Costs and Outcomes of Prolonged Cytomegalovirus Prophylaxis to Cover the Enhanced Immunosuppression Phase Following Lung Transplantation*

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**Background:** Cytomegalovirus (CMV) disease is one of the major challenges of lung transplantation that may determine outcome. The benefits of ganciclovir prophylaxis seem indisputable, but no consensus has been reached on the optimal duration of therapy. Results with different protocols suggest that efficacy is related to the duration of treatment.

**Materials and methods:** To evaluate the additional effect of a prolonged regimen throughout the maximal immunosuppression phase, we conceived a protocol administering ganciclovir, 5 mg/kg/d for 20 weeks from the first postoperative day, to all CMV-seropositive patients undergoing lung transplantation or receiving the lung from a seropositive donor. Virus shedding was routinely measured in body fluids including through BAL. Costs and outcomes are compared with those in shorter prophylaxis protocols from previous reported studies.

**Results:** Of 30 lung transplant recipients, 22 patients at risk for CMV reactivations were observed for (mean SD) 22.9 ± 13.2 months. CMV infections were detected in eight patients 8.6 ± 5.1 months after transplantation. CMV pneumonitis developed in one patient 9 months following the transplant event. Prolonged IV ganciclovir prophylaxis was, in general, well tolerated. However, five patients had bacteremia and one had a local thrombosis, with no long-term consequences. A prescription for 8 additional weeks of prophylaxis to cover the whole period of enhanced immunosuppression decreased the cumulative incidence of first CMV infections by 29% 1 year after transplantation compared to 12-week regimens reported in other studies that indicated a 50% reduction in the incidence of first CMV infection. The total cost of 20 weeks of IV ganciclovir prophylaxis was $8,010 (US dollars) per patient more expensive than 12 weeks of IV ganciclovir therapy. This was not offset by the reduced requirement for treatment of infections. Indeed, extrapolating to our cohort of patients, the additional cost per patient was seven times greater than the treatment for the infections that were reported after the 12-week prophylaxis protocol.

**Conclusion:** Prolonging ganciclovir prophylaxis to 20 weeks decreased by half the rates of CMV infection when compared to reports from centers using a shorter protocol of 12 weeks for ganciclovir prophylaxis. Additionally, a delay in the onset of the first infection was observed. Nevertheless, the increase in costs and the discomfort of long-term use of venous catheters are important factors that may favor a shorter regimen of 12 weeks followed by preemptive therapies each time CMV infections occur.

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**Key words:** cytomegalovirus; ganciclovir; lung transplantation

**Abbreviations:** BO = bronchiolitis obliterans; CMV = cytomegalovirus; D+ = CMV-seropositive donor; D− = CMV-seronegative donor; R+ = CMV-seropositive receptor; R− = CMV-seronegative receptor; SFR = Swiss francs

Cytomegalovirus (CMV), a recognized opportunistic agent, is known for its capacity to remain latent for a long period of time after primary infection, with reactivation that depends on host immunity. Immunosuppressive therapy following organ transplantation is one of the clinical interventions associated with an increased risk of opportunistic infections; the greater the immunosuppression, the higher the risk.1,2 The reported prevalence of CMV infection following lung transplantation in the absence of prophylaxis varies between 54% and 92% in groups at risk.3,4

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CMV infections may induce a number of serious complications. Pneumonitis following an infection is associated with high mortality in the absence of early and specific therapy. There is also evidence suggesting that the allograft may act as a target organ for infection, which enhances the patient’s risk for bacterial and fungal superinfection following a CMV infection. In addition, a number of still unclear cellular mechanisms that are involved during an infection may up-regulate immune responses, inducing allograft rejection in the immunosuppressed host.

Effective prophylactic strategies against CMV infection are crucial not only to decrease mortality, but also to avoid graft disease and functional deterioration, thereby improving the long-term outcomes of transplant patients. Ganciclovir has proved to be effective for both treatment and prophylaxis. Nevertheless, the optimal duration of prophylaxis in periods of enhanced immunosuppression is still uncertain. The analysis of different studies using progressively longer periods of prophylaxis suggest that improvement in rates of infection and even clearance of infection are crucial not only to decrease mortality, but to prophylaxis in the early phase following transplantation may achieve optimal prevention of rejection. Blood levels in patients targeted for tacrolimus were decreased between the third and the sixth month to achieve a blood concentration of 200 to 300 mg/mL for the first 6 months then 150 to 200 mg/mL after (determined using an enzyme-linked immunosorbent assay [Abbott Inc; Chicago, IL]).

