Alteration of Direct and Indirect Effects of Cytomegalovirus

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For recipients of a solid organ transplant, cytomegalovirus infection causes many pathological conditions including direct and indirect effects, most notably owing to the potency of the immunosuppressive medications used. Effects attributed to cytomegalovirus infection include graft rejection, decreased graft and patient survival rates, predisposition to other opportunistic infections, virally mediated malignancies, and various injuries specific to the transplanted organs (eg, accelerated coronary atherosclerosis following heart transplant, bronchiolitis obliterans syndrome in lung transplants, and vanishing bile-duct syndrome in liver allografts). Other indirect effects include posttransplant lymphoproliferative disorders, posttransplant new onset diabetes, and recurrence of hepatitis C virus infection. Direct effects are related to viral burden, whereas indirect effects may be observed even in the presence of low levels of cytomegalovirus replication. Being a function of the interaction between the virus and the host's immune and inflammatory responses, the underlying indirect effects of viral infection are not completely understood. Whereas it has been shown that cytomegalovirus prophylaxis can decrease the direct and indirect effects of the virus, recent data indicate that pre-emptive therapy has no long-term impact upon the indirect effects. Prevention of cytomegalovirus-related indirect effects might be achieved only with prophylaxis.

Key words: *CMV, Organ transplant, Kidney transplant, Prophylaxis, Valganciclovir, Antigenemia*

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Cytomegalovirus (CMV) is, evolutionarily, a very old virus. It belongs to the *Herpesviridae* family (subfamily *betaherpesvirinae*), as does human herpesvirus type 6. CMV is species-specific. Its seroprevalence in the general population ranges from 50% to 100%. Usually CMV primo-infection occurs in children and is often asymptomatic. Subsequently, CMV will remain latent, persisting in epithelial cells, monocytes/macrophages, endothelial cells, and fibroblasts. When immune surveillance decreases, the virus can become reactivated. The dynamics of CMV replication in humans are high, for example, virus-doubling time is about 1 day (1). CMV replication is under the control of T lymphocytes. Thus, in heart-transplant recipients, those with levels of CMV-specific CD4 T cells detectable during the first month after transplant have significant protection from high mean and peak posttransplant viral loads, acute rejection, and loss of allograft coronary-artery lumen and of whole-vessel area compared with patients who lack this immune response (2). Moreover, losses of lumen and vessel areas both are significantly correlated with the time after transplant at which a CD4 T-cell response is first detected plus the cumulative graft-rejection score (2). Low levels of CMV replication in lung-transplant recipients have been shown to be sufficient to both prime and recruit CMV-specific CD8+ T cells to the major-histocompatibility-complex–mismatched lung allograft (3). In addition, direct detection of CMV-specific T cells with an effector phenotype in the lung allograft suggests a protective antiviral function (3). In heart- and lung-transplant recipients, protection from CMV after transplant is correlated with an immediate, early, 1-specific CD8 T-cell, but not with a pp65-specific CD8 T-cell, response (4). In some renal-transplant patients, the absence of an anti-CMV T-cell response has been found to correlate with a lack of viral clearance after ganciclovir therapy, even when CMV isolates are not ganciclovir resistant (5).

The virologic diagnosis of CMV replication relies on the presence in blood of pp65 antigenemia or

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DNAemia. Conversely, RNAemia is less sensitive than pp65 antigenemia or DNAemia in indicating early CMV replication (6). In cases of primo-infection, CMV infection can be associated with the presence of anti-CMV IgM antibodies and eventually, with CMV IgG antibodies (7). Conversely, in the setting of CMV reactivation, CMV serology is of no use.

CMV infection results in direct and indirect effects (8). The direct effects are correlated with the peak of viremia and include the CMV syndrome (ie, a flulike syndrome with sustained fever); mononucleosis syndrome; and tissue-invasive diseases such as hepatitis, myocarditis, pneumopathy, pancreatitis, colitis, retinitis. There is a predilection for the greatest virological-related pathology to occur within the transplanted organ, that is, liver-transplant patients will have hepatitis, and lung-transplant patients have pneumonitis. CMV-infected-tissues show CMV antigens on the cell surfaces, which lead to host-immune responses. The immune response coupled with lysis of the infected cells, results in destruction of infected tissues.

The indirect effects of CMV infection are independent of a high level of CMV viremia and result in part from the effect of the virus on the host's immune response in the setting of long periods of low-level of CMV replication. This translates into organ allograft injuries (eg, acute or chronic rejections) and suppression of the systemic immune response, thereby leading to opportunistic infections or facilitated replication of viruses such as Epstein-Barr virus (EBV) (9) and hepatitis C virus (HCV) (10). It has been shown that CMV-related indirect effects are decreased or prevented by CMV prophylaxis in animal models (11,12) and in humans (13) but probably not by CMV pre-emptive therapies in humans (13).

