Immunologic Predictors of Late Cytomegalovirus Disease after Solid Organ Transplantation—An Elusive Goal?

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(See the article by La Rosa et al., on pages 633–44.)

Late cytomegalovirus (CMV) disease is a well-described clinical problem after solid organ transplantation in the era of universal prophylaxis with ganciclovir and valganciclovir [1–3]. This complication occurs after liver, heart, lung, kidney-pancreas, and kidney transplantation and is most significant in CMV-seronegative recipients of a graft from a seropositive donor (D+/R−), with ~25%–30% of these patients developing late CMV disease at a median of 5 months after transplantation [1, 2, 4–9]. An association of late CMV disease with drug-resistant virus has been reported in D+/R− transplant recipients following oral ganciclovir prophylaxis, and after lung transplantation [2, 5, 10]. Late CMV disease has also been associated with infection-related mortality after liver transplantation [4]. The clinical manifestations depend on the organ transplant setting but principally include CMV syndrome and visceral end-organ disease in roughly equal proportions [3, 4]. CMV has also been implicated in late rejection of the transplanted organ, especially in kidney, heart, and lung transplantation [11, 12]. Notably, late CMV disease may be a lesser problem in D+/R− liver transplant recipients who receive preemptive therapy with ganciclovir or valganciclovir instead of prophylaxis [13]; however, the studies indicating this possibility were relatively small, and a randomized comparison of the risks of late CMV disease in D+/R− transplant recipients with these 2 prevention strategies has not been done [14].

Several strategies have been used to prevent late CMV disease in solid organ transplant recipients, including continuation of prophylaxis beyond 3 months or continuation of virologic monitoring with preemptive therapy. However, these approaches have not been systematically studied, and both require continued monitoring of drug toxicity and/or CMV, which is costly, affects quality of life, represents an unnecessary intervention in approximately two-thirds of patients (since only one-third develop disease), and is often impractical for patients who live in remote locations. Continued surveillance and preemptive therapy may also miss cases of disease that occur soon after or concurrently with CMV infection [15]. Extending prophylaxis beyond 3 months carries additional problems, such as drug toxicity, and may simply delay the onset of late disease even further.

Because of the limitations of the current approaches to preventing late CMV disease, there has been interest in developing immunologic assays that might identify the patients at highest risk for late CMV disease. Immunologic parameters that identify hematopoietic stem cell transplant recipients at high risk for late CMV disease have been reported [16, 17]. In this issue of the Journal, La Rosa et al. report a longitudinal assessment of CMV-specific T cell responses in D+/R− liver transplant recipients who received 3 months of valganciclovir prophylaxis [15]. No antiviral intervention was given later than 3 months after transplantation. The study confirmed a high rate of late CMV disease and showed a strong association between late CMV disease and high-level plasma DNAemia. Interestingly, plasma DNAemia did not always precede CMV disease in this relatively small cohort. This may have partially resulted from the fact that patients were monitored biweekly. However, it does emphasize the potential limitations of late surveillance as a predictor for late CMV disease unless it is done weekly—which may not be feasible for all patients.

The major emphasis of the study by La Rosa et al. was on monitoring CMV-specific T cell responses by measuring interferon (IFN)-γ release after stimulation of
peripheral-blood cells with CMV lysate or peptide libraries spanning the pp65 and immediate early (IE) 1 CMV antigens. The investigators used a rigorous monitoring schedule and analyzed blood samples every other week between months 4 and 6 after transplantation (when late CMV disease peaks) and monthly thereafter. CD4+ and CD8+ T cells that produced IFN-γ in response to CMV antigens were detected in all patients, demonstrating that priming of CMV-specific T cell immunity occurs in the presence of immunosuppressive drugs given to prevent graft rejection. The key and somewhat unexpected finding of the study was that the presence or absence of T cell responses was not predictive of the occurrence of CMV disease or plasma DNAemia. Global measurements of immunosuppression, such as low lymphocyte counts, were also not predictive.

The results of the study by La Rosa et al. are noticeably different from those reported for CMV-seropositive hematopoietic stem cell recipients, in whom a protective role for CMV-specific T cell immunity occurs after transplantation (when late CMV disease peaks) and monthly thereafter. CD4+ and CD8+ T cells that produced IFN-γ in response to CMV antigens were detected in all patients, demonstrating that priming of CMV-specific T cell immunity occurs in the presence of immunosuppressive drugs given to prevent graft rejection. The key and somewhat unexpected finding of the study was that the presence or absence of T cell responses was not predictive of the occurrence of CMV disease or plasma DNAemia. Global measurements of immunosuppression, such as low lymphocyte counts, were also not predictive.

