Extended Valganciclovir Prophylaxis to Prevent Cytomegalovirus After Lung Transplantation

A Randomized, Controlled Trial

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Background: Cytomegalovirus (CMV) is the most prevalent opportunistic infection after lung transplantation. Current strategies do not prevent CMV in most at-risk patients.

Objective: To determine whether extending prophylaxis with oral valganciclovir from the standard 3 months to 12 months after lung transplantation is efficacious.

Design: Randomized, clinical trial. Patients were randomly assigned by a central automated system to treatment or placebo. Patients and investigators were blinded to treatment status. (ClinicalTrials.gov registration number: NCT00227370)

Setting: Multicenter trial involving 11 U.S. lung transplant centers.

Patients: 136 lung transplant recipients who completed 3 months of valganciclovir prophylaxis.

Intervention: 9 additional months of oral valganciclovir (n = 70) or placebo (n = 66).

Measurements: The primary end point was freedom from CMV disease (syndrome or tissue-invasive) on an intention-to-treat basis 300 days after randomization. Secondary end points were CMV disease severity, CMV infection, acute rejection, opportunistic infections, ganciclovir resistance, and safety.

Results: CMV disease occurred in 32% of the short-course group versus 4% of the extended-course group (P < 0.001). Significant reductions were observed with CMV infection (64% vs. 10%; P < 0.001) and disease severity (110 000 vs. 3200 copies/mL, \(P = 0.009\)) with extended treatment. Rates of acute rejection, opportunistic infections, adverse events, CMV UL97 ganciclovir-resistance mutations, and laboratory abnormalities were similar between groups. During the 6 months after study completion, a low incidence of CMV disease was observed in both groups.

Limitation: Longer-term effects of extended prophylaxis were not assessed.

Conclusion: In adult lung transplant recipients who have received 3 months of valganciclovir, extending prophylaxis by an additional 9 months significantly reduces CMV infection, disease, and disease severity without increased ganciclovir resistance or toxicity. A beneficial effect with regard to prevention of CMV disease seems to extend at least through 18 months after transplantation.

Primary Funding Source: Roche Pharmaceuticals.

Lung transplantation is an effective treatment of life-threatening lung diseases, but long-term survival remains disappointing, with only 50% of patients surviving 5 years after transplantation (1). Cytomegalovirus (CMV) is the most prevalent opportunistic infection in lung allograft recipients, and its occurrence portends a poor outcome. Direct manifestations of CMV infection include symptomatic viremia and pneumonitis. Cytomegalovirus may also increase the risk for other opportunistic infections, rejection, and long-term allograft dysfunction (2, 3).

Optimal CMV prevention in lung transplantation remains controversial. Most transplant centers have adopted regimens of intravenous or oral ganciclovir in at-risk patients for 30 to 90 days (4–6). Recently, there has been interest in oral valganciclovir, a highly bioavailable oral form of ganciclovir (7), as an alternative to intravenous or oral ganciclovir (4). A prospective randomized study of CMV prophylaxis in solid-organ transplant recipients recently demonstrated similar efficacy of oral valganciclovir and oral ganciclovir when given for 100 days; the study, however, excluded lung transplant recipients (8).

Unfortunately, despite current prophylaxis, most at-risk lung transplant recipients develop CMV infections within 1 year after transplantation (4, 9). Concerns about efficacy, toxicity, and viral resistance have limited interest in longer courses of prophylaxis. Although no prospective randomized studies have compared durations of CMV prophylaxis, we and others have suggested that longer courses are beneficial (9–12). Therefore, we sought to prospectively test the hypothesis that extended prophylaxis with oral valganciclovir for 12 months after lung transplantation is more effective than 3 months of prophylaxis in preventing CMV disease (syndrome or tissue-invasive) in transplant recipients. Because the feasibility of
Context
Despite receiving antiviral prophylaxis, most lung transplant recipients develop cytomegalovirus infections within 1 year after transplant, which results in symptomatic viremia and pneumonitis and may increase the risk for other infections, rejection, and long-term graft dysfunction.

Contribution
Extending the duration of antiviral prophylaxis from 3 months to 12 months decreased cytomegalovirus infections from 64% to 10% without increasing drug adverse effects or inducing drug resistance.