In experimental models of kidney, heart, liver, and lung transplants, CMV infection increases the risk of acute and chronic rejections, as well as an inflammatory response within the allograft (11, 12, 14, 15). These effects might be prevented or reduced by CMV prophylaxis with ganciclovir. In humans, before the era of CMV prophylaxis, Grattan and associates showed that CMV disease in heart-transplant recipients was significantly associated with the development of coronary artery vasculopathy. By 5 years after transplant, coronary artery vasculopathy was present in less than 10% of patients who did not have CMV disease compared with it being present in more than 35% of those who did have CMV disease (16). In lung-transplant patients, those who presented with subclinical infection (ie, asymptomatic DNAaemia or the presence of asymptomatic CMV in fluid following bronchoalveolar lavage) had a greater risk of developing bronchiolitis obliterans 4 years after transplant then did those who had never experienced CMV reactivation (17). CMV prophylaxis can reduce the risk of acute rejection in donor-positive (D+) and in recipient-negative (R-) renal-transplant patients receiving valaciclovir CMV prophylaxis (18), in kidney-pancreas recipients receiving ganciclovir prophylaxis (19), and in D+/R- heart-transplant patients receiving valganciclovir plus CMV hyper-immune globulin prophylaxis (20). Moreover, in heart-transplant recipients, CMV prophylaxis with valganciclovir can reduce the risk of coronary artery vasculopathy as demonstrated by intravascular ultrasound studies (20).

CMV infection is a risk factor for developing de novo diabetes after kidney transplant. Hjelmesaeth and associates found that de novo diabetes was present in 26% of kidney recipients who had asymptomatic CMV infection that had occurred during the first 100 days after transplant compared with only 6% of patients who had no CMV infection (P = .003) (21). However, it has not yet been shown that CMV prophylaxis prevents the development of diabetes after kidney transplant.

CMV infection increases the risk of developing posttransplant lymphoma. Manez and associates conducted a retrospective study in 37 EBV D+/R- liver-transplant recipients (9). Of these 37 patients, 95% developed an EBV primo-infection, and 37% developed posttransplant lymphoma. The only predictive factor that was significantly associated with the development of posttransplant lymphoma was CMV disease (relative risk, 7.3; CI 95%, 2.36-22.6; P = .0006). Moreover, prophylaxis against CMV infection also decreased the number of posttransplant lymphomas. In a multicenter case-control study, the benefits of antiviral treatment with ganciclovir or acyclovir on the development of posttransplant lymphoma in de novo renal-transplant patients were evaluated (22). Antiviral therapy reduced the risk of posttransplant lymphoma by 83%. For each 30-day period of CMV prophylaxis with ganciclovir, the risk of developing posttransplant lymphoma was reduced by 38% (odds ratio, 0.62; CI 95%, 0.38-1). Conversely, acyclovir CMV prophylaxis was less efficient in preventing posttransplant lymphoma (odds ratio, 0.83; CI 95%, 0.59-1.16).

In HCV-positive liver-transplant patients, it has been suggested that the pathogenesis of hepatitis C virus is influenced by CMV (10). However, a recent study showed that liver-transplant recipients with CMV infection, including high-risk D+/R- patients, when followed-up using a pre-emptive therapy

approach, had no significant difference in meaningful outcomes (eg, HCV recurrence rates and rejection and survival rates) when compared with patients in whom CMV infection had never developed and who had not received antiviral prophylaxis for CMV (23).

Evidence for CMV-related indirect effects has been reported in prophylaxis studies. In a recent meta-analysis, Kalil and associates reported that in multiorgan-transplant recipients, universal prophylaxis against CMV was associated with a significant decrease in all-cause mortality rates, as well as in CMV-related mortality (24). Another recent meta-analysis showed that compared with a placebo or no prophylaxis, CMV prophylaxis significantly decreased CMV infection, CMV disease, mortality related to CMV disease, and all-cause mortality (25). CMV prophylaxis also might modify the natural posttransplant history of some viruses, such as human herpesviruses 6, 7, and 8; Varicella zoster virus; EBV; polyomavirus; and adenovirus (26). Compared with placebo, prophylaxis against CMV reduced herpes type 1 and 2 infections by 73%, Varicella zoster infection by 35%, and protozoal infections by 69%. However, it did not significantly reduce fungal infections (see Figure 1) (25). With regard to acute rejection, Opelz and associates showed that, in heart-transplant recipients at risk for CMV (ie, D+/R-), patient survival rates were 8% higher in those who received CMV prophylaxis compared with patients who received no prophylaxis (27).

Although CMV prophylaxis has been shown to decrease the direct and indirect effects of CMV, it is not clear whether pre-emptive therapy has an impact on the indirect effects of CMV. Some recent data suggest that it does not (13). A recent study by Radermacher and associates showed that in renal-transplant recipients, compared with pre-emptive ganciclovir therapy, CMV prophylaxis with ganciclovir increased long-term allograft survival after 4 years of transplant by 13.9%. This differs from a recent small study in kidney transplant patients with a short follow-up that demonstrated that use of valganciclovir as a universal prophylaxis was equivalent to pre-emptive therapy with respect to efficacy and costs (28).

In conclusion, CMV is responsible for direct and indirect effects, and prophylaxis can prevent both of these. Conversely, prevention of CMV-related indirect effects is not achievable with pre-emptive therapy.

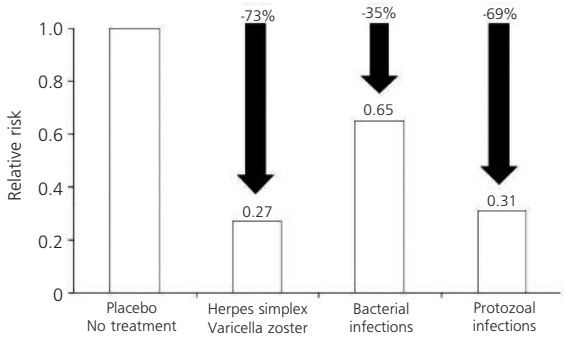

Figure 1: Effects of CMV prophylaxis on the occurrence of concomitant infections. Adapted from Hodson and associates (25).

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