The results of the study by La Rosa et al. are noticeably different from those reported for CMV-seropositive hematopoietic stem cell recipients, in whom a protective role for CMV-specific T cell responses was first described [16]. The findings also differ from recent results in solid organ transplant recipients showing that IFN-γ–producing pp65- or IE1-specific CD8 T cells correlated with protection from CMV infection or disease [18–20]. The latter studies were predominantly performed in seropositive recipients who had preexisting memory T cell responses to CMV. Thus, one possible explanation for the results obtained by La Rosa et al. is that the differentiation of CMV-specific T cells from naive precursors may be kinetically or qualitatively different in seronegative recipients receiving valganciclovir prophylaxis and immunosuppressive drugs. The acquisition of the ability to secrete IFN-γ alone may not be a sufficient indicator of a protective T cell response, and additional assays of effector function (e.g., interleukin-2, tumor necrosis factor–α, and degranulation), homing capabilities, or other parameters may be necessary to define protective T cell immunity to CMV [21, 22]. Recent studies have also identified a role for the up-regulation of inhibitory molecules, such as programmed death (PD)-1, in impairing the efficacy of T cell immunity to persistent viruses [23–26]. CMV-specific T cells express PD-1, and it is unknown whether the levels of this or other inhibitory molecules might be increased in D+/R- patients who develop a T cell response during immunosuppressive drug therapy. Finally, the T cell response to CMV recognizes a large number of viral determinants [27, 28], and measurement of responses to pp65 and IE1 may not always be a sufficient surrogate to define protective immunity.

How can late CMV disease be prevented, and is there a role for immunologic monitoring? The data presented by La Rosa et al. raise interesting questions with regard to the primary CMV immune response after valganciclovir prophylaxis. Clearly, additional studies are needed to better characterize the phenotype and functional properties of T cells that develop after antiviral prophylaxis in this setting. Optimally, one would like to perform a single test at the end of prophylaxis to stratify patients by risk into those who need additional prophylaxis or extended surveillance and preemptive therapy and those who need no further intervention. Given the rapid dynamics of CMV infection and disease as well as the potential complexity of immunologic responses during the period directly following prophylaxis, it appears doubtful that this can be readily accomplished. On the basis of the data currently available, serial immunologic testing (potentially even combined with virologic monitoring) would be required, which would raise feasibility and cost concerns similar to those present with virologic monitoring alone. Another possibility for risk stratification might be determining other, as-yet unknown factors of host susceptibility. This could include differences in innate immune functions conferred by Toll-like receptor gene polymorphisms or NK cell function [29, 30].

Also, currently available prevention strategies other than ganciclovir-based prophylaxis might be superior with regard to preventing the development of late CMV disease in D+/R- patients. It has been suggested that preemptive therapy results in less late CMV disease, even in D+/R- patients [31, 32]. A recent meta-analysis suggested no differences in overall CMV disease between prophylaxis and preemptive therapy [14]; however, the issue of late CMV disease was not specifically addressed in the D+/R- subset. A randomizated trial of the 2 strategies is needed to compare the risks of early and late CMV disease, the indirect effects of CMV infection (such as organ rejection and invasive non-CMV infections), and overall survival in D+/R- patients. Finally, augmenting CMV-specific immunity by vaccination in combination with antiviral prophylaxis is perhaps the most intriguing and promising strategy in the D+/R- setting. One possible strategy could be to vaccinate seronegative transplant candidates to induce CD4+ and CD8+ memory T cells before transplantation and exposure to immunosuppressive drugs, followed by posttransplantation antiviral drug prophylaxis with or without additional booster vaccination during prophylaxis. This might result in the generation of a pool of memory T cells capable of providing protective immunity when antiviral prophylaxis is discontinued and, therefore, eliminate the requirement for additional late prevention strategies. Candidate vaccines for CMV are available and should be tested in this setting.

References


3. Stilfin M, Tempe M, Poutsia D, Snyderman DR. Late and atypical cytomegalovirus