Caution
The optimal duration of antiviral prophylaxis is unknown.

Implication
The current practice of antiviral prophylaxis for 1 to 3 months should be extended to 12 months.

—The Editors

extended valganciclovir prophylaxis of this duration has not been previously tested in a multicenter prospective study, the major goals of our study were to establish the safety, toxicity, and effect on ganciclovir resistance of 12 months of extended valganciclovir prophylaxis during receipt of study medication and in short-term follow-up after study completion. In addition, we collected patient data through 6 months after study completion to assess the efficacy of both approaches in preventing the development of late-onset disease.

Methods

Design
We conducted a prospective, multicenter, double-blind, placebo-controlled, randomized study in lung transplant recipients at risk for CMV infection at 11 U.S. centers and compared the effect of extended valganciclovir prophylaxis (12 months) versus standard prophylaxis (3 months) on the incidence of CMV disease 13 months after transplant.

The study was conducted in accordance with Good Clinical Practice guidelines (13). The institutional review board approval the protocol for each site, and we obtained written informed consent from each patient before enrollment.

Setting and Participants
Adults receiving their first lung transplant at risk for CMV (positive serologic status of donor or recipient) were eligible for inclusion (see Appendix Table 1, available at www.annals.org, for full criteria). From July 2003 to January 2007, we screened 189 patients and enrolled 157 participants in an open-label phase of treatment with intravenous ganciclovir starting within 24 hours after surgery and continuing for 2 weeks or less, followed by open-label oral valganciclovir, 900 mg, once daily (dose adjusted for renal insufficiency) for 3 months (Figure 1).

Randomization and Interventions
We randomly assigned eligible participants who completed 3 months of open-label valganciclovir (n = 136) in a double-blind manner and in a 1:1 ratio to 9 additional months of extended-course prophylaxis (n = 70) or placebo (n = 66) (Appendix Figure 1, available at www.annals.org), stratified by site. An independent pharmacist dispensed medication according to a computer-generated randomization list created by the Duke Clinical Research Institute, Durham, North Carolina. The study ended 1 month after completion of randomized study medication (or 13 months after transplant).

All participants had serial plasma and bronchoscopic monitoring for primary and secondary outcomes. Plasma polymerase chain reaction (PCR) testing for CMV DNA was done every 2 weeks for the first 6 months and then monthly for the remainder of the study. Blinded site investigators did bronchoscopy with cultures and transbronchial biopsy before randomization and at 3-month intervals after transplant; we allowed additional serum PCR testing or bronchoscopy on the basis of clinical indications. Polymerase chain reaction analysis was done at a central laboratory (University of Washington, Seattle, Washington), as previously described (14).

Outcomes and Follow-up
The primary study end point was CMV end-organ disease determined by positive tissue immunostain or characteristic histopathology or CMV clinical syndrome, with either positive serum PCR (>1000 copies/mL of CMV) or positive culture for CMV from bronchoalveolar lavage and at least 2 of the following; fever, leukopenia (leukocyte count, <4.0 × 10^9 cells/L), thrombocytopenia (platelet count, <50 × 10^9 cells/L), elevated liver function test results (≥1.5 times greater than normal), malaise, reduction in pulmonary function (FEV₁) greater than 20% of baseline, or radiographic infiltrate consistent with CMV (all in the absence of other causes) (8).

Secondary outcomes included degree of viremia at the time of first CMV disease; CMV infection (disease or positive viremia or bronchoalveolar lavage culture not meeting primary end point); ganciclovir resistance (UL97 genotyping was done on all positive samples for CMV DNA at >1000 copies/mL) (15), with resistance defined by the presence of 1 or more mutations shown by marker transfer to confer phenotypic ganciclovir resistance (16); minimal or more than minimal acute rejection assessed by transbronchial biopsy and defined per accepted criteria (17); and opportunistic infections. We assessed routine laboratory evaluations, adverse events, neutropenia, severe adverse events, treatment-related adverse events, and death throughout the study. Patients were followed for 13 months after transplantation (or 10 months from random-
Figure 1. Study flow diagram.

