Clinical Utility of QuantiFERON-Cytomegalovirus Test in Management of Kidney Transplant Recipients

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ABSTRACT

Immune monitoring of cytomegalovirus (CMV) – specific T-cells responses has become an additional tool in the CMV risk assessment of kidney transplant recipients (KTRs). Some data demonstrated a potential use of QuantiFERON-CMV assay (QF-CMV) in stratifying CMV risk before transplantation, at the end of prophylaxis and during pre-emptive strategy. High risk for CMV disease was also reported in KTRs with indeterminate QF-CMV results in which both mitogen and CMV antigen responses were absent.

Twenty-five KTRs in the first year after kidney transplantation (KT), including 17 KTRs after CMV infection treatment (CMV-KTR), were studied by QF-CMV assay.

Positive QF assay (QF+) was present in 16 of 25 (64%) of KTRs, negative (QF−) in 5 of 25 (20%), and indeterminate (QF0) in 4 of 25 (16%). The QF0 patients, in comparison to the combined group of QF+ and QF−, presented an increased incidence of CMV disease (4 of 4 [100%] vs. 7 of 21 [33.3%]; $P < .05$) and severe infectious complications such as sepsis, and systemic mycosis (4 of 4 [100%] vs. 6 of 21 [29%]; $P < .02$). Of 17 CMV-KTRs, 11 of 17 (64.7%) were QF+, 2 of 17 (11.8%) were QF−, and 4 of 17 (23.5%) were QF0. The incidence of CMV disease and severe infectious complications was not different among these groups. CMV-KTRs with interferon-γ <3.5 IU/mL vs. >3.5 IU/mL in mitogen tube, irrespective of QF-CMV status, showed an increased incidence of CMV disease (8 of 9 [88.9%] vs. 3 of 8 [37.5%]; $P < .05$) and severe infectious complications (8 of 9 [88.9%] vs. 2 of 8 [25%]; $P < .02$).

In conclusion, indeterminate result of QF-CMV or interferon-γ <3.5 IU/mL in mitogen tube seems to be related to impaired immunity. The QF-CMV assay appears to be a useful tool in clinical practice, identifying the group of KTRs with increased risk of infectious complications who may benefit from immunosuppression reduction and maintenance of antiviral prophylaxis.

CYTOMEGALOVIRUS (CMV) belongs to the most common and important pathogens affecting patients after kidney transplantation. The presentation of active infection may be asymptomatic (evidence of CMV replication in the absence of clinical symptoms) or symptomatic CMV disease (CMV syndrome or tissue invasive disease). These direct effects of CMV combined with indirect effects, such as the immunological consequence of CMV infection, result in a significant impact on morbidity and mortality of transplant recipients [1]. Therefore, CMV prevention is an important issue in post-transplantation patient care. Two major strategies, universal prophylaxis and pre-emptive therapy, are applied: they depend, so far, on serologic donor and recipient CMV status, type of transplanted organs, and intensity of immunosuppression [2]. The benefits associated with universal prophylaxis (ease of implementation, prophylaxis of other herpes viruses, and possible prevention of indirect effects of CMV infection), caused widespread use of valganciclovir in many transplant centers, but revealed some problems (drug cost, toxicity, risk of resistance, and late CMV disease). Therefore, an individual

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0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2016.01.046

approach and risk assessment is postulated, highlighting the role of cellular immunity [3,4]. Recent studies showed that CMV-specific CD8+ T cells play the crucial role in protection against CMV, and immune monitoring of CMV-specific T-cell responses may become an additional tool in defining individual risk for CMV infection [5,6]. QuantiFERON (QF)–CMV assay, based on interferon-γ (IFN-γ) release by CD8+ cells is commercially available in the European Union (EU). Some data demonstrated its potential use in stratifying CMV risk before transplantation, at the end of prophylaxis, and during pre-emptive strategy [7–10]. As the immunological monitoring techniques became clinically available, the aim of the presented study was to evaluate the clinical utility of QF-CMV test in the management of kidney transplantation patients in our center.

MATERIALS AND METHODS

Study Population

Twenty-five patients in the first year after kidney transplantation, including 17 patients after CMV infection treatment (CMV- kidney transplant recipients [CMV- KTR]), were enrolled to the study. The characteristics of the study population are given in Table 1. The serological CMV status of both recipient and donor was assessed before transplantation, and is also presented in Table 1; seronegative recipients were additionally evaluated after CMV infection to determine possible seroconversion. The type of antiviral preventive strategy depended on CMV donor (D)/recipient (R) status and the use of anti-lymphocyte globulin. The occurrence of CMV disease (CMV-D), severe infectious complications (SIC), defined as sepsis or systemic mycosis, and a number of clinical and demographic features were specified.

