

MAJOR ARTICLE

Ganciclovir/Valganciclovir Prophylaxis Decreases Cytomegalovirus-Related Events and Bronchiolitis Obliterans Syndrome after Lung Transplantation

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Background. Until recently, cytomegalovirus (CMV) infection represented a major threat to lung transplant recipients. Preliminary studies have shown that antiviral prophylaxis might improve the outcome for these patients.

Methods. We extended our initial pilot trial of prolonged prophylaxis with either oral ganciclovir (1 g 3 times per day) or valganciclovir (450 mg twice per day). The trial included 96 patients who were at risk for CMV-related events.

Results. CMV prophylaxis resulted in a significant decrease in CMV-related events (i.e., active infection and disease), from 75% in a control group and for 274 cases from the literature who did not receive prophylaxis to a cumulative incidence of 27% ($P < .001$). Only 11% of the prophylaxis recipients experienced CMV disease ($P < .001$). Moreover, at 5 years, there was a significant decrease in the rate of bronchiolitis obliterans syndrome, from 60% to 43% ($P = .002$), and an improved rate of survival, from 47% to 73% ($P = .036$), irrespective of the immunosuppressive regimen received. CMV strains with UL97 mutations were recovered from 7 of 12 analyzed cases, but the presence of this mutation had no impact on the severity of CMV disease.

Conclusions. A regimen of prolonged ganciclovir or valganciclovir prophylaxis decreased the rate of active CMV infection and disease, reduced the incidence of bronchiolitis obliterans syndrome, and improved the survival rate. Drug-resistant CMV strains may occur, but such strains appeared to have no impact on the outcome of CMV-related events.

Until some years ago, cytomegalovirus (CMV) represented a major threat to lung transplant recipients. Most early series described a cumulative incidence of CMV-related events (i.e., active infection and disease) of >50%, and figures of up to 80% for CMV disease and up to 100% for active CMV infection have been reported [1–9]. In the first reports, death was not infrequent [2, 3, 10], and an increased incidence of bronchiolitis obliterans syndrome (BOS) [5, 11, 12] and serious secondary infections [13] has been suggested.

The first attempts to prevent active CMV infection

and disease after lung transplantation included oral acyclovir [10, 11] and short courses of intravenous ganciclovir [14, 15], but both regimens proved to be ineffective. After Duncan et al. [11] demonstrated that administration of intravenous ganciclovir for 90 days decreased the incidence of CMV-related events, our group was one of the first to administer oral ganciclovir prophylaxis for an even more prolonged time, and we reported our preliminary findings in 1999 [12]. We demonstrated a significant decrease in the incidence of CMV disease and BOS, lower CMV-related costs, and improved rates of survival. Here, we report our extended experience with a consecutive series of 96 patients.

MATERIALS AND METHODS

Study population. We prospectively recorded data for 175 consecutive patients who underwent lung transplantation during the period November 1992 through March 2005 at Zurich University Hospital (Zurich,

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Switzerland). Sixty-four CMV-seronegative patients who had received a graft from a CMV-seronegative donor and 7 recipients who died within 30 days after transplantation were excluded from the study, because they were judged not to be at risk for CMV disease. The clinical data for the remaining 104 eligible lung transplant recipients who were at risk of developing CMV-related events are shown in table 1. The overall mean duration of follow-up (\pm SD) was 4.5 ± 3.0 years (range, 0.1–12.4 years).

Ninety-six patients who received CMV prophylaxis were compared with 8 historical control subjects who underwent transplantation before May 1994. To support the relevance of the outcome in our small control population, we performed an exhaustive search of the Medline database and compiled all available articles that contained a full data set for patients who underwent lung transplantation ($n = 274$) during 1982–1999 and who had not received CMV prophylaxis. Data with respect to the incidence of CMV-related events and disease from 4 observational studies [1–4] and from the historical control subjects of 5 nonrandomized trials of ganciclovir prophylaxis [5–9] were compared with data from the current series. With respect to BOS and survival, data were available for only 139 cases reported in the literature [4, 5, 8, 9].

Study protocol. Our protocol was described in detail in our pilot study [12]. As a consequence of its impressive results, and because a randomized, controlled trial was judged to be un-

feasible, we decided to continue use of ganciclovir as a routine prophylaxis regimen.

