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Cytomegalovirus Infection in Lung Transplantation: Importance of Specific Cellular Immune Response Assessment

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ABSTRACT

This article reviews the importance of CMV infection in lung transplantation, the importance of prophylaxis, and the importance of using biomarkers to guide this prophylaxis.

Keywords: Cytomegalovirus. ELISPOT. Lung transplant. Quantiferon. Specific cellular immune response.

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INTRODUCTION

Cytomegalovirus (CMV) infection/disease is very prevalent in solid organ transplant (SOT) recipients, especially in lung transplantation. CMV infection/disease is important because of the direct morbidity and mortality of the infection itself and because of the indirect effects it presents. These indirect effects are related to the immunomodulatory effect of the virus which increases the risk of chronic graft dysfunction, other infections and overall mortality[1-3]. The incidence of infection/disease without prophylaxis is between 38-75% according to different studies in CMV seropositive patients (R+) and up to more than 90% in seronegative patients who receive a lung from a seropositive donor (D+/R+).

CMV infection is asymptomatic in most patients and can be detected by PCR in bronchoalveolar lavage or blood samples. If the infection progresses, the disease in lung transplantation manifests as a flu-like syndrome and more severely as pneumonitis. Other forms of CMV disease such as hepatitis or enteritis are also possible but are rarer.

Treatment of the infection is aimed at preventing the development of the disease, especially pneumonitis. Pneumonitis, in addition to a high mortality rate, has a high percentage of sequelae in the form of chronic respiratory failure. It is also implicated in the medium and long term with the development of chronic lung allograft dysfunction (CLAD) and decreased survival.

Treatment of the infection is indicated when the DNA levels of the virus in blood or plasma exceed a certain level; this level is specific to each hospital. Treatment of the infection is based on the use of intravenous (i.v.) ganciclovir or valganciclovir, a prodrug that can be administered orally. CMV resistance to these drugs is currently rare but when it occurs, it is a very complicated situation. Depending on the mutation identified as responsible for the resistance, it may be sufficient to increase the dose of ganciclovir or switch to cyclodofovir or foscarnet. Other times the resistance is to ganciclovir and also to cidofovir or foscarnet, making the treatment of the infection very complicated. Recently, marivavir has been approved as a treatment for resistant CMV infection; this drug is effective and has a more manageable adverse effect profile[4].

The incidence of CMV infection or disease without prophylaxis is between 38-75% according to different studies in R+ and up to more than 90% in D+/R-. These figures are much higher than in other solid organ transplants[1].

With such high incidences of CMV infection, CMV prophylaxis was introduced shortly after the start of lung transplant programs in the early 1990s. The type and duration of CMV prophylaxis have changed over the years (i.v. ganciclovir for three months, a few weeks of i.v. ganciclovir followed by oral ganciclovir or preemptive therapy).

Currently, prophylaxis is performed with valganciclovir. Since the introduction of valganciclovir, the trend has been to prolong the duration of prophylaxis. Although the duration is not really well defined, most groups perform prophylaxis for 6-12 months depending on donor/recipient serology and their own experiences. There is evidence that in R+, 180-day

prophylaxis is an independent protective factor for the development of CMV disease compared to shorter prophylaxis schedules[3].

Although current prophylaxis strategies have clearly reduced the occurrence of CMV disease, the incidence of infection remains high[4]. CMV infection and disease occur when prophylaxis is stopped; the likelihood of infection after the end of prophylaxis is around 25-30% in R+[5]. Although infection has not been clearly established as a risk factor for further complications, it is the first step in the development of late CMV disease. For this reason, monitoring of viral replication in these patients in the months following discontinuation of prophylaxis should be very frequent. A major problem during prophylaxis is the toxicity of valganciclovir. About 20% of patients have to stop prophylaxis early because of some adverse effect, usually leukopenia[5]. Currently, letermovir, a drug with similar efficacy to vanganciclovir but with a better safety profile (it does not cause leukopenia), is approved for the prophylaxis of CMV infection in bone marrow transplantation[6]. In some patients with SOT with severe leukopenia due to valganciclovir, letermovir is already being used off-label.

CMV is a herpes virus that remains latent in the organism of healthy people after a primo infection that is usually pauci- or asymptomatic. In Spain, it is estimated that between 80-90% of the population is seropositive for CMV. The latency state implies a state of equilibrium between CMV and the immune system, especially the cellular immunity that controls the proliferation of the virus. After transplantation, the use of immunosuppressive drugs in R+ alters this balance leading to infection. In recipients who have not had contact with the virus (R-), infection occurs when they receive an organ from a D+; this implies a primo-infection in an immunosuppressed patient, which implies a higher probability of CMV disease, as well as more severity and earlier onset.

The CMV-specific cellular immune response has been identified as an essential factor in the control of CMV infection. In particular CD8+ cytotoxic T cells play a key role because they specifically recognize and destroy CMV-infected cells, as do CD4+ helper T cells that provide signals necessary for stimulation. However, this immunity against CMV, already present in R+ cells, is altered by immunosuppressive treatment[10]. The quality of the specific T-cell response to the primary CMV infection in D+/R- and the kinetics with which the immune response recovers in R+ post-transplantation determine the number of subsequent reactivation episodes and the susceptibility of patients to develop CMV disease[10].

