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Cytomegalovirus infection in kidney transplant patients: what is the best way to prevent it?

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The article published in this issue by Guirado et al.[1] analysed the results of a prospective study conducted in the 2004-2006 period in a group of patients receiving kidney transplants in whom the intervention to prevent infection by cytomegalovirus (CMV) (prophylaxis or pre-emptive therapy) was selected based on the infection risk of the patient. Authors identified as patients with a high risk for developing CMV disease negative recipients from positive donors (D+/R-), patients receiving antilymphocytic sera, and patients who need increased immunosuppression due to rejection episodes. This group received prophylaxis with valganciclovir for 100 days. Some positive PCR measurement was found in 47%, but only 4.5% developed CMV disease after prophylaxis was completed. In the low risk group, including receptor-positive patients, 30% had some positive PCR measurement. Most infections were asymptomatic, but 4.7% of patients developed the disease.

CMV infection occurs in 30%-80% of patients undergoing solid organ transplantation, but its incidence and the presence of symptomatic disease vary depending on transplant type, the presence of associated risk factors, and the prevention strategies used.[2,3]

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Not all patients transplanted solid organs have the same risk of developing CMV infection or disease. The main risk factor for CMV disease in solid organ transplant is transplantation from a seropositive donor (D+) to a seronegative recipient (R-) (D+/R-). Patients receiving antilymphocyte antibodies, such as antilymphocyte or antithymocyte polyclonal antibodies or monoclonal antibodies OKT3, are also considered high-risk patients. These preparations contain cytotoxic antibodies to antigens expressed in human lymphocytes and induce T cell depletion and release of cytokines, mostly tumour necrosis factor, leading to reactivation of infections caused by herpesviruses (mainly CMV and EBV).

The period with the highest risk of CMV infection is from the first to the sixth months, with a peak incidence between the second and third months. In primary infection (D+/R-), the lack of specific immunity in the recipient allows for a significant replication of CMV, resulting in symptomatic infection (CMV disease) that is sometimes highly severe. In reactivations, humoral and cellular immunity of the recipient decreases virus replication dynamics, therefore reducing disease incidence and severity.

In addition to direct effects, CMV infection also has indirect effects. Indirect effects are caused by inflammatory response, including cytokine production and release, or by changes in immune and inflammatory host responses. CMV replication induces an immunosuppression status due to the functional changes it causes in lymphocytes and monocytes, impairing response capacity and production of cytokines. These changes in immune response may explain the frequent association of CMV with other hospital-acquired infections (bacterial or fungal) or the development of opportunistic infections such as *P. jirovecii* pneumonia and invasive aspergillosis. CMV infection has also been associated to activation of other herpesviruses such as the herpes simplex, varicella-zoster, Epstein-Barr (associated to transplant-associated lymphoproliferative syndromes), or human herpes viruses (HHV-6, -7, -8).

Another indirect effect of CMV, related to host immunoactivation caused by the virus, is the development of graft rejection. This relationship appears to be bidirectional. Potential mechanisms include overexpression of molecules of major histocompatibility antigens, growth factors, and inflammatory cytokines enhancing expression of HLA class I antigens. In kidney transplant there is evidence of the influence of CMV infection on graft loss. CMV disease has been associated to the two main causes of late graft loss, cardiovascular disease and chronic graft rejection.[4-8]

A study published by Hartmann et al. reported the natural course of CMV infection and disease in a large cohort of kidney transplant recipients with no prophylaxis or pre-emptive therapy for CMV. This study allowed for understanding the impact of CMV on renal graft, graft and patient survival, and development of diabetes mellitus after transplant. The overall incidence of CMV infection in all patients during the first 100 days after transplant was 63%. Incidence of CMV disease was three times higher (56% *vs* 20%) among seronegative recipients from seropositive donors as compared to the other groups of seropositive recipients (D+/R+ y D-/R+). It may therefore be concluded that the incidence of CMV disease is particularly high in D+/R- patients in the absence of prophylaxis

or pre-emptive therapy, and use of measures to prevent CMV infection is recommended. With regard to diabetes development, a multivariate analysis found a four-fold incidence of diabetes among patients with asymptomatic infection as compared to patients without infection. This study also found that CMV was significantly associated to recipient death and graft loss within 100 days of transplant.[9]

There are two potential approaches for preventing CMV infection in transplant patients, *prophylaxis* and *pre-emptive therapy. Pre-emptive therapy* consists of regular monitoring using sensitive microbiological diagnostic procedures (pp65 antigenemia or CMV PCR) to detect the presence of CMV. If tests are positive based on a defined cut-off point, variable depending on the type of transplant and the procedure used, antiviral treatment is started until test negativisation and clinical resolution. Antiviral drugs used have varied over the years. For *prophylaxis*, an antiviral drug is continuously administered during the period of greatest risk following transplant.[10-13]

Pre-emptive therapy has shown beneficial effects in graft course and patient survival. The advent of an oral drug, such as valganciclovir (VGCV), with a good oral bioavailability and the development of sensitive diagnostic techniques such as pp65 antigenemia and PCR have allowed for taking this action in groups with less risk of CMV infection or disease, such as the D+/R+ group, and which are not receiving antilymphocyte antibodies (as induction or rejection treatment). Pre-emptive therapy costs less than because it is received by less patients. Drug exposure is shorter, which decreases toxicity associated to treatment and the risk of occurrence of antiviral resistance. In addition, the presence of low grade viremia allows for immune reconstitution against CMV.[11] Disadvantages of pre-emptive therapy include the need for frequent monitoring using sensitive diagnostic techniques, and good patient compliance in regular follow-up. Weekly monitoring for 3-4 months is not feasible in all settings. Moreover, according to some studies, the efficacy of this measure for preventing the indirect effects caused by asymptomatic CMV replication, such as risk of rejection and graft dysfunction, has not been elucidated.[14]