All 96 consecutive patients who underwent lung transplantation and who were at risk for CMV disease received intravenous ganciclovir (5 mg/kg twice per day) during postoperative days 7–21. Thereafter, patients received oral ganciclovir (1 g 3 times per day) until the point at which the prednisone dose had been tapered to <0.1 mg/kg per day. Since April 2003, the 25 most recent patients have received valganciclovir (450 mg twice per day orally) instead of ganciclovir. Those patients who were still receiving ganciclovir at that time switched their regimen to valganciclovir ($n = 27$).

Clinical management and immunosuppression. Postoperative management has been described elsewhere [16]. Recipients who were seronegative for CMV received organs from CMV-seronegative donors, if possible; otherwise, they received organs from CMV-seropositive donors, without restrictions, through the entire period. The immunosuppressive regimen originally consisted of prednisone, cyclosporine, and azathioprine; the latter agent was replaced by mycophenolate mofetil in 1999.

In addition to routine clinical, laboratory, functional, and radiological evaluations, all patients were assessed quantitatively for the presence of CMVpp65 antigen in peripheral blood leukocyte specimens at regular intervals (usually twice weekly during the first postoperative month). Thereafter, clinical assess-

Table 1. Characteristics of the literature patients and the current study population.

Characteristic	Literature data: ^a no receipt of GCV/VCV ($n = 274$)	Current study		P^b
		No receipt of GCV/VCV ($n = 8$)	Receipt of GCV/VCV prophylaxis ($n = 96$)	
Age, mean years	40	42	44	NS
Female sex	49	87	49	NS
Diagnosis ^c				
Cystic fibrosis, bronchiectasis	12	0	33	
Emphysema	32	12	29	
Parenchymatous lung disease	28	25	18	
Pulmonary hypertension	19	25	12	
Lymphangioleiomyomatosis	2	38	4	
Redo	2	0	4	
Donor age, mean years	NA	25	40	.003
CMV-negative recipient of a transplant from a CMV-positive donor	27	50	46	NS

NOTE. Data are percentage of subjects, unless otherwise indicated. CMV, cytomegalovirus; GCV/VCV, ganciclovir/valganciclovir; NA, not available; NS, not significant.

^a Data compiled from an exhaustive literature search [1–9].

^b Comparison with respect to the present study (e.g., between patients who received and did not receive prophylaxis).

^c In 5% of the literature cases, no specific diagnosis was given.

Table 2. Outcome of the literature patients and the current study population.

Outcome	Percentage of patients			P ^b
	Literature data: ^a no GCV/VCV (n = 274)	Current study		
		No GCV/VCV (n = 8)	GCV/VCV prophylaxis (n = 96)	
Active CMV infection at 5 years ^c	68	75	31	<.001
CMV disease at 5 years ^c	54	75	16	<.001
BOS grade 1 at 5 years ^{c,d}	78	60	43	.002
Survival at 5 years ^{c,d}	50	47	73	.036

NOTE. BOS, bronchiolitis obliterans syndrome; CMV, cytomegalovirus; GCV/VCV, ganciclovir/valganciclovir.

^a Data were compiled from an exhaustive literature search [1–9].

^b Comparison with respect to the present study (e.g., between patients who received and those who did not receive prophylaxis).

^c Cumulative percentages were calculated by the Kaplan-Meier method.

^d For calculation of BOS and survival rates, data were available for only 139 patients described in the literature [4, 5, 8, 9].

ment was performed weekly during the second postoperative month and then every second or third week for the next 4 postoperative months. Surveillance bronchoalveolar lavage and transbronchial lung biopsy specimens were obtained monthly for the first 6 postoperative months, as reported previously [17].

Definitions and study end points. Active CMV infection was defined as identification of the virus by shell-vial or conventional culture of blood, urine, throat swab, or bronchoalveolar lavage fluid specimens (i.e., viral shedding) or by detection of pp65 antigenemia. CMV disease was defined as clinical signs and symptoms plus histologic evidence of pneumonia, colitis, or gastroenteritis, accompanied by a positive viral culture result, detection of CMV by PCR of biopsy specimens, and active CMV infection. CMV-related events were defined as CMV disease and/or active CMV infection. CMV disease was considered to be mild, moderate, or severe on the basis of the duration of hospitalization and whether the patient survived, as follows: mild disease, duration of hospitalization of <1 week; moderate disease, duration of hospitalization of 1–3 weeks; and severe disease, duration of hospitalization of >3 weeks or death due to CMV-associated disease. Because of progressive increases in pp65 antigen levels and/or presence of symptoms despite continued oral prophylaxis, intravenous ganciclovir treatment was initiated for 9 patients, and subsequent intravenous foscarnet was administered to 1 of these 9 patients. BOS was defined according to the updated criteria of the International Society for Heart and Lung Transplantation [18].