Azathioprine, 1.5 to 2.0 mg/kg, was administered IV 1 to 2 h prior to anesthesia. The postoperative induction treatment included cyclosporine, azathioprine, and antilymphocyte Ig. Maintenance treatment consisted of a combination of cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and prednisone as follows:

- Cyclosporine, 2 to 4 mg/kg IV from the end of the transplant operation changing to oral administration bid as soon as possible to obtain a blood concentration of 200 to 300 mg/mL for the first 6 months then 150 to 200 mg/mL after (determined using an enzyme-linked immunosorbent assay [Abbott Inc; Chicago, IL]).
- Azathioprine, 1 to 2 mg/kg/d IV, then orally. Doses were modified if the WBC count was < 4,000 cells/μL. Substitution to mycophenolate mofetil (CellCept; Roche Pharma AG; Switzerland), 1.5 to 2.0 g/d, was recommended for patients presenting with recurrent acute rejections.
- Prednisone was started between the seventh and the 10th postoperative day, after cessation of antilymphocyte Ig, at 0.5 mg/kg during the first 3 months and was progressively decreased between the third and the sixth month to achieve 0.2 mg/kg/d or less (average dose, 15 mg/d).

Acute rejections were controlled with standardized corticosteroid therapy. Antilymphocyte globulins (ATGAM; Upjohn Co; Kalamazoo, MI), 15 mg/kg/d, were kept as an option for recurrent rejections. Tacrolimus was given to all patients who had more than one episode of rejection that was greater than or equal to grade A2 on the International Society for Heart and Lung Transplantation scale or who had a clinical event consistent with rejection. Blood levels in patients targeted for tacrolimus were between 8 μg/L and 12 μg/L (according to Abbott Inc).

Diagnostic Criteria

Infection was defined as the detection of CMV through the shell vial assay (early antigen) on blood, sputum, or BAL fluid samples. Serologic conversion was considered to have occurred when a fourfold increase of anti-CMV IgG antibody titers, or when a conversion of anti-IgM from negative to positive was found. CMV disease was established when a symptomatic infection was accompanied by lung function decline, radiologic infiltrates, or the presence of viral inclusions on histologic specimens obtained through biopsies, without the presence of any other identified pathogen to suggest a concomitant causal disease.

Bronchiolitis obliterans (BO) syndrome was diagnosed when a sustained drop of 20% on FEV1 compared to the best baseline FEV1 after transplantation was observed, in the absence of any other explanation. BO was considered when findings typical of BO were found in results of histologic testing following transbronchial biopsies.

Anti-CMV Prophylaxis

Irrespective of the CMV serology of the donor and the recipient, only products derived from CMV-negative blood were used. Ganciclovir, 5 mg/kg IV once a day for 5 months (the first 12 patients received ganciclovir bid for the initial 2 weeks, then once a day), was administered to all patients at risk for CMV infections to decrease by 50%.

Later, Soghikian et al. showed the incidence of early CMV infection may relate to the extension of prophylaxis. An analysis of different studies using enhanced immunosuppression is still uncertain. The analysis of different studies using progressively longer periods of prophylaxis suggests that improvement in rates of infection and even clearance of infection are crucial not only to decrease mortality, but to prophylaxis in the early phase following transplantation may achieve optimal prevention of rejection. Blood levels in patients targeted for tacrolimus were decreased between the third and the sixth month to achieve a blood concentration of 200 to 300 mg/mL for the first 6 months then 150 to 200 mg/mL after (determined using an enzyme-linked immunosorbent assay [Abbott Inc; Chicago, IL]).

