germany). Sixty CMV seropositive patients were included (20 KT, 20 HD, and 20 HC). Baseline characteristics of patients are presented in Table 1. In KT patients, 100% had thymoglobulin as the induction therapy, 100% received tacrolimus as the maintenance therapy, 75% received mycophenolate mofetil, and 20% received steroids. There was no significant statistical association between immunosuppressive therapy and IFNγ secretion (data not shown). The time since transplantation was 8.0 ± 6 years. Time since transplantation was negatively correlated with QF-CMV response using Spearman's correlation ($P = 0.03$, $r = -0.49$). Thirteen of the KTs were CMV D+/R+ and 7 were CMV D−/R+. The mean time of dialysis duration in the HD group was 3.9 ± 5.9 years. Time of dialysis was not correlated with QF-CMV response ($P = 0.34$, $r = -0.2$). Of note, we found a higher total lymphocyte counts at inclusion in the HC group as compared to KT and HD groups (Table 1). However, in the whole cohort, total lymphocyte count was not significantly correlated to anti-CMV INFγ secretion ($P = 0.86$). ANOVA statistical analyses were performed to compare quantitative variables such as IFNγ secretion at post-CMV antigenemia *in vitro* stimulation in all three groups. Chi-squared test was used for categorical variables. There was no statistical difference in IFNγ secretion using the QF-CMV assay between the three groups (Table 1). The median QF-CMV response was 1.05 [0–10] UI/ml in the KT group, 0.99 [0–10] UI/ml in the HD group and 4.28 [0–10] UI/ml in the HC group, $P = 0.47$. According to the manufacturer, we used a positive threshold of

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Table 1. Baseline characteristics and interferon-γ response to cytomegalovirus (CMV) antigenemia.

	Kidney transplanted patients (n = 20)	Hemodialysis patients (n = 20)	Healthy controls (n = 20)	P-value
Baseline characteristics at inclusion				
Age (years)	59 ± 8	58 ± 14	62 ± 13	0.58
Sex (male) N (%)	12 (60)	10 (50)	7 (35)	0.12
Total lymphocyte count (cells/mm^3)	1500 ± 600	1200 ± 500	2000 ± 600	0.025
Anti-CMV antibody IgG titer (UI/ml)	11 233 ± 8703	26 571 ± 6579	16 531 ± 9735	0.93
QF-CMV response				
CMV Interferon-γ response (UI/ml)	1.05 [0–10]	0.99 [0–10]	4.28 [0–10]	0.47
Mitogen Interferon-γ response (UI/ml)	10 [2.78–10]	10 [1.49–10]	10 [10–10]	0.10

CMV, cytomegalovirus; QF-CMV, QuantiFERON®-CMV.

Numeric values are given as mean ± SD or median [min – max].

0.2 UI/ml for a positive QF-CMV test. We found no difference in the positive test results from all three groups (65%, 71%, and 79% of positive tests, respectively, in the KT, HD, and HC groups; P = 0.79).

Some studies that have assessed QF-CMV at post-transplantation have shown that a negative QF-CMV seemed to be a strong predictor of CMV infection after postprophylaxis discontinuation [4]. Yet, one limitation may be the impact of immunosuppression therapy on QF-CMV results. We found no statistical difference in baseline QF-CMV results between KT and HD patients. In HC, although the median QF-CMV reactivity was higher, it did not reach significance. Moreover, the literature reports some controversial results for QF-CMV to predict CMV infections in kidney transplant recipients. In a recent meta-analysis, Ruan *et al.* compared the results of 12 articles using QF-CMV and CMV-ELISPOT assays. They reported less predictive results of QF-CMV for CMV infection in kidney transplant recipients, as compared to ELISPOT. Indeed, pooled sensibility, specificity, and diagnostic odds ratio were lower in QF-CMV 1.02 (95% CI, 0.17–6.00) as compared to IE-1 CMV-ELISPOT 5.07 (95% CI, 3.26–7.89) [5].

In conclusion, we found that cellular anti-CMV immunity did not statistically differ between KT and HD patients. Our results raise questions about the impact of kidney failure and immunosuppression regimens on anti-CMV cellular immunity, particularly with the QF-CMV assay.

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Conflicts of interest

The authors declare no conflicts of interest.

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