Statistical analysis. Data are expressed as mean ± SD. Between-group comparisons were performed with the Mann-Whitney *U* test for continuous variables and with Fisher's exact test for discrete variables. Survival was calculated by the Kaplan-Meier cumulative proportion of surviving patients, and be-

tween-group differences were determined by the log rank test. Significance was defined as *P* < .05.

RESULTS

There were 96 consecutive lung transplant recipients at risk of acquiring CMV disease. The patients received ganciclovir or valganciclovir prophylaxis for 507 ± 398 days.

The main outcomes for patients and the characteristics of CMV-related events (i.e., active infection and disease) for the present series are shown in tables 2 and 3. Fifteen patients in the prophylaxis group had asymptomatic active CMV infection, with pp65 antigen detected in peripheral blood leukocytes, 299 ± 245 days after transplantation. The peak pp65 antigen level was 35 ± 48 cells/250,000 leukocytes, and the overall duration was 145 ± 143 days, with a prolonged waxing and waning course in 7 patients.

Six (75%) of 8 lung transplant recipients in the control group developed CMV disease, compared with 11 (11%) of 96 patients who received prophylaxis (*P* < .001) (figure 1A). The overall incidence of CMV disease among the patients described in the literature was 56%.

Summing up the cases of active CMV infection and disease resulted in a cumulative incidence of CMV events of 75% (6 cases) in the historical control group, compared with 27% (26 cases) in the prophylaxis group (*P* < .001) (figure 1B). The overall incidence of CMV-related events in our control group was identical to that for the 274 patients described in the literature [1–9], who did not receive any CMV prophylaxis.

Eleven (42%) of 26 patients who received prophylaxis experienced active CMV infection or disease; these events occurred after the discontinuation of prophylaxis. Treatment con-

Table 3. Characteristics of cytomegalovirus (CMV) events in the current study population.

Characteristic	Historical control (n = 8)	GCV/VCV prophylaxis (n = 96)	P
Active CMV infection only			
All patients	...	15	<.001
Early antigen appearance, mean postoperative days (range)	NA	299 (69–796)	
Early antigen, mean maximum no. of positive cells/250,000 leukocytes during infection (range)	NA	35 (3–189)	
Duration of early antigen positivity, mean days (range)	NA	145 (15–409)	
CMV disease			
All patients	6	11	<.001
Diagnosis definite	6	4	
Diagnosis probable	...	7	
Main organ involved			
Lungs	5	6	NS
Gastrointestinal tract	1	5	
Severity of disease			
Mild	...	4	NS
Moderate	1	3	
Severe	5	4	
Active CMV infection and disease, overall	6	26	<.001
Occurrence of active CMV infection or disease			
During GCV/VCV prophylaxis	NA	15	NA
After discontinuation of GCV/VCV	NA	11	
Management of active CMV infection or disease			
Intravenous ganciclovir	6	9	
Continuation of GCV/VCV prophylaxis	NA	9	.02
Resumption of GCV/VCV prophylaxis	NA	5	.02
Change from GCV to acyclovir	NA	1	.02
None	NA	2	
No. of patients with mutations of UL-97 open reading frame of CMV/no. with wild-type or nondetectable mutations by PCR	NA	7/5 ^a	
Requirement of intravenous GCV, no. of patients with/without mutations	NA	3/2	NS

NOTE. Data are no. of patients, unless otherwise indicated. GCV, ganciclovir; NA, not available; NS, not significant; VCV, valganciclovir.

^a CMV genotyping of UL97 was attempted for only the last 12 patients.

sisted of resumption of prophylaxis in 5 of these patients. Four patients required intravenous ganciclovir treatment, and 2 were merely observed. For the 15 patients in whom active CMV infection or disease occurred during prophylaxis, only 5 required intravenous ganciclovir treatment; for the others, prophylaxis was simply continued.