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infections. Transplant candidates having a positive CMV serology or receiving the organ from a CMV-seropositive donor (D+) were eligible for posttransplant CMV prophylaxis, and no attempt was made to give differentiated regimens to patients at potentially higher risk, i.e., the donor-positive group. A long-lasting catheter (Port-a-Cath; SIMS Deltec, Inc; St. Paul, MN) placed in a central vein for parenteral treatment after surgery was retained for use during the whole period of prophylaxis. The majority of our patients managed the drug administration and the venous catheter care themselves after hospital discharge. In addition, ganciclovir was reintroduced for 4 weeks, for rejection episodes each time immunosuppression increased. In this study, all but two recently transplanted patients completed the anti-CMV prophylaxis with ganciclovir. Six patients belonging to the CMV-seronegative donor (D−)/CMV-seronegative recipient (R−) group did not receive prophylaxis and were not considered for analysis; in two of these patients, a risk for herpetic infections was noted (donor or recipient positive for herpes simplex virus), and acyclovir, 200 mg bid, was recommended. None of the patients developed a CMV infection.

Long-term Follow-up

Patients were periodically followed up with evaluations of lung function, fiberoptic bronchoscopy, and early detection of antigens for CMV. Patients measured their own FEV1 and FVC on a daily basis at home, and a decrease of 10% sustained for >2 days indicated the need for further investigation. Complete lung function evaluations were performed regularly in the pulmonary function laboratory. Bronchoscopy procedures were performed as part of our postoperative surveillance at days 0, 2, 7, 14, and 28 and at months 3, 6, 9, and 12 to evaluate anastomotic complications, and rejection and infection were evaluated through BAL cellularity, transbronchial biopsies, Gram’s stain, and bacteria and viral cultures.

A search for CMV by the shell vial method was performed in all BAL samples, as well as in blood and sputum samples, twice a month in the first year following transplantation and once a month thereafter. Renal function was checked and blood cell counts were performed frequently in the perioperative period and after hospital discharge each time patients came for periodic outpatient control. Adverse effects of ganciclovir were considered when a 20% increase in serum creatinine according to predictive values, a polymorphonuclear neutrophil count of >5×10^3/L, or transaminases increased.

Costs

The total cost of ganciclovir prophylaxis has been calculated as the individual expenditure for an average daily 300-mg dose of ganciclovir for 20 weeks. In addition, direct and indirect expenses of the prophylaxis and the treatment of infections were included. These related to the costs of the IV catheter for ganciclovir administration (material, catheter placement, and ablation) and to the medical care and home visits of a nurse. The market prices for drugs in Switzerland (as of the time of this writing) were used.

Data Analysis

Data are summarized as absolute values, as mean ± SD (range), and as median. The Kaplan and Meier product-limit method was used to calculate the cumulative overall survival rate and the incidence of first infections. The adjusted incidence rate of infections was calculated as the number of CMV episodes per 100 patient-months in order to estimate the excess incidence between shorter protocols and our extended prophylaxis protocol.

Results

Patient characteristics are outlined in Table 1. In 15 recipients, the CMV serotype, either positive or negative, did not match the donors.

The median time on the waiting list for transplantation was 135 days (range, 89 to 306). The duration of ischemia for the transplanted lungs varied from 2 to 7 h (median, 3 h, 53 min). Follow-up time ranged from 9 to 43 months (median, 18.0 months). The 3-year actuarial survival rate of the studied group was 67%. Five patients died 4, 9, 11, 12, and 33 months after transplant, respectively, from respiratory syncytial virus pneumonia, from sepsis caused by Klebsiella spp and Pseudomonas spp, from progressive graft dysfunction, and from BO. Among them, two were CMV-seropositive receptor (R+)/D− and three were R+/D+ for CMV IgG at transplantation. In four of five patients, a CMV infection was never diagnosed; nevertheless, recurrent infections and the development of a chronic dysfunction were identified in the last described patient.

CMV-Related Events

Details on follow-up are shown in Table 2. According to diagnostic criteria, a total of eight patients (36%) developed CMV infections during follow-up. They belonged to the following at-risk groups: R−/D+ (n = 1), R+/D− (n = 4), and R+/D+ (n = 3). Diagnosis was made according to positive results from cultures of blood specimens in six patients and from cultures of BAL fluid in two lung recipients. The results of specimen cultures became negative in all patients following the reintroduction