CMV Antigenemia

CMV replication was monitored by CMV antigenemia using a commercially available kit for the determination of CMV pp65 antigen, CMV Brite Turbo Kit (IQ Products, Groningen, The Netherlands). Identification of a minimum of 1 positive cell in spot prepared with 100,000 peripheral blood mononuclear cells was regarded as a positive test result, and the treatment with ganciclovir or valganciclovir was induced depending on clinical symptoms.

Table 1. Characteristics of Study Patients

Characteristics	All (N = 25)
Age (years; mean ± SD)	53.2 ± 15.1
Gender (male/female)	19/6
Type of donor	
Deceased/living	25/0
Type of treatment before KT	
HD/PD/PE	15/8/2
Pretransplant donor/recipient CMV serostatus	
D−/R−	1
D−/R+	2
D+/R−	9
D+/+	13
Immunosuppression regimen	
Steroids/Cs/MMF	7
Steroids/TAC/MMF	18
Induction therapy (thymoglobulin)	2
Acute rejection	5
Patients after CMV infection	17
Asymptomatic/disease	6/11

Abbreviations: KT, kidney transplantation; HD, hemodialysis; PD, peritoneal dialysis; PE, pre-emptive transplantation; D, donor; R, recipient; TAC, tacrolimus; Cs, cyclosporine; MMF, mycophenolate mofetil; CMV, cytomegalovirus.

QF-CMV Assay

The CMV-specific T-cell immunity was determined using QF-CMV response by quantifying IFN-γ released after ex vivo stimulation with CMV CD8+ cell epitopes from viral proteins, including pp65, pp50, gB, IE-1, et cetera [7,11]. The blood samples for the test were assessed once at a mean of 4.38 ± 2.73 months after transplantation. The assay was performed per the producer's instructions. Briefly, the patient's whole blood was obtained in three specialized tubes. One tube contained CMV CD8+ T-cell synthetic antigens, the second tube contained mitogen (phytohemagglutinin) as a positive control, and the third tube containing heparin was a negative control. After overnight incubation at 37°C, the plasma was harvested and IFN-γ concentrations (IU/mL) were measured by enzyme-linked immunosorbent assay (ELISA). Per the manufacturer's guidelines, the result is positive/reactive if the value in CMV tube is ≥0.2 IU/mL, negative/nonreactive if the level is below 0.2 IU/mL and mitogen control is ≥0.5 IU/mL, and indeterminate if the IFN-γ concentration in CMV antigen tube is <0.2 IU/mL, and in mitogen tube <0.5 IU/mL.

Statistical Analysis

The statistical analysis was performed by Statistica 10 Software. The data was collected and the diagrams were created using Microsoft Excel (Microsoft, Redmond, WA, USA). Verifications of significant difference ($P < .05$) between median values was performed with the U Mann-Whitney test, and for categorical variables by the Fisher's exact test.

RESULTS

The incidence of positive (QF+), negative (QF−) and indeterminate (QF0) QF-CMV assay is shown in Figure 1.

The patients with an indeterminate test result in comparison to the combined group of QF+ and QF− individuals presented an increased incidence of CMV disease (4 of 4 [100%] vs. 7 of 21 [33.3%], $P < .05$) and SIC (4 of 4 [100%] vs. 6 of 21 [29%], $P < .02$) (Fig 2).

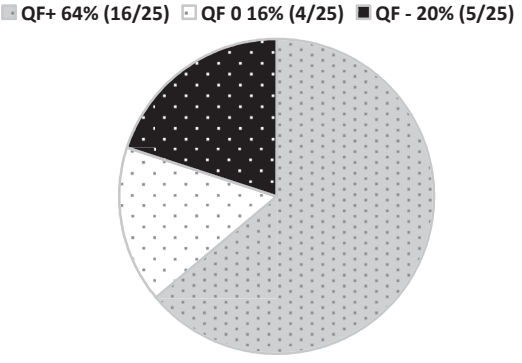

Fig 1. Cell-mediated immunity against cytomegalovirus in patients in the first year after kidney transplantation. Abbreviation: QF, QuanitFERON.