Participants screened (n = 189)

Participants enrolled in open-label valganciclovir phase (n = 157)

Participants successfully completed open-label phase (n = 136)

Participants randomly assigned to placebo (n = 66)

Withdraw consent (n = 1)
Died (n = 3)
Withdraw due to adverse event (n = 6)
Withdraw at physician’s discretion (n = 9)
Withdraw for other reasons (n = 2)

Completed study (n = 45)

Participants randomly assigned to valganciclovir (n = 70)

Withdraw consent (n = 2)
Died (n = 4)
Withdraw due to adverse event (n = 11)
Withdraw at physician’s discretion (n = 6)
Withdraw for other reasons (n = 1)

Completed study (n = 46)

Withdraw before randomization (n = 21)
Died: 2
Positive result for CMV: 1
Adverse event: 2
Met exclusion criteria: 3
Based on physician judgment: 4
Withdraw consent: 5
Other reasons: 4

CMV = cytomegalovirus.

Statistical Analysis

Assuming a minimum expected rate reduction for symptomatic CMV syndrome or invasive disease from 50% to 25% with valganciclovir treatment for 12 months and a 20% withdrawal rate during the study, enrollment of 150 patients in the open-label phase would be needed to achieve at least 80% power at a 2-sided, type I error rate of 0.05 for the randomized study (18).

All randomly assigned participants were included and analyzed on an intention-to-treat basis (that is, patients were analyzed according to the group in which they were randomly assigned; all randomly assigned patients were included in the analysis). We compared safety outcomes and CMV rates after study completion by using the t test for continuous variables and the Pearson chi-square or Fisher exact test for dichotomous variables, as appropriate. Cytomegalovirus disease (primary end point), CMV infection, acute rejection, and opportunistic infection were analyzed...
by using 2 methods: unadjusted Kaplan–Meier rates and multivariable Cox proportional hazards model with pre-specified covariates. The proportional hazards assumptions were verified graphically and by using time-by-covariate interaction terms in the model. Time-to-event analyses began at study entry on the date of randomization (study day 0) and ended at study day 300. We did all analyses by using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

An independent data safety and monitoring board convened after approximately half of the participants had been followed for at least 1 month after randomization. The data safety and monitoring board reviewed all serious adverse events to monitor safety; no interim efficacy analysis was done. The study was permitted to continue after this assessment.

Role of the Funding Source

Roche Pharmaceuticals funded the study. The funding source provided the study drug and placebo but had no role in the design, conduct, analysis, or decision to submit this manuscript for publication.

## RESULTS

### Randomized Cohort Characteristics

The primary study cohort comprised 136 participants who completed 3 months of open-label valganciclovir and met criteria for randomization (21 enrolled participants withdrew before randomization; only 1 developed CMV before randomization [1 of 157; 1%]). We assigned 66 participants to an additional 9 months of placebo (short-course therapy) and 70 participants to an additional 9 months of valganciclovir prophylaxis (extended-course therapy). A total of 98% (65 of 66) of participants who were assigned short-course therapy and 96% (67 of 70) who were assigned extended-course therapy received the blinded study drug. Study groups had similar baseline demographic and transplant characteristics, posttransplant immunosuppression, acute rejection or prophylaxis before randomization, or postrandomization monitoring (Table 1).

### Primary Outcome

There was a significantly greater incidence of CMV disease in participants who received placebo at study conclusion (32% [95% CI, 20.1% to 44.1%]) than in participants who received extended-course valganciclovir (4% [CI, 0.0% to 8.5%]; P < 0.001), as shown in Table 2 and the top panel of Figure 2. In multivariable analysis (Table 2), a significant reduction in the primary CMV end point occurred with extended treatment and remained after adjustment for CMV mismatch status (that is, positive or negative CMV serologic status of donor or recipient, respectively) (hazard ratio [HR], 0.09 [CI, 0.021 to 0.39]; P = 0.001). Each component of the primary composite also showed a significant reduction with extended prophylactic valganciclovir treatment.
Table 2. Clinical Outcomes, by Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Short Course (n = 66)*</th>
<th>Extended Course (n = 70)*</th>
<th>P Value†</th>
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<tbody>
<tr>
<td>Rates for primary and secondary outcomes, by event</td>
<td></td>
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<tr>
<td>CMV syndrome or disease</td>
<td>32.1 (20.1–44.1)</td>
<td>3.57 (0.0–8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Invasive disease</td>
<td>20.6 (10.1–31.0)</td>
<td>1.56 (0.0–4.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>CMV syndrome</td>
<td>19.0 (8.9–29.2)</td>
<td>3.57 (0.0–8.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>PCR at diagnosis, copies/mL‡</td>
<td>110 000 (40 000–361 569)</td>
<td>3200 (2700–3700)</td>
<td>0.009</td>
</tr>
<tr>
<td>Any CMV infection§</td>
<td>63.9 (49.9–77.9)</td>
<td>10.3 (2.5–18.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Biopsy-proven acute rejection</td>
<td>32.7 (20.7–44.6)</td>
<td>21.2 (10.9–31.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Non-CMV infection†</td>
<td>53.0 (39.6–66.5)</td>
<td>54.6 (38.9–70.9)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Hazard Ratio (95% CI)  P Value