We were able to search for mutations of the UL-97 open reading frame of CMV for the last 12 patients in the current series. In 7 patients, the following mutations in amino acids could be detected: Ala594Ser (2 patients), Ala594Leu (1 patient), Ala594Val (1 patient), Lys595Ser (1 patient), and Cys603Try (2 patients). Among patients with CMV disease, the peak pp65 antigen level was higher in patients with a mutation (136 ± 127 cells/250,000 leukocytes) than in those without a mutation (82 ± 99 cells/250,000 leukocytes), although the dif-

ference was not statistically significant ($P = .22$). Among the 25 patients who received valganciclovir, only 2 experienced pp65 antigenemia (pp65 antigen level, 5 and 19 positive cells/250,000 leukocytes, respectively). There were no mutations detectable in these 2 patients. All other CMV-related events in the prophylaxis group occurred in patients who were receiving ganciclovir ($P = .009$). Intravenous ganciclovir treatment was used to control CMV infection or disease in only 3 of the 7 patients with known mutations, compared with 2 of the 5 patients who had either wild-type UL97 ($n = 2$) or undetectable UL97 ($n = 3$). The only patient who required intravenous foscarnet treatment, which was administered because of clinical deterioration despite receipt of intravenous ganciclovir, had a documented wild-type UL97 open reading frame.

Patients who received ganciclovir or valganciclovir prophylaxis

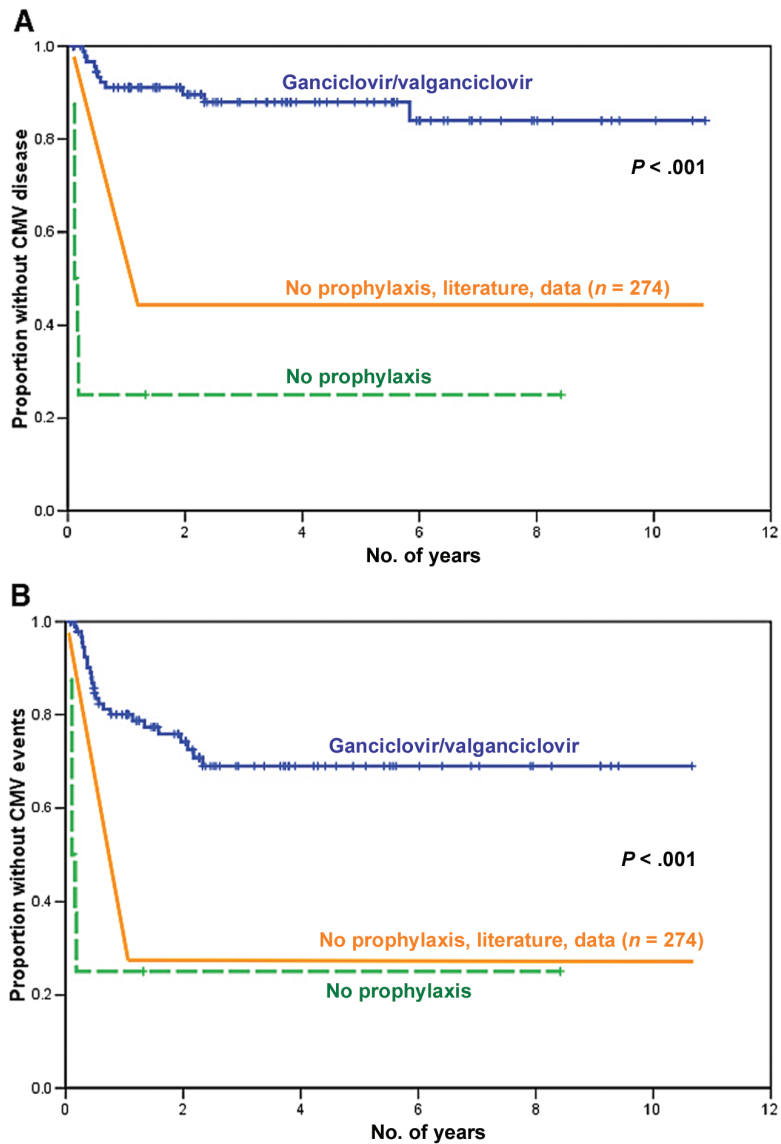


Figure 1. Kaplan-Meier estimates of the likelihood of not experiencing cytomegalovirus (CMV) disease (A) or a CMV-related event (B; i.e., CMV infection or disease). *P* values compare patients receiving prophylaxis with historical control subjects. In addition, data obtained from the literature are shown. CMV prophylaxis with ganciclovir or valganciclovir significantly reduced the cumulative incidence of CMV disease (A; $P < .001$, by log rank test) and CMV-related events (B; $P < .001$, by log rank test).

