DOI: 10.26717/BJSTR.2018.02.000776
Fausto Baldanti. Biomed J Sci & Tech Res

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574-1241

Mini Review Open Access

HCMV-Specific Immune Monitoring in Solid Organ Transplant Recipients

Irene Cassaniti[1,2] and Fausto Baldanti[1,2]*

[1]*Microbiology and Virology Department, Fondazione IRCCS Policlinico San Matteo, Italy*

[2]*Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Italy*

Received: February 02, 2018; **Published:** February 20, 2018

***Corresponding author:** Fausto Baldanti, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy, Email: fausto.baldanti@unipv.it

Abstract

Solid organ transplant recipients (SOTRs) are at high risk of viral opportunistic infections, especially during the first six months post-transplant. Human cytomegalovirus (HCMV) remains one of the most important pathogens in transplant recipients, despite the great efforts in diagnosis and effective antiviral therapies. Immunological monitoring could be useful in order to guarantee a better management of the patients. In this setting, several methods have been employed. The review summarizes the most important approaches in immunological monitoring of HCMV-specific T-cell response in transplant setting.

Keywords: Human cytomegalovirus; Transplant; T-cell response; Quantiferon; Elispot assay

Abbreviations: SOTR:Solid Organ Transplant Recipients; HCMV: Human Cyto Megalo Virus; IFNγ: Interferon gamma

Introduction

Solid organ transplant recipients (SOTRs) are at high risk of viral opportunistic infections, especially during the first six months post-transplant, due to the immunosuppressive treatments. Human cytomegalovirus (HCMV) remains one of the most important pathogens in transplant recipients, despite the great efforts in diagnosis and effective antiviral therapies [1]. HCMV infections are thought to be responsible of both "direct effect" in the allograft, including inflammation, vasculopathy and fibrosis, and "indirect effect", that are mainly immune-mediated [2]. Great efforts have been devoted in order to implement advanced diagnostic techniques for monitoring HCMV infections in transplant recipients [3-5]. Furthermore, in recent years, the introduction of antiviral prophylaxis and pre-emptive strategies reduced HCMV-related mortality and morbidity [6].

So far, evaluation of HCMV serological status in organ donor (D) and recipient (R) represents the only available marker of risk stratification [7]. However, this traditional stratification presents some limitation. In fact, HCMV seropositive recipients are considered at intermediate risk, but they could present HCMV reactivation with consequent HCMV-related complication. On the other side, a role of HCMV-specific T-cell response has been suggested. In this setting, there has been a growing interest in the development of new approaches for monitoring immune response [8]. However, unique immunological monitoring strategies for evaluation of HCMV-specific T-cell response have not been defined yet.

Several methods have been suggested and developed in order to quantify HCMV-specific T-cell response in transplant setting, based on IFN-γ production after appropriate HCMV-specific stimulation, including intracellular cytokine staining (ICS), Enzyme-linked Immunospot (ELISPOT) assay and QuantiFERON-CMV (QF-CMV) assay. The two more used assays are QF-CMV assay and CMV ELISPOT assay. While both QF-CMV and CMV ELISPOT assays measure IFN-γ to detect HCMV-specific T-cell response, their characteristics and principles, as well as their results are different. QF-CMV is an assay for detection of IFN-γ on whole blood by enzyme-linked immunosorbent assay (ELISA) after ex vivo stimulation of CD8+ T cells with human leukocyte antigen (HLA)-restricted HCMV peptides [9].

The ELISPOT assay is a sensitive and specific method for measuring antigen-specific T-cell responses after appropriate stimulation, by detection of functionally relevant cytokines, such as IFN-γ [10]. Whole antigens, proteins or peptides could be used as HCMV-specific stimuli. In different settings, we observed

that the use of antigen-specific 15-mers 11 overlap peptide pools represents a good compromise for stimulating both CD4+ and CD8+ T-cell response [11-13]. However ELISPOT assay does not allow to distinguish between CD4+ and CD8+ T cell responses unless antigens for detecting CD4+ and CD8+ response are used separately or lymphocyte subset depletion is performed [11]. Alternatively, the normalization of net spots/million of PBMC on CD4 and CD8 T cell count could be performed in order to estimate the role of HCMV-specific CD4+ and CD8+ T-cell response [12]. Standardization and cut-off values for positive HCMV-specific ELISPOT response have to be better defined.

