Preemptive versus Prophylactic Approaches in the Management of Cytomegalovirus Disease in Solid Organ Transplant Recipients: What We Know and What We Do Not Know

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(See the article by Small et al. on pages 869–80)

Different approaches have been used to mitigate the morbidity and mortality associated with cytomegalovirus (CMV) infection after solid organ transplantation [1]. Agents such as CMV hyperimmune globulins, acyclovir, valaciclovir, ganciclovir, and valganciclovir have been used preemptively or prophylactically in numerous clinical studies. However, a majority of these studies were neither designed nor powered adequately to answer the most important questions they were supposed to have addressed. In fact, a few large prophylactic studies [2–4] have helped promote prophylaxis, but there is still a significant debate between supporters of the preemptive and of the prophylactic methods [5–7], resulting in somewhat complex guidelines for the management of CMV infection [8, 9]. In addition, over the years, it has been recognized that, aside from direct effects (i.e., morbidity directly attributable to CMV infection), CMV as an immunoregulatory virus is also responsible for indirect effects (i.e., acute and perhaps chronic allograft rejection and secondary fungal and bacterial infections) [10]. Finally, it has been realized that prophylaxis against CMV disease modifies the time course of the viral infection, causing late-onset disease, which typically occurs after prophylaxis discontinuation [3, 11]. This has led to the definition of new end points and to an increase in the duration of follow-up as necessary parts of any study evaluating the management of CMV infection after transplantation. In view of the paucity of evidence and the lack of consensus regarding the optimal method for preventing CMV infection, it was tempting to try to make the best use of data by meta-analysis of existing studies.

In this issue of *Clinical Infectious Diseases,* Small et al. [12] publish the fourth meta-analysis of antiviral therapies for preemptive or prophylactic approaches to CMV infection in solid organ transplant recipients [13–15]. Unlike the studies by Hodson et al. [14] and Strippoli et al. [15], which are meta-analysis studies comparing universal prophylaxis and preemptive therapy with placebo, respectively, Small et al. [12], like Kalil et al. [13], conducted a meta-analysis of randomized, controlled studies using either the preemptive or the prophylactic approach and calculated the relative risk for CMV disease, mortality, organ rejection, graft loss, and opportunistic infection for each approach, compared with placebo. In addition, Small and colleagues statistically compared the relative risk conferred by each antiviral approach. Small and colleagues have used somewhat different inclusion criteria regarding quality of randomization and blinding leading to the analysis of a set of studies that is larger than that of previous meta-analyses [13–15]. Perhaps more importantly, Small and colleagues used a restricted definition of active anti-CMV therapy based on the use of ganciclovir or valganciclovir, compared with any other approach (including acyclovir based-regimens) that was deemed suboptimal enough to be considered a control. In so doing, it focused on a somewhat more homogeneous group of studies regarding the active arm (ganciclovir or valganciclovir), but it included as controls quite inhomogeneous groups of patients who may have received partly effective anti-CMV drugs, which probably accounted in part for the extraordinary range of CMV disease incidence in the control groups (5%–

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90%). Of note is that this methodology led to the exclusion of the largest prophylaxis study of kidney transplant recipients, in which the active arm received a large dose of valaciclovir, an effective prophylactic regimen [3]. Indeed, it is interesting to compare the results of the various meta-analyses that have been performed to date and to see what they reveal (or do not reveal) in terms of CMV infection prevention efficacy.

Regarding the incidence of CMV disease, the present analysis suggests a statistically nonsignificant trend of greater risk reduction with preemptive therapy, compared with universal prophylaxis. By comparison, Kalil et al. [13] found a higher risk reduction with universal prophylaxis, and these discordant trends may be explained by the differences in the definition of the control group, as noted above. In addition, a pitfall exists in the analysis of the preemptive approach that pertains to the time of randomization. In some studies [16], patients were monitored for viremia and were randomized at the time they tested positive for viremia to receive either preemptive therapy or placebo. In this strategy, patients presenting with concurrent viremia and CMV disease are not eligible for enrollment, although, arguably, they should be counted as failures of the preemptive approach. In fact, among patients considered for enrollment in preemptive studies included in the meta-analysis by Strippoli et al. [15], 0%–32% were excluded because CMV disease developed before (or concurrently with) CMV viremia, possibly leading to an overestimate of the efficacy of the preemptive approach at preventing CMV morbidity.