laxis had a significantly lower cumulative incidence of BOS 1, compared with the historical control subjects (43% vs. 60%; $P = .002$) (figure 2). There was also a significant decrease in the incidence of other BOS stages (data not shown; e.g., for BOS 0-p, $P = .006$; for BOS 2, $P < .001$; and for BOS 3, $P = .029$). The cumulative incidence of patients reaching the composite end point of graft loss due to BOS or death after 5 years was 18% in the prophylaxis arm versus 50% in the nonprophylaxis arm (data not shown; $P = .018$). With regard to all BOS stages or graft loss due to BOS, there was no difference

between ganciclovir recipients and valganciclovir recipients (data not shown).

The rate of survival was significantly improved among patients who received prophylaxis with ganciclovir or valganciclovir, compared with patients who did not received prophylaxis (73% vs. 47%; $P = .036$) (figure 3), and the rate was even better for valganciclovir recipients than for ganciclovir recipients (92% vs. 70% at 3 years; $P = .029$; data not shown). In a comparison of the outcomes for our historical control group with those for patients described in the literature who had not

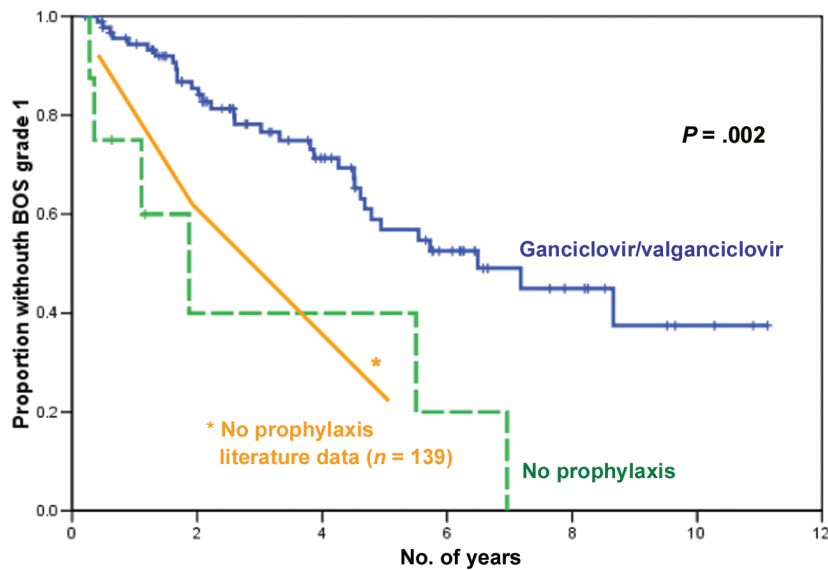


Figure 2. Kaplan-Meier estimates of the likelihood of not experiencing bronchiolitis obliterans syndrome (BOS) grade 1. *P* values compare patients receiving prophylaxis with historical control subjects. In addition, data from the literature are shown. Cytomegalovirus prophylaxis with ganciclovir or valganciclovir significantly reduced the cumulative incidence of bronchiolitis obliterans syndrome ($P = .002$, by log rank test).

received prophylaxis with ganciclovir, the cumulative incidence of BOS at 3 years was comparable (60% vs. 54%), and the rate of survival at 5 years was identical (46%).

DISCUSSION

This is, to our knowledge, the largest study to date to show that ganciclovir or valganciclovir prophylaxis significantly decreases the cumulative incidence of CMV-related events, if compared with a historical control group and data from the literature, and to our knowledge, it also has the longest follow-up period. There were no CMV-related deaths, and only 4 of 96 patients in the study group experienced severe CMV disease, compared with 5 episodes of severe disease among 8 historical control patients. In addition, our regimen of CMV prophylaxis resulted in a significant reduction in the cumulative incidence of all BOS (of all stages) and of graft loss due to BOS, as well as a significant improvement in overall survival.

In consideration of the fact that, without prophylaxis, CMV causes serious disease in approximately one-half of lung transplant recipients (occasionally involving a fatal outcome), all lung transplantation centers now have adopted use of some kind of prophylactic regimen. Since the advent of oral ganciclovir and its prodrug valganciclovir, most centers have chosen these drugs as their prophylactic mainstay.