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<table>
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</thead>
<tbody>
<tr>
<td>CMV syndrome or disease†</td>
<td>0.09 (0.021–0.39)</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Any CMV infection†</td>
<td>0.11 (0.047–0.29)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Biopsy-proven acute rejection**</td>
<td>0.50 (0.24–1.03)</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Non-CMV infection**</td>
<td>0.94 (0.563–1.56)</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Death†</td>
<td>1.23 (0.274–5.476)</td>
<td></td>
<td>0.79</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; PCR = polymerase chain reaction.
* Kaplan–Meier rates 300 d after randomization, intention-to-treat population (95% CI).
† Log-rank test.
‡ Median (interquartile range).
§ Inclusive of CMV syndrome, invasive disease, or CMV infection not meeting primary end point.
§ Models from randomization to 300 d after randomization, intention-to-treat population.
¶ Adjusted for CMV-positive donor or recipient.
** Adjusted for acute rejection before randomization.
†† Unadjusted analysis, because of limited numbers of death in either group.

laxis for short-course versus extended-course therapy: CMV syndrome (19% vs. 4%; P < 0.004) and invasive CMV disease (21% vs. 2%; P < 0.001) (Appendix Figure 2, available at www.annals.org).

To account for possible competing risks due to death, we also did a sensitivity analysis that assumed that all patients who died had developed CMV disease on the day of their death (n = 7). This analysis produced similar results, demonstrating a significant benefit for extended therapy.

Secondary Outcomes

Incidence of CMV infection was 64% (CI, 50% to 78%) in participants who received short-course treatment versus 10% (CI, 3% to 18%) in participants who received extended-course treatment (P < 0.001), as shown in Table 2 and the bottom panel of Figure 2. In multivariable analysis (Table 2), these differences remained significant after adjustment for CMV mismatch status (HR, 0.11 [CI, 0.047 to 0.27]; P = 0.001). In addition, the quantity of viremia at diagnosis of CMV disease was significantly reduced with extended-course therapy, from a median of 110 000 copies/mL (interquartile range, 40 000 to 361 569 copies/mL) in participants who received short-course versus 3200 copies/mL (interquartile range, 2700 to 3700 copies/mL) in participants who received extended-course therapy (P = 0.009) (Table 2).

We found no significant differences between groups in the incidence of non-CMV opportunistic infections or acute rejection after randomization, adjusted for acute rejection before randomization (Table 2). However, we did find fewer cases of acute rejection with extended-course therapy than with short-course therapy (HR, 0.50 [CI, 0.24 to 1.03]; P = 0.061) (Table 2).

Only 1 participant in each group had a CMV UL97 mutation known to confer ganciclovir resistance (L595S [extended-course group] and A594V [short-course group]). One additional participant in the extended-course group had a mutation not known to confer resistance but occurred at a site previously associated with resistance mutations (M460T).

Six months after study completion, we observed a low incidence of CMV syndrome or tissue-invasive disease in both groups. Among patients who were alive at study conclusion and who had complete 6-month follow-up data, CMV syndrome or disease developed in 3% (2 of 58) of patients who received extended-course prophylaxis and in 2% (1 of 55) of patients who received short-course prophylaxis.