ICS allows the characterization of both CD4+ and CD8+ T cells after T-cell stimulation with appropriate antigens in the presence of secretion inhibitors (Brefeldin A or Monensin) by flow cytometry analysis, using markers for lymphocytes differentiation and for measurement of T cell function. However, the assay is complex and labor-intensive [14]. In this setting, the characterization of HCMV-specific T-cell response among transplant recipients should be employed in order to better stratify the risk of HCMV reactivation or infection, allowing a personalized management of the patients. HCMV-specific T cells, especially effector CD4+ and CD8+T cells are considered to be crucial in the control of HCMV replication. Furthermore, interferon-γ (IFN-γ) has been suggested to play a critical role in controlling HCMV infection [15].

The lack of IFN-γ production detected by QF-CMV was predictive of development of HCMV disease in high-risk patients after discontinuation of antiviral prophylaxis [16]. In a study performed on 124 HCMV-seropositive kidney transplant recipients, evaluating HCMV-specific T-cell response using both QF-CMV and CMV-ELISPOT assay, it was observed that post-transplant HCMV-specific T-cell response measured by ELISPOT assay could be useful for identifying patients at risk of HCMV DNAemia. On the contrary, no differences were observed between KTR with CMV DNAemia (+) and KTR with CMV DNAemia (-) from QF-CMV assay results [17]. Furthermore, study evaluating CMV-specific CD4+ and CD8+ T-cell response detected using CMV-infected immature dendritic cells and flow cytometry analysis showed that CMV-specific CD4+ and CD8+ T-cell level > 0,4/μl in the first month post transplant could confer protection from CMV infection [18].

A possible role of CMV-specific T-cell response detected by ELISPOT assay at pre-transplant could be suggested [19]. In another study [20] CMV-specific T CD8+ response at pre-transplant seemed to be predictive of the risk of CMV replication after transplantation in solid organ transplant recipients. In more detail, pre-transplant immediate early 1 (IE1-)-specific T-cell response could be involved in protection for CMV infection after kidney transplant, supporting the potential value of CMV-specific T-cell response evaluation as prognostic marker of CMV infection or reactivation [21]. Conclusion and Perspectives Studies have highlighted the role of CMV-specific CD8+ and CD4+ T cells, measured at pre-transplant and in post-transplant in controlling CMV infection after transplant. Although a great effort has been profused, further analysis are required in order to standardize immunological methods for the evaluation of CMV-specific T-cell response as well as to better characterize its possible prognostic role.

Acknowledgment

We thank Daniela Sartori for careful preparation of the manuscript.