There is, however, uncertainty about the optimal duration of prophylaxis. In our opinion, there is currently a compelling body of evidence that the minimum duration of administration of ganciclovir or valganciclovir in at-risk lung transplant recipients is at least 180 days after transplantation or until the

prednisone dosage is tapered to 0.1 mg/kg per day, as in the present study. The first attempts at preventing CMV disease among lung transplant recipients consisted of administration of intravenous ganciclovir for 3 [14], 6 [15], or 12 [6, 19] weeks, but all regimens failed to show any benefit. The same was true in the study by Weill et al. [20], who administered intravenous ganciclovir, followed by oral ganciclovir, for 6–12 weeks, with the addition of intravenous immune globulin for more than one-half of the patients. Also, Soghikian et al. [5] demonstrated improvement in survival associated with a reduction in the severity of CMV disease with receipt of a regimen of intravenous ganciclovir until day 35 or until the prednisone dose had reached a baseline of 0.2 mg/kg per day (compared with 0.1 mg/kg per day in the present study), although they experienced an unacceptably high cumulative incidence of CMV diseases (54%). This is in line with the findings of Humar et al. [21], who reported an incidence of active CMV infection and disease of 43% and 19%, respectively, with administration of a 12-week prophylactic course of either ganciclovir (1 g 3 times per day) or valganciclovir (900 mg once per day); the difference between the 2 regimens was not significantly different. On the other side of the spectrum, Palmer et al. [8] reported a reduced incidence of active CMV infection and disease—from 65% and 29%, respectively, to 35% and 5%, respectively—associated with prophylaxis involving oral ganciclovir (1 g 3 times per day) continued indefinitely. Recently, Zamora et al. [22] nicely addressed the issue of duration of CMV prophylaxis in a comparison of 5 regimens that were administered anywhere from <100 days to up to 365 days; they

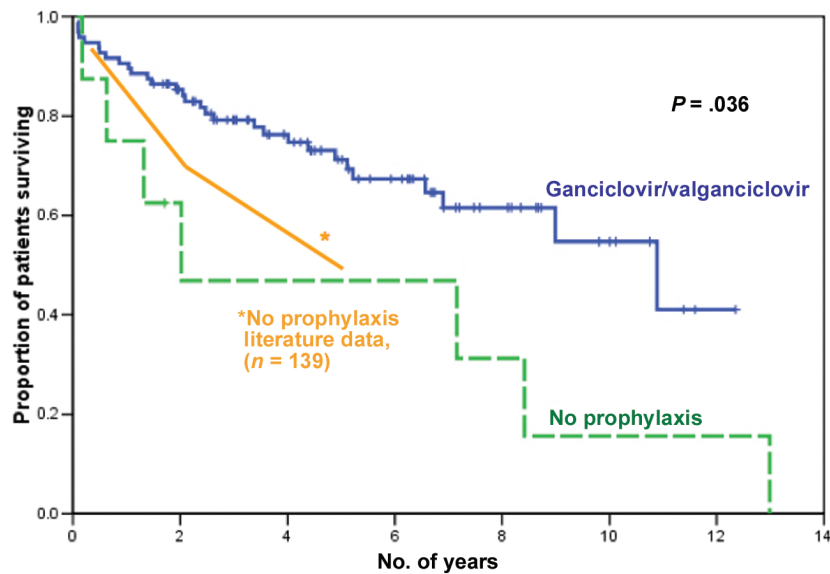


Figure 3. Kaplan-Meier estimates of the likelihood of survival. *P* values compare patients receiving prophylaxis with historical control subjects. In addition, data from the literature are shown. Cytomegalovirus prophylaxis with ganciclovir or valganciclovir significantly improved the cumulative survival rate (*P* = .036, by log rank test).

found that prophylaxis should be continued for at least 180 days after transplantation to significantly reduce the incidence of CMV disease. However, the number of patients receiving the various prophylactic regimens was rather small. All of these data stand in contradistinction with the study by the colleagues from Papworth [9], who achieved a spectacularly low incidence of 4% for cases of CMV disease after adopting a regimen of 12 weeks of oral ganciclovir. The reason for this discrepancy is not quite clear, but it has to be mentioned that, in that study, the percentage of CMV-seronegative recipients of grafts from CMV-seropositive donors was only 17% of all patients who received prophylaxis, compared with 46% in the present study. In addition, those authors described a high cumulative incidence of BOS at 5 years of ~80%, and CMV prophylaxis did not influence this figure significantly. Thus, it may be argued that this research group tapered immunosuppressive therapy more rapidly than did other research groups, resulting in a low occurrence of CMV disease but, conversely, a high incidence of BOS.

