Randomized Trial of Pre-Emptive or Prophylactic Valganciclovir Therapy for Prevention of Cytomegalovirus Infection in Renal Transplantation

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In this issue of JASN, Reischig et al.1 report important information on a randomized trial of pre-emptive or prophylactic valganciclovir therapy in renal transplant recipients. It is the follow-up of a prospective trial of 70 initial patients transplanted between October 2003 and August 2006 who were randomized to receive either preemptive valganciclovir (VGCV; n=36), 900 mg twice daily for 2–3 weeks, on detection of significant cytomegalovirus (CMV) viremia (>2000 copies per milliliter of blood) or prophylactic valacyclovir (VACV; n=34), 2 g four times daily for 3 months, adjusted for renal function as necessary.2 The study used an intention-to-treat analysis. This is important because 32% of the patients needed a dose reduction or discontinuation of VACV because of hallucinations, other neurologic difficulties, and cytopenias. Another important finding in the initial study was that patients in the VACV prophylaxis arm experienced significantly less early acute rejection by 1 year (16% versus 36%) and less subclinical rejection (6% versus 11%).

The lower incidence of acute rejection in the VACV prophylaxis-treated group was surprising, but confirmed the authors’ previous work comparing VACV to oral ganciclovir (OGCV) prophylaxis and deferred therapy in which they found acute rejection rates by 1 year of 12%, 34%, and 58%, respectively.3 The lower rejection rate partially confirmed the work of others showing that VACV was associated with less acute rejection in the CMV donor seropositive/recipient seronegative group (CMV D+/R−), but not when the recipient was CMV seropositive (R+).4 The relationship with CMV and rejection is complex. Others have previously shown that symptomless CMV may appear histologically as acute rejection that responds to intravenous ganciclovir rather than increased immunosuppression in patients with late acute rejection occurring 2–7 years after transplant.5 Important differences between these studies, however, are that in the present study there were only two patients in the pre-emptive group with CMV disease after 1 year and only three patients in the prophylactic group with CMV disease. Furthermore, there was only one patient in the prophylactic group with an acute rejection episode after 1 year in the present study.1

At first glance, these remarkable findings suggest that VACV may be one of the best immunosuppressants introduced in the last two decades. Alternatively, control of CMV, especially early, by whatever means, may lessen the rate of acute rejection. The present paper provides a nuance to what it means to control CMV.

In this follow-up study, 55 patients were available to undergo protocol biopsies at 3 years, but only 49 actually underwent biopsies and had enough tissue for mRNA analyses.1 At 3 years, the intrarenal allograft biopsies showed that the incidence of moderate to severe interstitial fibrosis and tubular atrophy (IFTA) was 38% in the VACV prophylaxis arm and 19% in the VGCV pre-emptive group (odds ratio, 2.50; 95% confidence interval [CI], 0.74–8.43; P=0.222), and IFTA with inflammation was seen in 42% and 19% (P=0.082), respectively. These were not statistically significant because the sample size was small, particularly because of graft loss in the VACV arm (two deaths and seven graft failures, which may
be important; see below), and the incidence of IFTA (27% overall) was low compared with the expected 60% rate used for the power analyses. These trends were further surprising because, on 3-month protocol biopsies, there was less early acute rejection, less subclinical rejection, and no difference in the incidence of chronic allograft nephropathy (CAN) between groups.

Although not statistically significant, the findings are clinically significant. This is supported by the finding that the 4-year graft survival was better with pre-emptive VGCV therapy compared with prophylactic VACV therapy (92% versus 74%; hazard ratio, 0.25; 95% CI, 0.06–0.96; P=0.044). The difference was mostly attributable to the effect of CMV viremia after 3 months of prophylaxis in the VACV group and that the intrarenal fibrogenic mRNA transcripts were more common in biopsies from those in the prophylactic VACV group.