Universal prophylaxis is related to risk of delayed-onset CMV disease (occurring after the end of prophylaxis) and risk of development of resistance to ganciclovir (GCV) due to long-term exposure to antivirals.[15] As regards occurrence of resistance in patients on prophylaxis, a study by Eid et al. analysing this risk has recently been published. During a 4-year period, 225 recipients of D+/R- transplants received VGCV as prophylaxis for a median duration of 92 days. Twenty-nine percent of patients developed late-onset primary CMV disease. Resistant viral strains, with documented mutations in UL97 or UL54, were found in 6.2%.[16]

Arthurs et al. reported a liver transplant study examining the frequency of late-onset primary CMV infection in D+/R- patients administered VGCV prophylaxis for the first 100 days. Primary CMV infection was seen in 29% of patients 12-24 months after discontinuation of antiviral prophylaxis.[17]

There are several studies analysing the efficacy of VGCV for prophylaxis, particularly in the high-risk group. Akalin et al. analysed use of VGCV, GCV, or acyclovir in a group undergoing kidney or pancreas and kidney transplants. This study included patients receiving treatment with antilymphocyte antibodies, mismatched D+/R- patients, and patients with low or moderate risk. Overall disease incidence in the first year after transplant was 14%, with the greatest incidence occurring in D+/R- patients (47%). In addition, 25% of patients with antilymphocyte antibodies developed CMV disease.[18]

An additional study showed the efficacy of VGCV prophylaxis for preventing CMV in D+/T- patients. Overall incidence of CMV 12 months after transplant was 17.2% (*vs* GCV 18.4%).[12]

Another study by Taber et al. assessed the efficacy of valganciclovir for prophylaxis.[18] This was an analysis of the overall safety and efficacy of treatment with VGCV in patients at high risk of developing CMV disease, and also compared the safety and efficacy of prophylaxis in the D-/R+ group versus the group receiving antilymphocyte antibodies. Patients were given prophylaxis with VGCV for three months. The median follow-up time was almost one year after prophylaxis completion in both risk groups. The frequency of CMV disease in the D+/R- group was increased as compared to the ALA group (17% *versus* 0%).[19]

It was concluded that VGCV prophylaxis is safe and effective for preventing CMV disease in high-risk kidney or pancreas and kidney transplants. While a three-month prophylaxis following transplant appears to be sufficient for seropositive patients and those receiving antilymphocyte antibodies, the optimal duration of prophylaxis in D+/R- patients is not established. Some authors conclude that VGCV is as effective as GCV for preventing CMV, but high-risk patients may require higher doses or a longer duration.

Guidelines prepared by GESITRA-SEIMC and RESITRA in 2005 on the prevention and treatment of cytomegalovirus infection in transplant patients recommend use of prophylaxis in high-risk patients (D+/R-) and patients treated with antilymphocyte sera.[20]

In a D+/R- setting, prophylaxis is recommended with oral valganciclovir 900 mg/day or oral valacyclovir 2 g/6 h, or intravenous ganciclovir 6 mg/kg/day in the event of oral intolerance, for up to 3 months after transplant. Doses should be adjusted to kidney function in all cases. Shorter treatment durations have not been adequately evaluated.

In patients treated with antilymphocyte sera, use of intravenous ganciclovir 5 mg/kg/day, with kidney function adjustment, for at least 2 weeks was recommended during treatment with antithymocyte sera, plasmapheresis, or anti-CD20 antibodies. After publication of these recommendations, studies in high-risk patients also showing the efficacy of oral valganciclovir in this patient group have been reported.[19,21]

In patients with a low to moderate risk (R+), there are data supporting use of pre-emptive therapy with intravenous ganciclovir (5 mg/kg/12 h) adjusted to kidney function for 2 weeks

KEY CONCEPTS

1. Cytomegalovirus (CMV) is an herpesvirus that causes infection in 30%-80% of transplant patients.

2. CMV has both direct and indirect effects on evolution of patient and graft.

3. The period with a highest risk for CMV infection is from 1 to 6 months after transplant.

4. The group of patients with a high risk for CMV disease includes seronegative patients receiving organs from positive donors (D+/R-), patients given antilymphocyte antibodies, and patients receiving increased immunosuppression during rejection episodes.

5. There are two potential approaches for preventing CMV disease in transplant patients, prophylaxis and pre-emptive therapy.

6. Use of prophylaxis is recommended in the high-risk group, while preemptive therapy may be administered to the low-risk group.

under monitoring. It is desirable that replication parameters are negative or show a clear titre reduction. It is not uncommon for PCR values to remain positive for a longer time than antigenemia measurements. Good bioavailability of oral ganciclovir and its good results in high-risk patients make it likely to be effective in this indication at doses of 900 mg/12 h, adjusted to kidney function. Studies and data supporting use of VGCV for pre-emptive therapy have been reported.[22] There is a study analysing viral kinetics during treatment with VGCV or intravenous GCV. The median reduction in CMV DNA viral load was similar in both groups.[23]

The article by Guirado et al.[1] is an interesting contribution. The decision about treatment used to prevent CMV infection may be adapted to patient risk, selecting the preventive measure that is most effective and safe for the patient and also decreases the risks of unnecessary toxicity and long-term exposure. Results achieved with prophylaxis in the high-risk group and with pre-emptive therapy in the low risk group support this approach.

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