References

1. Fishman JA (2017) Infection in Organ Transplantation. Am J Transplant 17(4): 856-879.
2. Kaminski H, Fishman JA (2016) the Cell Biology of Cytomegalovirus: Implications for Transplantation. Am J Transplant 16(8): 2254-2269.
3. Abbate I, Piralla A, Calvario A, Callegaro A, Giraldi C, et al. (2016) AMCLI - Infections in Transplant Working Group GLaIT.Nation-wide measure of variability in HCMV, EBV and BKV DNA quantification among centers involved in monitoring transplanted patients. J ClinVirol 82: 76-83.
4. Navarro D, San Juan R, Manuel O, Giménez E, Fernández Ruiz M, et al. (2017) Cytomegalovirus infection management in solid organ transplant recipients across European centers in the time of molecular diagnostics: An ESGICH survey. Transpl Infect Dis 19(6).
5. Furione M, Rognoni V, Cabano E, Baldanti F (2012) Kinetics of human cytomegalovirus (HCMV) DNAemia in transplanted patients expressed in international units as determined with the Abbott RealTime CMV assay and an in-house assay. J Clin Virol 55(4): 317-322.
6. Mattes FM, Vargas A, Kopycinski J, Hainsworth EG, Sweny P, et al. (2008) Emery VC.Functional impairment of cytomegalovirus specific CD8 T cells predicts high-level replication after renal transplantation. Am J Transplant 8(5): 990-999.
7. Schachtner T, Stein M, Reinke P (2017) CMV-Specific T Cell Monitoring Offers Superior Risk Stratification of CMV-Seronegative Kidney Transplant Recipients of a CMV-Seropositive Donor. Transplantation 101(10): e315-e325.
8. Calarota SA, Aberle JH, Puchhammer-Stöckl E, Baldanti F (2015) Approaches for monitoring of non virus-specific and virus-specific T-cell response in solid organ transplantation and their clinical applications. J Clin Virol 70: 109-119.
9. Lisboa LF, Kumar D, Wilson LE, HumarA (2012) Clinical utility of cytomegalovirus cell-mediated immunity in transplant recipients with cytomegalovirus viremia. Transplantation 93(2): 195-200.
10. Calarota SA, Chiesa A, Zelini P, Comolli G, Minoli L, et al. (2013) Detection of Epstein-Barr virus-specific memory CD4+ T cells using a peptide-based cultured enzyme-linked immunospotassay. Immunology 139(4): 533-544.
11. Calarota SA, Baldanti F (2013) Enumeration and characterization of human memory T cells by enzyme-linked immunospotassays. Clin dev Immunol p. 8.
12. Calarota SA, Chiesa A, Scaramuzzi L, Adzasehoun KM, Comolli G, et al. (2014) Normalizing ELISPOT responses to T-cell counts: a novel approach for quantification of HCMV-specific CD4(+) and CD8(+) T-cell responses in kidney transplant recipients. J Clin Virol 61(1): 65-73.
13. Cassaniti I, Calarota SA, Adzasehoun KM, Chiesa A, Comolli G, et al. (2016) Memory T cells specific for HBV enumerated by a peptide-based cultured enzyme-linked immunospot assay in healthy HBV-vaccinated subjects. Hum Vaccin Immunother 12(11): 2927-2933.
14. Jung T, Schauer U, Heusser C, Neumann C, Rieger C (1993) Detection of intracellular cytokines by flow cytometry. J Immunol Methods 159(1-2): 197-207.
15. Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, et al. (2013) Transplantation Society International CMV Consensus Group. Updated international consensus guidelines on the management of

cytomegalovirus in solid-organ transplantation. Transplantation 96(4): 333-360.

16. Kumar D, Chernenko S, Moussa G, Cobos I, Manuel O, et al. (2009) Cell-mediated immunity to predict cytomegalovirus disease in high-risk solid organ transplant recipients. Am J Transplant 9(5): 1214-1222.

17. Lee H, Park KH, Ryu JH, Choi AR, Yu JH, et al. (2017) Cytomegalovirus (CMV) immune monitoring with ELISPOT and QuantiFERON-CMV assay in seropositive kidney transplant recipients. PLoS One 12(12): e0189488.

18. Gerna G, Lilleri D, Fornara C, Comolli G, Lozza L, et al. (2006) Monitoring of human cytomegalovirus-specific CD4 and CD8 T-cell immunity in patients receiving solid organ transplantation. Am J Transplant 6(10): 2356-2364.

19. Rittà M, Costa C, Sidoti F, Ballocco C, Ranghino A, et al. (2015) Pre-transplant assessment of CMV-specific immune response by Elispot assay in kidney transplant recipients. NewMicrobiol 38(3): 329-335.

20. Cantisán S, Lara R, Montejo M, Redel J, Rodríguez Benot A, et al. (2013) Pretransplant interferon-γ secretion by CMV-specific CD8+ T cells informs the risk of CMV replication after transplantation. Am J Transplant 13(3): 738-745.

21. Bestard O, Lucia M, Crespo E, Van Liempt B, Palacio D, et al. (2013) Pretransplant immediately early-1-specific T cell responses provide protection for CMV infection after kidney transplantation. Am J Transplant 13(7): 1793-1805.

Submission Link: http://biomedres.us/submit-manuscript.php