Classically, the risk of developing CMV infection/disease is identified by pretransplant serology. However, recent studies have shown that monitoring the specific memory/effector T cell response can better stratify the risk of infection[11,12]. On the other hand, the study of the cellular response in combination with the study of CMV-specific B cell responses provides an explanation for discordant situations where seronegative patients have no infection/disease events or conversely where seropositive patients have recurrent CMV infections[11].

Therefore, knowledge of the specific cellular immune response to CMV in each patient

could be an additional strategy to the current one to assess the specific risk of developing CMV infection/disease. This would allow the establishment of individualized prophylaxis strategies. Currently, the CMV-specific cellular response can be assessed by different in vitro laboratory tests, each of them with very specific characteristics. Among the techniques that have demonstrated the greatest capacity to monitor the cellular response to CMV are the enumeration of IFN-γ-producing T lymphocytes by flow cytometry, the study of IFN-γ production by circulating lymphocytes in whole blood measured in an ELISA platform (Quantiferon), or the evaluation of the rate of IFN-γ-producing T lymphocytes specific by the ELISPOT IFN-γ technique. Currently, the two most widely used are the latter two; Quantiferon (Q-CMV, Cellestis/QIAGEN, Australia) and the IFN-γ ELISPOT technique (T-SPOT.CMV test, Oxford Immunotec, Oxford).

Although both QuantiFERON-CMV and ELISPOT assays measure the release of IFN-γ, there are several differences between them. QuantiFERON-CMV measures IFN-γ production in a defined volume of blood after ex vivo stimulation with class I-restricted CMV peptides, while the ELISPOT assay is performed on a defined number of peripheral blood mononuclear cells (PBMCs) and allows quantification of the number of cells secreting IFN-γ. Although there are several known CMV-specific proteins, pp65 and IE-1 have been identified as the predominant ones, and those are used with CMV ELISPOT. In general, QuantiFERON-CMV is simpler and faster to perform than CMV-ELISPOT because it does not require PBMC extraction. However, ELISPOT allows detection of both CD4 and CD8, whereas QuantiFERON-CMV detects only the CD8 response and is HLA type-dependent[13].

The use of QF-CMV has been shown to be a good predictor of CMV disease after cessation of anti-viral prophylaxis[14,15] and also after cessation of anti-viral treatment[16] in SOT, with a high negative predictive value in both cases. However, in lung transplantation and in R+, the value of QF-CMV as a predictive test for infection or disease is more doubtful. Thus, Wesseslindtner L et al.[10], in a single-center study involving 39 seropositive recipients, observed that 13/39 developed CMV infection (33%). The rate of CMV infection in those who had a specific immune response measured by QF-CMV was 18% (4/22) and 53% (9/17) in those who did not (p = 0.12). Using an IFNG concentration of 0.145 IU/ml as a cut-off point, the sensitivity was 30.7% and the specificity 30.7% for the prediction of significant CMV infection[10]. In another prospective, multicenter study in R+ positive QF-CMV lung transplant patients did not discriminate which patients developed significant CMV infection or disease after completion of prophylaxis. Thus, 14 (20%) of 69 patients with specific immune response measured by QF-CMV at the end of prophylaxis developed a significant infection or CMV disease compared with 2 of 16 (14.3%) without specific immune response (p = 0.185)[17].

The CMV ELISPOT technique has been shown to have a high predictive capacity, with the advantage of not having such a high rate of non-valuable tests because it does not depend on HLA antigens. In a study published by Lee et al.[13], they compared CMV ELISPOT with QF-CMV to predict CMV infection in

124 R+ renal transplant recipients in the first three months post-transplant. QF-CMV was not associated with the development of CMV infection but CMV ELISPOT were. With a cut-off level of 10 spots/200000 cells, it showed a sensitivity of 90 % and a specificity of 54 % with a positive predictive value of 25.9 % but a negative predictive value of 94.5 %. Other authors have reported similar results[18].

Risk stratification of CMV infection measured by CMV-specific cellular response prior to transplantation to adjust prophylactic treatment has already been investigated in an international clinical trial in renal transplant recipients. Briefly, Jarque et al.[19] studied 160 D+/R+ stratified by their baseline CMV-ELISPOT results and randomized to receive preemptive or 3-month antiviral prophylactic treatment[25]. The authors found that patients classified as high risk of infection (IE-1 < 20 spots/3x10^5 PBMCs), developed significantly higher CMV infection rates than patients at low risk with both preemptive (73.3% versus 44.4%; OR, 3.44 [95% CI, 1.30–9.08]) and prophylaxis (33.3% versus 4.1%; OR, 11.75 [95% CI, 2.31–59.71]) approaches. The authors concluded that monitoring CMV-specific cellular response can help in choosing the most appropriate CMV prophylaxis strategy in renal transplant recipients. It would be interesting to have a similar clinical trial in the lung transplantation. For the time being, what is available to us is a retrospective study published by our group[20], where we observed a higher rate of CMV infection with high levels of DNAemia in patients with CMV ELISPOT for IE-1 < 55 spots /3x10^5 PBMC when the valganciclovir prophylaxis was withdrawn.

In summary, CMV infection in lung transplantation is very frequent and can lead to disease if not treated in time. The most frequent and severe form of disease in lung transplantation is pneumonitis, with a high morbi-mortality due to both direct and indirect effects of the disease. The introduction of current prophylaxis strategies has significantly reduced CMV disease. However, these prophylaxis strategies have safety problems. New drugs and individualized prophylaxis strategies based on the study of the specific cellular immune response are being used to prevent these problems with promising results.

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