<table>
<thead>
<tr>
<th>Table 1—Characteristics of Lung Recipients (n = 22)</th>
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<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Lung transplant</td>
</tr>
<tr>
<td>Single</td>
</tr>
<tr>
<td>Double</td>
</tr>
<tr>
<td>Mean age, yr (range)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>CMV IgG serology</td>
</tr>
<tr>
<td>R+/D+</td>
</tr>
<tr>
<td>R−/D+</td>
</tr>
<tr>
<td>R+/D−</td>
</tr>
<tr>
<td>Lung transplant indication</td>
</tr>
<tr>
<td>Emphysema</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Lymphangioleiomomatosis</td>
</tr>
<tr>
<td>Idiopathic pulmonary hypertension</td>
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<tr>
<td>Paraquat intoxication</td>
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</tbody>
</table>
of IV ganciclovir therapy for 4 weeks. The calculated incidence rate of infection was 2.2 per 100 patient-months. In an attempt to compare this protocol with shorter prophylaxis protocols, the incidence rates of infection from other reported studies were estimated and are presented in Table 3. The results obtained after the extension of prophylaxis from 12 to 20 weeks suggest a drop in the number of infections from 5.4 to 2.2 per 100 patient-months. Cumulative incidences of CMV infections are detailed in Figure 1. They were calculated as 5%, 29%, and 46%, respectively, at 6, 12, and 24 months following transplantation. The majority of CMV infections occurred beyond the 8-month follow-up (median, 11 months after transplantation). Nevertheless, in one patient, an earlier CMV infection was detected through the results of a blood culture 4 months after transplantation, while the patient was still receiving prophylaxis. Two patients presented with recurrent CMV infections, one with positive results of a BAL culture persisting 14 months after the first treatment, while the other presented with multiple episodes of infection treated at 12, 18, and 31 months posttransplant. CMV disease without lung function decline developed in one patient 9 months following transplantation, and resolution occurred after conventional treatment. There were no deaths due to CMV in our series.

**Chronic Allograft Dysfunction**

In 20 of 22 patients, the follow-up period was > 6 months, making those patients higher risks for

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### Table 2—Site of First CMV Infections and Prophylaxis-Related Adverse Events According to Follow-up

<table>
<thead>
<tr>
<th>Infections and Adverse Events, No.</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 6 mo</td>
</tr>
<tr>
<td>Infections</td>
<td>(n = 22)</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>1</td>
</tr>
<tr>
<td>BAL</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
</tr>
<tr>
<td>Adverse drug effects</td>
<td>4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>3</td>
</tr>
<tr>
<td>Central catheter events</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
</tr>
<tr>
<td>Obstruction</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 3—Comparative Cost-effectiveness of CMV Prophylaxis Related to Duration of Therapy*

<table>
<thead>
<tr>
<th>Cost-effectiveness Variables</th>
<th>Length of Therapy, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3† (n = 12)</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>25</td>
</tr>
<tr>
<td>CMV infections§, No.</td>
<td>19</td>
</tr>
<tr>
<td>Cumulative CMV infections at 1 yr, %</td>
<td>75</td>
</tr>
<tr>
<td>CMV infections, No. of incidences/100 patients/mo</td>
<td>6.9</td>
</tr>
<tr>
<td>CMV disease, No.</td>
<td>4</td>
</tr>
<tr>
<td>CMV-attributed mortality, No.</td>
<td>0</td>
</tr>
<tr>
<td>Cost of CMV prophylaxis per patient, US dollars</td>
<td>$1,202</td>
</tr>
</tbody>
</table>

*One 300-mg dose of ganciclovir = 55.68 SFR (538.98). NM = not mentioned in study.
†Duncan et al.10
‡Soghikian et al.9
§Numbers include recurrent infections.
‖Number at end point of study after 8 months of follow-up.
chronic dysfunction. Lack of pulmonary function with histologic evidence of BO was seen in two patients (both belonging to CMV serotypes R+/D−), in whom a CMV infection never developed, 12 and 14 months posttransplantation. In two other patients, a persistent fall of 20% in FEV1 without positive histologic findings indicated BO syndrome.

Ganciclovir-Related Adverse Events

The prophylactic protocol using ganciclovir for 20 weeks with the additional 4-week treatment when CMV flared up or when a seroconversion was identified was, in general, well tolerated. Although extended treatment with ganciclovir could potentially induce the development of resistant CMV strains, our patients were all responsive to ganciclovir treatment for infections, and results of specimen cultures became negative after standard therapy. Adverse events due to long-term catheter utilization and drug side effects are summarized in Table 2. Their occurrence was equally distributed during the initial period of prophylaxis and the subsequently required treatments. Ten patients presented at least one complication that could be attributed to either ganciclovir use or to long-term catheter maintenance. Impairment of renal function or appearance of leukopenia required dose adjustments. Bacteremia originating from catheter colonization was caused by Staphylococcus epidermidis in four patients and Escherichia coli in one patient. Three catheter-related infections occurred beyond 3 months of follow-up. Subclavian/axillary vein thrombosis occurred in one patient 11 months after transplantation.