Withdrawal and Safety

Early termination occurred in 31% (21 of 66) of participants who received short-course therapy and 34% (24 of 70) who received extended-course therapy (P = 0.76). Reasons for terminations were similar by group (Figure 1). Terminations due to adverse events did not differ significantly by group, with 9% (6 of 66) in the short-course group versus 16% (11 of 70) in the extended-course group (P = 0.31). No significant between-group differences were noted for short- versus extended-course treatment in incidence of adverse events (97% [64 of 66] vs. 100% [70 of
Figure 2. Primary study and secondary outcomes in randomized study cohort (intention-to-treat population).

Randomly assigned to extended course
Randomly assigned to short course

Probability of CMV Disease or Syndrome, %

$P < 0.001$

Probability of Any CMV Infection, %

$P < 0.001$

CMV = cytomegalovirus. Top. Probability of CMV disease or syndrome from randomization to 10 months (300 days) after randomization. Bottom. Probability of any CMV infection from randomization to 10 months (300 days) after randomization.

70); $P = 0.23$); treatment-related adverse events (18% [12 of 66] vs. 27% [19 of 70]; $P = 0.21$); or serious adverse events (53% [35 of 66] vs. 54% [38 of 70]; $P = 0.88$). Presumed treatment-related serious adverse events occurred in 2% (1 of 66) of participants who received short-course treatment and 6% (4 of 70) of those who received extended-course treatment ($P = 0.36$) During the study, the frequency of abnormal hemoglobin levels, hematocrit, leukocyte counts, absolute neutrophil counts, creatinine levels, and liver function test results were not significantly different between the groups, as shown in Appendix Table 3 (available at www.annals.org). These serum laboratory values were also similar at study conclusion visits in both groups (Appendix Table 4, available at www.annals.org). During the course of the study, significantly more patients in the extended-course group had reduced platelet counts ($<180 \times 10^9$ cells/L) and had a lower median platelet count at study conclusion than did those in the short-course group (Appendix Tables 3 and 4).

Discussion

Because of the serious consequences of CMV infection in lung transplant recipients, effective prevention strategies are essential to improving long-term outcomes in this population. Current approaches include short posttransplant courses of intravenous or oral ganciclovir, valganciclovir, or CMV hyperimmunoglobulin (2, 5, 18, 19). Unfortunately, these practices are based almost entirely on retrospective, nonrandomized studies. Furthermore, despite these approaches to prevention involving short-course prophylaxis, CMV infection still frequently occurs shortly after prophylaxis is discontinued.

We provide results from the first prospective, multicenter, randomized, placebo-controlled trial of CMV prevention in lung transplantation. Our study design compared short-course (3 months) with extended-course (12 months) valganciclovir prophylaxis in a double-blind manner. We clearly demonstrated that extended prophylaxis effectively prevents CMV disease in patients who are receiving treatment and for 30 days after completion of treatment compared with short-course therapy. Furthermore, extended follow-up for 6 months after study completion demonstrates a low incidence of CMV disease in both groups, suggesting that extended prophylaxis prevents, rather than simply delays, the onset of CMV disease. In addition, our study carefully addresses several important concerns about extending valganciclovir prophylaxis to 12 months; namely, the development of ganciclovir resistance and drug toxicity. We found no significant differences in adverse events, serious laboratory abnormalities, or ganciclovir-resistant UL97 mutations with extended prophylaxis compared with short-course therapy.

Strengths of our study include the serial virologic and bronchoscopic monitoring for CMV, analysis of all samples at a core laboratory, and molecular sequencing of every CMV isolate for UL97 ganciclovir-resistant mutations. Additional strengths include the prospective randomized design. The effectiveness of randomization is illustrated by the markedly similar immunosuppression and induction used in each group, despite allowed variation in practice by center (Table 1). The absence of previous prospective randomized studies of CMV prevention in lung transplantation reflects the complexity of conducting trials in this rare and highly ill patient population. Although the overall rate of early withdrawal in our study was 33%, the rate did not differ by group and reflects the acuity of the patient population, with a high rate of adverse events and serious adverse events reported in all participants throughout the first year after lung transplantation.