Indeed, the analysis by Small et al. [12] would be a lot more informative if the study data allowed for separate analysis of the incidence of early-onset (<3 months) and late-onset (>3 months) CMV disease and if the analysis had been performed by stratifying patients in high-risk (donor [+]/recipient [−]) and intermediate-risk (donor [+]/recipient [+] and donor [−]/recipient [+]) groups. From several large-scale prophylactic studies [2, 3], we know that universal prophylaxis, especially use of state-of-the-art valganciclovir [4], is close to 100% effective at suppressing viremia and preventing CMV disease, even in high-risk patients, for the period of prophylaxis. During that period, the preemptive approach will have at least a failure rate corresponding to the concurrent presentation of viremia and disease.

After discontinuation of prophylaxis, some patients experience late-onset CMV disease, but at a reduced rate and severity, compared with what they would have experienced earlier in the absence of prophylaxis [3, 4]. It has been hypothesized that the preemptive approach, by allowing some early CMV replication and immune stimulation, may be associated with a reduced rate of late-onset CMV disease, compared with prophylaxis [17]. However, there are very few data from randomized studies to support this view. At our institution, in a noncomparative study of the preemptive approach, we reported that donor (+)/recipient (−) recipients were at a high risk of experiencing a protracted course of CMV infection lasting up to several months, a result that is inconsistent with the hypothesis that some early viral replication in the frame of the preemptive strategy is sufficient to generate protective immune responses [18]. Overall, although this new meta-analysis reveals a similar efficacy of the prophylactic and preemptive approach (reducing CMV disease incidence by approximately two-thirds), it fails to reveal important information regarding the efficacy of prophylaxis during and after drug administration, as shown by large prophylactic studies [2–4].

Regarding acute rejection, one is struck again by the extraordinary range of acute rejection incidence among trials (3%–74%). Besides inclusion of different organ transplant categories and different definitions of acute rejection, this high range may be a result of the large time period during which these studies were conducted, a period during which there has been major progress in the immunosuppressive regimens. It is an irony that this meta-analysis excluded the Lowance study [3], which demonstrated that CMV prophylaxis reduces the rate of acute rejection in high-risk (donor [+]/recipient [−]) patients, and that, interestingly, the post-prophylaxis recrudescence of late-onset CMV disease does not translate into an increase in acute rejection. Again, we wonder whether the present analysis failed to detect a significant risk reduction for acute rejection, in contrast to the findings of Kalil et al. [13], because in some studies, quite active prophylaxis was considered to be a control.

As acknowledged by Small et al. [12], the failure of detecting effects regarding other end points, such as mortality, graft loss, and opportunistic infection, may reflect the lack of data rather than the lack of effect of either approach. Indeed, other meta-analyses have indicated that universal prophylaxis is associated with a decrease in the incidence of viral, bacterial, and fungal infections, as well as a decrease in the number of patient deaths [13, 14].

In fact, the present paper is a new and useful attempt at making the best use of data generated over the past 15 years. Considering the small number of eligible studies, especially studies of the preemptive approach, and the relatively small size of the majority of those studies (see tables 1 and 2 of Small et al. [12]), one can only agree with the authors' conclusion that, ultimately, "additional trials that directly compare the 2 prevention strategies are warranted and needed before the CMV prevention debate can be resolved" [12, p. 878]. Such clinical trials should monitor for CMV infection and disease at least for 1 year after transplantation and analyze data by stratifying patients according to their CMV donor/recipient serostatus and analyzing late CMV disease separately. More importantly, such trials should also include data regarding chronic allograft dysfunction, because it is suspected that CMV-related events and their management in the early months following trans-

plantation may affect subsequent chronic allograft injury [19].