Costs

Summarized individual expenditures according to the duration of prophylaxis are given in Table 3. In an attempt to compare the costs and benefits of different regimens, the rates of CMV infection from different studies using shorter prophylaxis protocols and their potential expenses for ganciclovir treatment are also presented in Table 3. Since the rate of complications found in our patients was similar to that reported in the 12-week prophylaxis study, and because discrepancies in the way complications are managed in different centers may affect costs, these were not included in the analysis. The placement of a long-term catheter after transplantation that remained for > 5 months during follow-up largely simplified the prevention and treatment of recurrent CMV infections since daily drug administration was given at home or at day-care centers. Because of this practice, our patients were treated mostly at home, avoiding extra hospitalizations. The cost of 20 weeks of ganciclovir prophylaxis for a single patient has been calculated to be 19,080 Swiss francs (SFR) ($13,357) per patient, while a conventional prescription of 12 weeks would have cost 10,496 SFR ($7,347). Thus, the difference in costs between the two regimens for one patient would be 8,584 SFR ($6,010), or 188,848 SFR ($132,220) for the entire observed group. The treatment of each CMV infection, assuming that patients were managed as outpatients, is calculated at 5,024 SFR ($3,517). The largest impact of CMV prophylaxis is to be expected in the first year following transplantation. According to our observation, five CMV infections flared up in this period, and an additional five infections would have occurred if one extrapolates to the percentage of infections reported after only 12 weeks of prophylaxis. Thus, the costs of the prevented infections could be estimated at 25,120 SFR ($17,585). This is sevenfold less than the additional cost of the prolonged prophylaxis for our patients. In other words, the additional length of treatment will prevent one CMV infection in 4.4 patients at an extra cost of $17,585 per infection prevented.

Discussion

Despite early diagnostic techniques, the potential complications of a CMV infection remain a threat for the outcome of all lung transplant recipients. In addition to the high morbidity and mortality related to CMV disease, associated increased risks for acute and chronic rejections are major concerns.

Ganciclovir is being used in a variety of prophylactic regimens for the treatment of CMV disease. Reported drug maintenance protocols varying from 2 to 12 weeks suggest that the effectiveness of CMV prophylaxis is related, among other factors, to duration of therapy. However, there is still no consensus on the optimal duration of prophylactic therapy. Our protocol was designed to evaluate the additional benefits of prolonging posttransplant ganciclovir prophylaxis given to lung recipient patients throughout the maximal immunosuppression phase, a period of major risks for CMV disease and its complications due to decreased host defenses.

Our results show a lower long-term rate of CMV infections in a group of patients treated for 20 weeks compared to reported rates in patients on various other regimens. Among the few longitudinal studies addressing the issue of CMV prophylaxis duration, an important observation has been made by Duncan et al. The authors describe a drop of about 50% (38% vs 91%) in the prevalence of early CMV infections using ganciclovir for 3 weeks. Prophylaxis was subsequently extended to 12 weeks, and
the authors reported an additional decline in the rate of infections and disease together with a delay in their onset, therefore suggesting more effective prevention. Controlled trials using ganciclovir to prevent CMV infections in bone marrow, liver, and heart transplant recipients have reported similar beneficial results.12–14

