Optimal Prevention of Late-Onset Cytomegalovirus (CMV) Disease and Other Sequelae of CMV Infection in Organ Transplant Recipients

To the Editor—Legendre et al. [1] address an important and topical issue—namely, late-onset cytomegalovirus (CMV) disease in transplant recipients who receive antiviral prophylaxis. A number of points in their report, however, warrant clarification or closer scrutiny. The authors assuage the profound clinical relevance of late-onset CMV disease by noting that this entity—at least in renal transplant recipients—is a mild event [1]. A recent study [2] found that CMV disease developed in 29% of previously CMV-negative recipients of renal transplants from CMV-positive donors receiving long-term antiviral prophylaxis; CMV disease comprised tissue-invasive disease in 51% of these cases and was clinically attributable to ganciclovir-resistant virus in 16%. Tissue-invasive CMV disease was independently associated with allograft loss and mortality [2]. Late-onset CMV disease was also independently predictive of mortality in the first year after liver transplantation [3]. Thus, late-onset CMV disease cannot be considered a benign occurrence.

The lynchpin of the authors’ viewpoint is that extending the duration of antiviral prophylaxis will improve outcomes in transplant recipients [1]. Supportive data are cited that indicate a 7% prevalence of CMV disease among renal transplant recipients who received antiviral prophylaxis for 24 weeks, compared with a 31% prevalence of CMV disease among those who received a 12-week course [4]. It should, however, be noted that the 7% incidence of CMV disease in the former group is still high, compared with the rates of 2%–6% that are attainable with preemptive therapy in the current era [5, 6].

In support of long-term antiviral prophylaxis, the authors’ argument concerning the association of CMV viremia with CMV disease and graft survival is valid. However, subclinical viremia, if promptly aborted, and viral replication that is not allowed to progress to prolonged or sustained CMV viremia are not associated with suboptimal outcomes [7]. Existing data show that it is persistent or sustained CMV viremia that is a contributor to CMV disease or allograft dysfunction [8–10]. Indeed, preemptive treatment of controlled viral replication with a potent antiviral agent has been shown to be an effective approach in preventing CMV disease, even in high-risk transplant recipients [6, 11, 12].

Finally, the fact that ganciclovir is an antiproliferative agent with the potential to impair virus-specific host responses cannot be discounted. Ganciclovir decreased T cell proliferation by 50%, which cannot be discounted. Ganciclovir decreased T cell proliferation by 50%, which is similar to the reduction observed with cyclosporine [13]. Delayed maturation of CMV-specific IgG correlated with prolonged viremia, and receipt of ganciclovir delayed IgG seroconversion [14]. Indeed, CMV disease occurred shortly after discontinuation of a 5-year course of ganciclovir, suggesting that the risk of late-onset CMV disease persists even after prolonged antiviral prophylaxis and as long as virus-specific or yet-to-be-defined CMV host defenses remain suboptimal [15]. Thus, simply prolonging the duration of antiviral prophylaxis to achieve optimal CMV-related outcomes must take into consideration the complex host-virus interactions during receipt of antiviral prophylaxis. We agree that the Improved Protection Against CMV in Transplants (IMPACT) study, which compared a 100-day regimen of valganciclovir prophylaxis with a 200-day regimen in a group of renal transplant recipients, is an important step in discerning the effect of duration of prophylaxis on outcome [1]. However, this study will not address whether preemptive therapy is a comparably effective approach for optimizing CMV-related outcomes in transplant recipients.

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Reply to Singh

TO THE EDITOR—We read the letter from Singh [1] with great interest, because she outlined several important issues that may not be easy to clarify. The recent article by Arthurs et al. [2], which was not available when we wrote our review, suggests that late-onset cytomegalovirus (CMV) disease may not be as mild as has been previously reported by others. In our long-lasting experience with anti-CMV prophylaxis [3], late-onset CMV disease was perceived and evaluated as a relatively mild event, at least in kidney transplant recipients, with few symptoms and a benign course after receipt of ganciclovir or valacyclovir therapy. It should be noticed that the figures reported by Arthurs et al. [2] were unusually high: a 29% incidence of late-onset CMV disease, compared with incidences of 16% in the valganciclovir group in the study by Lowance et al. [3] and 17.2% (in the valganciclovir group) and 18.4% (in the oral ganciclovir group) in the pivotal study by Paya et al. [4]. In our own experience, 17% of kidney transplant recipients develop late-onset CMV disease (data not shown). Although the cause is not clear (because these transplant recipients were at high immunological risk), the relatively high figures reported by Arthurs et al. [2] may have affected the results regarding the impact of late-onset CMV in terms of allograft loss or mortality.

The discussion about the consequences of late-onset CMV disease is more than an academic debate. Indeed, it is aimed at answering relevant questions regarding the best means to prevent post-transplantation CMV disease. Data from a recent meta-analysis indicated that both prophylaxis and preemptive treatment reduced the incidence of CMV disease and of acute transplant rejection; however, prophylaxis without preemptive treatment did reduce the incidence of bacterial and fungal infections and death [5]. When prophylaxis and preemptive treatments were compared with one another, there was, indeed, no statistically significant difference with regard to efficacy in the prevention of CMV disease [6, 7]. However, in the study by Reischig et al. [6], there were slight and statistically significant benefits in the prophylaxis group with regard to CMV-DNAemia at 12 months, incidence of biopsy-proven acute rejection, and CMV-associated costs. Moreover, in the recent study by Kliem et al. [7], long-term graft survival at 2, 3, and 4 years was significantly improved in the prophylaxis group. These recent data, together with the simple use of prophylaxis after transplantation, suggest that the prophylactic approach may become a more attractive strategy to prevent CMV disease after organ transplantation.

Finally, as mentioned by Singh [1], the issue of the most appropriate duration of antiviral prophylaxis will be partly solved by the ongoing Improved Protection Against Cytomegalovirus in Transplant (IMPACT) study. If, among high-risk patients undergoing donor-positive recipi-ent-negative transplantations, the incidence of late-onset CMV disease decreases as the length of anti-CMV prophylaxis increases, this may have a beneficial impact on morbidity and mortality that would be an important new step in defining the optimal CMV disease prevention strategies.

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