Because of the potential concern that extended CMV prophylaxis with valganciclovir could lead to the development of viral resistance, genotyping at UL97 for resistance mutations was done in all positive CMV isolates. Ganciclovir requires phosphorylation by a CMV protein encoded by the UL97 gene in order to have antiviral activity, and mutations in this region account for more than 90% of ganciclovir-resistant clinical isolates (16). Although previous studies suggest that extended exposure to oral ganciclovir might increase resistance (20, 21), we demonstrated that proven ganciclovir-resistant mutations occurred at similar, very low levels with short-course versus extended-
course therapy. Unlike oral ganciclovir, valganciclovir has high bioavailability and effectively suppresses high levels of viral replication that have been implicated in the emergence of CMV resistance to oral ganciclovir in transplant recipients and patients with HIV (2, 22–24). Furthermore, dose reduction of valganciclovir in our study was based on renal function only (not hematologic abnormalities), which may have prevented suboptimal drug dosing and thus prevented resistance from developing. Consistent with our results, recent studies of valganciclovir prophylaxis in other solid-organ transplant populations found low rates of ganciclovir resistance (8, 25). In summary, our results seem to refute the idea that the development of ganciclovir resistance is an inevitable consequence of longer durations of CMV prophylaxis, although additional longer-term follow-up is ongoing to confirm that resistance does not develop at later time points.

Although we demonstrate the effectiveness of extended therapy in the prevention of CMV disease, we could not confirm reductions in acute rejection or opportunistic infections, as have been reported previously in some retrospective studies of CMV prophylaxis (3, 5, 12, 26). Because these studies compared historical cohorts, changes in infection prophylaxis, epidemiology of opportunistic infections, or immunosuppression regimens could have contributed to these differences (27). Similar to previous studies, however, fewer cases of acute rejection were observed in our study with extended prophylaxis (HR, 0.50; \( P = 0.061 \), adjusted analysis). Because our study was designed and powered on the basis of CMV prevention, we cannot exclude the possibility that extended prophylaxis has beneficial effects on acute rejection or opportunistic infections.

Previous studies also suggest that CMV disease increases the risk for the bronchiolitis obliterans syndrome, a condition of progressive allograft dysfunction responsible for most late deaths after lung transplantation (27). Elevation of specific chemokines, such as CCL2, has been noted to occur with episodes of CMV pneumonitis and contribute to the development of the syndrome (28). It is thus interesting to speculate that a significant reduction in posttransplant CMV disease, as was observed in the extended-therapy group, could have a beneficial effect on the prevention of the bronchiolitis obliterans syndrome. A recent retrospective study of CMV prophylaxis is consistent with this idea (29).

The main limitation of our study is the relatively short poststudy follow-up. Although we collected additional follow-up data for 6 months after study completion, and although these data demonstrate a low incidence of CMV disease in both study groups during this period, certain limitations remain. During the poststudy follow-up, centers generally continued to do serial CMV monitoring and surveillance bronchoscopies as part of routine care. It is possible that with more rigorous sampling, a higher incidence of CMV disease might have been detected in either group. In addition, it is possible that late-onset disease still occurs but after this 6-month interval. Most previous studies in lung transplantation, however, have found that late-onset CMV disease occurs predominately in the first 3 to 6 months after discontinuation of prophylaxis (30). In fact, our study confirms that most CMV infection (>60% incidence) or disease (>30% incidence) occurred within 6 months of discontinuation of prophylaxis in the short-course group. We therefore believe that our follow-up data are adequate to conclude that there is no appreciable burden of late-onset CMV disease occurring after discontinuation of extended prophylaxis.

Our results thus serve as the foundation for the development of future clinical studies of CMV prevention in lung transplantation. Although an intermediate duration of 200 days of CMV prophylaxis (compared with 100 days) has been found to be more effective in high-risk renal transplant patients, these results cannot be directly extrapolated to lung transplant recipients, who have a much higher burden of CMV disease than renal transplant patients (31). Prophylaxis for periods less than 12 months, however, might be effective in lung transplantation if the duration of CMV prophylaxis could be based on individualized assessment of CMV-specific immunity. In a recent study, serial posttransplant measurement of CD8+ T-cell CMV-specific immunity was assessed by using HLA-restricted peptides derived from CMV phosphoprotein-65 and immediate early-1 in lung transplant recipients during and after 5 months of valganciclovir prophylaxis (32). The study demonstrated considerable variation in the timing and magnitude of CMV-specific immunity. Of importance, many CMV-seropositive patients developed viral-specific immunity while they still were receiving valganciclovir prophylaxis, demonstrating that extended therapy does not prevent the development of immunity (one postulated mechanism of late-onset disease).