The mean duration of CMV prophylaxis was 507 days (median, 364 days; range, 113–2024 days), which was quite high. The reason for this prolongation of our prophylactic regimen was because (1) almost one-half of CMV-related events occurred after discontinuation of prophylaxis (making the team members reluctant to stop ganciclovir/valganciclovir prophylaxis too early), (2) our very slow tapering regimen of steroids, as well as (3) the continuation of prophylaxis in cases with recurrent acute rejection episodes or BOS, necessitating increased immunosuppression. Although we demonstrated, in our pilot trial, that prophylaxis with a median duration of 210

days (and of up to 320 days) is a cost-effective approach, the cost-effectiveness of the significantly longer period of prophylaxis in this extended series remains to be confirmed.

An important finding of the current study is the fact that CMV prophylaxis both significantly reduced the occurrence of BOS and improved overall survival, and this was independent of the changes in the immunosuppressive regimens over recent years. The decrease in the incidence of BOS is in line with earlier [5, 11, 12] and recent findings [23]. Thus far, to our knowledge, only our pilot trial [12] and 3 other studies [5, 8, 23] have demonstrated an improved rate of survival. Most of the remaining studies either did not mention these 2 outcome parameters [7, 20, 21], had a follow-up period that was too short [22], or found no difference in the occurrence of BOS and survival [9]. (A criticism of the latter study was already discussed above.) In the current study, although there was no difference between regimens with regard to the occurrence of BOS, the rate of survival was even better among valganciclovir recipients than among ganciclovir recipients. This finding cannot be explained by the current data.

A caveat for prolonged prophylaxis with ganciclovir or valganciclovir may be the fear that resistant CMV strains may arise. However, in a recent study, all CMV strains obtained from 49 patients with antigenemia underwent UL97 sequencing, and only 3 drug-resistant strains were found [21]. In 2 of these cases, foscarnet was necessary to control CMV infection. In the current study, a CMV mutation could be found in 7 of 12 patients in whom CMV UL97 gene sequencing was attempted. The occurrence of a mutation, however, had no clinical impact in our series; for example, the requirement of in-

travenous ganciclovir was the same for patients with and the patient without a mutation. The single patient who had to be treated with foscarnet had a documented UL97 wild-type CMV strain.

Interestingly, only 2 of 25 valganciclovir recipients had low-level, asymptomatic pp65 antigenemia. All other CMV-related events—including all events in persons with UL97 mutations—occurred among recipients of ganciclovir prophylaxis ($P = .009$). Because the overall level of drug exposure is only 60% for daily 3-g doses of ganciclovir, compared with 900-mg doses of valganciclovir [24], it is possible that the lower drug levels resulting from receipt of oral ganciclovir predispose patients to selection of low-grade UL97 resistance mutations and to later accumulation of other mutations and, thus, greater resistance [25].

A drawback of the present study is its design with use of a historical control group. However, because of the impressive results of our pilot trial, a randomized study was considered not to be ethical. In addition, the data of our small control group with respect to CMV events, BOS, and survival were enhanced by the comparison with 274 literature cases that did not receive CMV prophylaxis. Moreover, it has to be emphasized that, thus far, there have been no randomized studies comparing antiviral agents and placebo after lung transplantation, and such a trial probably will never be performed.

Preemptive treatment may be an attractive approach. However, a recent study revealed that 5 of 19 patients developed CMV disease, which was not predicted by antigenemia [26]. This unsatisfactory sensitivity may also occur if PCR is used—especially for gastrointestinal CMV disease, for which the sensitivity of PCR may be as low as 50% [27]. In addition, it has to be underscored that our control group in fact had been treated with a preemptive approach involving weekly (and, later, biweekly) determinations of the CMVpp65 antigen level.

In conclusion, we can confirm the results from other studies that have found a decrease in active CMV infection and disease using a regimen of prolonged prophylaxis with ganciclovir or valganciclovir. Moreover, there was a decrease in the occurrence of BOS and an improved survival rate that was not attributable to newer immunosuppressive therapies. Drug-resistant CMV strains may arise, but they do not seem to be of clinical relevance in these patients. Because the duration of our prophylactic regimen was longer than that of previous studies, its cost-effectiveness needs to be addressed in the future.

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