Where do we go from here? For the most part, the transplant infectious disease community has been working in a relatively small-scale, single-center, single transplant–program manner, and the time has come to organize larger prospective transplant cohorts to facilitate the analysis of sufficient numbers of transplant patients. The organization of a large, randomized, controlled trial, such as the one proposed by Small et al. [12], would certainly reveal to us the relative merits of the preemptive approach versus the prophylactic approach, particularly regarding late-onset CMV disease, chronic allograft injury, and cost effectiveness. After taking into account the different incidences of CMV disease in various organ transplant populations and serostatus patterns, the answers may be found to vary accordingly. Similar multicenter studies should also address questions regarding optimal dose and duration of universal prophylaxis with modern efficacious agents, such as valganciclovir. It is likely that a few well-organized, randomized, controlled trials will produce much more evidence than well-conducted meta-analyses of many small, nonstandardized studies.

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References

1. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med **1998**; 338: 1741–51.
2. Gane E, Saliba F, Valdecasas GJC, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. Lancet **1997**; 350:1729–33.
3. Lowance D, Neumayer HH, Legendre CM, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. N Engl J Med **1999**; 340:1462–70.
4. Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant **2004**; 4:611–20.
5. Singh N. Preemptive therapy versus universal prophylaxis with ganciclovir for cytomegalovirus in solid organ transplant recipients. Clin Infect Dis **2001**; 32:742–51.
6. Singh N. Late-onset cytomegalovirus disease as a significant complication in solid organ transplant recipients receiving antiviral prophylaxis: a call to heed the mounting evidence. Clin Infect Dis **2005**; 40:704–8.
7. Snydman DR. Counterpoint: prevention of cytomegalovirus (CMV) infection and CMV disease in recipients of solid organ transplants: the case for prophylaxis. Clin Infect Dis **2005**; 40:709–12.
8. Preiksaitis JK, Brennan DC, Fishman J, Allen U. Canadian society of transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final report. Am J Transplant **2005**; 5:218–27.
9. Cytomegalovirus. Am J Transplant **2004**; 4: 51–8.
10. Rubin RH. The indirect effects of cytomegalovirus infection on the outcome of organ transplantation. JAMA **1989**; 261:3607–9.
11. Akalin E, Sehgal V, Ames S, et al. Cytomegalovirus disease in high-risk transplant recipients despite ganciclovir or valganciclovir prophylaxis. Am J Transplant **2003**; 3:731–5.
12. Small LN, Lau J, Snydman DR. Preventing post–organ transplant cytomegalovirus disease with ganciclovir: a meta-analysis comparing prophylactic and preemptive therapies. Clin Infect Dis **2006**; 43:869–80 (in this issue).
13. Kalil AC, Levitsky J, Lyden E, Stoner J, Freifeld AG. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. Ann Intern Med **2005**; 143:870–80.
14. Hodson EM, Jones CA, Webster AC, et al. Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: a systematic review of randomised controlled trials. Lancet **2005**; 365:2105–15.
15. Strippoli GF, Hodson EM, Jones C, Craig JC. Preemptive treatment for cytomegalovirus viremia to prevent cytomegalovirus disease in solid organ transplant recipients. Transplantation **2006**; 81:139–45.
16. Paya CV, Wilson JA, Espy MJ, et al. Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. J Infect Dis **2002**; 185:854–60.
17. Singh N. Cytomegalovirus infection in solid organ transplant recipients: new challenges and their implications for preventive strategies. J Clin Virol **2006**; 35:474–7.
18. Muheim C, Vogel G, Seydoux C, et al. Determinants of protracted cytomegalovirus infection in solid-organ transplant patients. Transplantation **2002**; 74:226–36.
19. Valantine HA, Gao SZ, Menon SG, et al. Impact of prophylactic immediate posttransplant ganciclovir on development of transplant atherosclerosis: a post hoc analysis of a randomized, placebo-controlled study. Circulation **1999**; 100:61–6.