Benefits of extended valganciclovir prophylaxis in preventing CMV must be balanced against adverse consequences. We observed no significant differences in adverse events, serious adverse events, or presumed treatment-related adverse events by treatment group, although the incidence of such events was high in both groups because of underlying characteristics of the study population. Furthermore, the incidence of laboratory abnormalities at study termination was similar between groups. The rate of neutropenia did not significantly differ between groups, which is consistent with the results from a previous study; however, reduced platelet counts were observed with extended treatment (8). Collectively, our findings suggest that valganciclovir is efficacious in this population and does not add significant risk. We caution, however, against drawing the inference that longer durations of valganciclovir therapy are invariably better. As courses lengthen, the possibility of adverse consequences, including permanent effects on bone marrow function, must be assessed. Although extended prophylaxis might prove beneficial in
other patient populations at high risk for CMV, such as bone marrow transplant recipients or patients with HIV, we caution against extrapolating our results to these populations until additional well-designed, prospective studies are completed.

Our study demonstrates the feasibility, safety, and effectiveness of a 12-month regimen of oral valganciclovir. We believe that 12 months may represent the optimal duration of prophylaxis in this patient population and provides effective prophylaxis during the period of highest CMV risk, as well as demonstrating a low incidence of CMV disease in the 6 months after study completion. Additional studies, however, are needed to define the long-term consequences of extended prophylaxis on CMV prevention and the bronchiolitis obliterans syndrome. Ideally, such studies could use a duration of prophylaxis based on a combination of clinical risk assessment and emerging elegant CMV-specific immune monitoring. Effective CMV prevention after lung transplantation is an important step toward improving overall outcomes in this high-risk patient population.

From Duke University Medical Center and Duke Clinical Research Institute, Durham, North Carolina; University of Washington Medical Center, Seattle, Washington; Cleveland Clinic and Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio; Emory University, Atlanta, Georgia; University of Minnesota, Minneapolis, Minnesota; Vanderbilt University Medical Center, Nashville, Tennessee; Respiratory and Critical Care Consultants, Indianapolis, Indiana; University of California, San Diego, San Diego, California; University of Michigan, Ann Arbor, Michigan; University of North Carolina Hospitals, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; University of Chicago Medical Center, Chicago, Illinois; and Texas Transplant Center and University of Texas Medical Branch, Galveston, Texas.

Note: Drs. Davis and Avery contributed equally to this work.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M09-1859.

Reproducible Research Statement: Study protocol: Available from Dr. Palmer (e-mail: palme002@mc.duke.edu). Statistical code and data set: Not available.

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References
21. Limaye AP, Corey I, Koelle DM, Davis CL, Boekh M. Emergence of

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Papers published in the year following submission are eligible for the award in the year of publication. First author status at the time of manuscript submission will determine eligibility. Authors should indicate that they wish to have their papers considered for an award when they submit the manuscript, and they must be able to provide satisfactory documentation of their eligibility if selected for an award. Announcement of awards for a calendar year will occur in January of the subsequent year. We will provide award winners with a framed certificate, a letter documenting the award, and complimentary registration for the American College of Physicians’ annual meeting.

Please refer questions to Mary Beth Schaeffer at mschaeffer@acponline.org.
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APPENDIX

Study Committees and Members

Steering Committee: Scott M. Palmer (principal investigator and study chair) and Missy Banks (project leader).

Independent Data and Safety Monitoring Committee: Joseph Govert (chair), Alistair Smith, and Marc Vallee.