This paper is especially significant not only because of its fairly long follow-up of a prospective, randomized study, albeit with small numbers, but also because it provides important translational support to explain the observed differences in the patient-centered outcomes. Much of the data is presented in the Supplementary Tables and is worth reading. In brief, the authors looked at 95 target genes (Supplemental Table 1) that were selected for relevant analysis gleaned from the literature. The authors assessed the expression of these on 3-year protocol allograft biopsies using real-time PCR. Twenty-five profibrogenic genes were found to be upregulated in the prophylactic VACV group compared with the pre-emptive VGCV group (Table 3). Nineteen genes were found to be upregulated in those with IFTA compared with those without IFTA (Supplemental Table 6). Eleven profibrotic genes were found to be upregulated in those with late CMV viremia, defined in this study as viremia after 3 months, compared with those with no late CMV viremia (Supplemental Table 7).

The differences might be explained in part by the maintenance immunosuppression. At 36 months, the use of cyclosporine compared with tacrolimus was associated with upregulation of 20 profibrotic genes (Supplemental Table 8). However, limiting the analysis to the patients on tacrolimus maintenance therapy, there were 13 profibrotic genes that were upregulated in the VACV prophylaxis group compared with the VGCV pre-emptive group (Supplemental Table 9), providing further support for the detrimental effect of CMV viremia, especially CMV viremia after prophylaxis is completed, independent of cyclosporine use.

Previously it had been reported that DR mismatching was associated with poor allograft survival among those diagnosed with CMV disease/syndrome. This study was unable to confirm these findings (Supplemental Table 10). This may have been because there were only five cases in this study with CMV syndrome or disease (two in the VGCV pre-emptive group and three in the VACV prophylactic group).

This study is further noteworthy because interpretation of real-time PCR is more intuitive than use of microarrays. Microarrays are being used with increasing frequency but require sophisticated bioinformatics and are difficult to understand. The results of this study are readily usable by others to design studies to examine, not only at the differences in the upregulated genes, but also the other 70 genes without upregulation.

This study supports the findings of others that even asymptomatic CMV is associated with a poor long-term outcome. For example, in one study that did not use induction therapy or prophylactic therapy, asymptomatic CMV as detected by antigenemia was associated with a hazard ratio of 2.9 for death compared with no CMV by 4 years.

The greatest limitation to the interpretation of this study is that VACV was used as prophylaxis. Although these authors and others have provided evidence that high-dose VACV can be effective for prevention of CMV, which was supported by only a 9% breakthrough incidence of CMV on VACV prophylaxis in this study, the high dose of VACV is poorly tolerated because of neurologic and cytopenic side effects and is associated with a large pill burden. Additionally, theoretically, acyclovir and, by extension, VACV, would be ineffective against CMV because the virus lacks the thymidine kinase necessary to phosphorylate VACV to become an active drug. Instead, the CMV gene UL97 product is an enzyme that has protein kinase activity and can effectively phosphorylate ganciclovir but ineffectively phosphorlates acyclovir.

Despite this limitation, this study shows at a patient-centered outcomes level, supported by basic translational research, that prevention of late CMV is important to sustain allograft survival. This is most likely to result from the prevention of the development of chronic allograft nephropathy/interstitial fibrosis and tubular atrophy (CAN/IFTA) prevented by control of CMV. Whether this is best accomplished by preemptive therapy or sustained prophylaxis is still unclear.

A recently published, retrospective study of D+/R+ patients receiving VGCV pre-emptively or prophylactically reported 12-month data showing that CMV infection and disease were significantly less in the prophylaxis group compared with the pre-emptive group. The investigators plan to extend this study, which will provide further information on the 4-year follow-up on CMV infection, allograft, and patient survival, including translational data. A study of prophylactic oral ganciclovir compared with pre-emptive therapy with intravenous ganciclovir showed that prophylaxis was associated with improved 4-year graft survival, and the greatest benefit was in the CMV D+/R+ group. In contrast to these studies, a prospective, randomized study of pre-emptive compared with prophylactic VGCV showed that 1- and 4-year follow-up graft outcomes did not differ based on management strategy, but death was more common in the prophylaxis group at 4 years.

Thus, despite the impressive advances in the management of CMV over the last 15 years, there is still room for increased understanding of the biology of CMV, its impact on patient and graft survival, and how best to manage it. The present
study provides important translational research data to improve our understanding. In the case of CMV in renal transplantation, it is still too early to declare, “Mission accomplished.”

DISCLOSURES
D.C.B. is a member of the Speakers Bureau for Genentech.

REFERENCES