Study Sites, Number of Randomly Assigned Participants, Principal Investigators, and Study Coordinators


Annals of Internal Medicine
Appendix Table 1. Eligibility Criteria for Study Enrollment and Randomization

Open-label phase inclusion criteria
- Lung transplant recipient
- Aged ≥18 y
- At risk (donor or recipient with positive serologic status for CMV)
- Prophylaxis with intravenous ganciclovir ≤2 wk immediately after transplant
- Adequate hematologic, liver, and renal function
- Able to tolerate oral medications
- Negative baseline serum PCR and bronchoscopy results for CMV
- Provide informed consent

Open-label phase exclusion criteria
- Undergoing retransplantation
- On mechanical ventilation at study entry
- Previous or current intravenous or oral ganciclovir outside of the study protocol
- Invasive fungal infection
- Participating in another investigational study
- Using disallowed anti-CMV therapy or other prohibited medications
- Severe diarrhea or malabsorption, liver failure, renal failure, or pregnancy
- History of severe reaction to ganciclovir

Randomized phase inclusion criteria
- Completion of open-label phase of study
- Negative serial posttransplant serum PCR measurements for CMV
- Negative bronchoscopy for CMV at day 75 measurement
- Continuing to meet first-phase enrollment criteria at day 75

Randomized phase exclusion criteria
- Experienced serious adverse event during open-label phase
- Withdrew consent to be randomized

CMV = cytomegalovirus; PCR = polymerase chain reaction.

Appendix Table 2. Medications Disallowed During the Study

- Ganciclovir*
- Valganciclovir
- Acyclovir†
- Famciclovir†
- CMV hyperimmunoglobulin†
- Foscarnet
- Cidofovir

CMV = cytomegalovirus.
* Except as specified in study protocol for ≤2 wk with augmented immunosuppression or intolerance of oral medications.
† Treatment permitted for ≤2 wk for acute herpes simplex or zoster.
‡ Use of non-CMV-specific intravenous immunoglobulin was permitted for documented hypogammaglobulinemia.

Appendix Figure 2. Probability of tissue-invasive CMV disease to 10 months (300 days) after randomization.

Randomly assigned to extended course
Randomly assigned to short course

P = 0.001

CMV = cytomegalovirus.

Appendix Table 3. Frequency of Patients With Laboratory Abnormalities From Randomization to Study Conclusion, by Treatment Group*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Short Course (n = 66)</th>
<th>Extended Course (n = 70)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin level</td>
<td>98.5</td>
<td>97.1</td>
<td>0.99</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>100.0</td>
<td>95.7</td>
<td>0.24</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>32.3</td>
<td>36.4</td>
<td>0.63</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>27.3</td>
<td>23.3</td>
<td>0.66</td>
</tr>
<tr>
<td>Platelet count</td>
<td>19.7</td>
<td>41.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Creatinine level</td>
<td>11.7</td>
<td>9.4</td>
<td>0.67</td>
</tr>
<tr>
<td>Albumin level</td>
<td>92.5</td>
<td>91.4</td>
<td>0.99</td>
</tr>
<tr>
<td>AST level</td>
<td>5.6</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td>ALT level</td>
<td>9.1</td>
<td>3.7</td>
<td>0.43</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
* Frequency is the percentage of patients with ≤1 laboratory abnormality, that is, a value outside normal reference values for individual sites.
### Appendix Table 4. Laboratory Values at Study Conclusion, by Treatment Group*

<table>
<thead>
<tr>
<th>Value</th>
<th>Short Course (n = 66)</th>
<th>Extended Course (n = 70)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin level, mmol/L</td>
<td>11.3 (10–13)</td>
<td>11.3 (10–13)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>33 (26–38)</td>
<td>32.8 (27–38)</td>
<td>0.37</td>
</tr>
<tr>
<td>Leukocyte count, × 10⁹ cells/L</td>
<td>6.2 (4–8)</td>
<td>5.3 (4–7)</td>
<td>0.95</td>
</tr>
<tr>
<td>Absolute neutrophil count, × 10⁹ cells/L</td>
<td>3.9 (2–5)</td>
<td>3.4 (2–5)</td>
<td>0.42</td>
</tr>
<tr>
<td>Platelet count, × 10⁹ cells/L</td>
<td>275 (200–331)</td>
<td>217 (165–251)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine level µmol/L</td>
<td>114.9 (88.4–176.8)</td>
<td>123.7 (88.4–176.8)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>1.3 (1–2)</td>
<td>1.4 (1–2)</td>
<td>0.63</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>38 (30–40)</td>
<td>40 (40–40)</td>
<td>0.32</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>27 (22–31)</td>
<td>26.5 (21–31)</td>
<td>0.67</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>22.5 (17–32)</td>
<td>22 (17–29)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

* Reported values are medians (interquartile ranges).