Our data on infection rates differ from those previously reported. The lower incidences verified throughout the observation, but especially between 6 and 12 months following transplantation, may reflect the impact of the extended prophylaxis on patients at risk. The group followed by Duncan,10 which received 12 weeks of prophylaxis, seems comparable to our group, in particular with regard to diagnostic criteria, immunosuppression protocol, and duration of follow-up. They report a 58% cumulative incidence of first infections of CMV in 1 year. Extending CMV prophylaxis to 20 weeks, we observed a 29% CMV infection rate at the same end point. Comparing results originated from different studies may be troublesome. Prerequisites such as criteria for patient selection, distribution of donor/recipient CMV status, immunosuppression scheme, and use of induction therapy with CMV Igs and ganciclovir during augmented immunosuppression may affect results and have to be taken into account before further conclusions can be drawn. Nevertheless, we may project a 50% reduction in CMV infection rates at 1 year using the extended prophylaxis protocol. Conversely, the long-term adjusted incidence rates for CMV infection showed only an additional 3.2 infections per 100 patient-months of follow-up for the aforementioned group treated with a shorter protocol compared to the number of infections in the group using the extended regimen of 20 weeks. This finding could support the notion that early prophylaxis therapy does not prevent the onset of late CMV infections, thus highlighting the need for their longitudinal screening.

Prophylaxis during periods of higher immunosuppression may prevent the onset of infections and their progression to disease, an event related to increased morbidity and potential mortality.15,16 The decreased number of infections that we observed may also have influenced the significantly lower incidence of CMV pneumonitis found in our patients. Yet, the occurrence of CMV disease, manifested in only one of our patients, differed considerably from other reports in which prevalence varied between 15% and 59%, according to the prophylaxis scheme.3,8,11 As shown in Table 3, rates of CMV disease may reach 54% even under a prophylaxis regimen sustained for 5 weeks following transplantation.9 However, when compared to a 12-week ganciclovir protocol,10 the prevalence of pneumonitis when using the prolonged regimen remains unchanged, and, therefore, the prolonged regimen does not substantially affect outcomes.

The efficacy of CMV prophylaxis may be seen in the decreased rate of BO, which can exceed 40% in lung transplant recipients.17 Its prevalence appears to relate to the occurrence of CMV disease rather than infection.18,19 Only one patient developed pneumonitis in our group, and this may be one explanation for the low BO rates that we have found. The incidence of BO is considered to be multifactorial, and, as expected, a clear relationship between the occurrence of CMV infections and the development of chronic dysfunction was not found in our patients. In three of four patients who developed BO, a definite CMV infection was not detected before the BO diagnosis. However, the duration of follow-up may not have been sufficient for further conclusions to be drawn.

The delay in the occurrence and the lower prevalence of infections observed with the extended protocol, in comparison with other regimens, may have an additional impact on outcomes and survival. Indeed, a CMV infection may occur in association with bacterial and fungal infections, aggravating their clinical consequences, but the additional effects of a prolonged CMV prophylaxis regimen for preventing those combined infections are difficult to determine. None of our patients who developed a CMV infection died from this complication. Deaths in our series, as reported by others, were essentially caused by non-CMV-related infections that resulted in sepsis.

Complications such as impairment of renal function and appearance of leukopenia are often multifactorial and notably occur in the first weeks following transplantation, so that the identification of a single drug as the cause for these complications may be problematic. The secondary effects on bone marrow and the renal toxicity of ganciclovir are known.20 Prolonged and universal use of ganciclovir increases the risk of side effects. According to a recent review, adverse reactions using 12 weeks of IV ganciclovir therapy led to granulocytopenia (40%) and thrombocytopenia (15%) and to a 20% increase in serum creatinine level.21 In another series, with the same duration of prophylaxis,10 the use of IV ganciclovir induced side effects in 62% of lung recipients, which is not significantly different from the incidence of 58% found in our patients. Six of our patients had side effects related to the catheter, and these complications could have been partially avoided with an earlier withdrawal. The adjustments of ganciclovir dosage, when impaired renal function was detected, prevented the development of severe kidney dysfunction and bone marrow toxicity.
The development of more sensitive techniques for the early detection of incipient infections would allow more selective use of elective therapy. The finding of CMV antigenemia in WBCs has been shown to be a better diagnostic tool to indicate preemptive therapy only when the titers of antigenemia rise. Recent data reporting predictive values for CMV complications in lung recipients allow to expect a good sensitivity of CMV antigenemia levels in WBCs for the diagnosis of infection, although it seems less powerful in determining those patients who are at higher risk for disease. Under this criterion, mandatory preemptive therapies are required for all patients who have values above a certain level of antigenemia. The clinical role of positive but lower levels of antigenemia in discriminating viral reactivations from residual marks of previous infections remains to be determined in the specific context of the transplanted lung.

The additional costs of prolonged prophylaxis ought to be comparatively examined regarding the risk and discomfort of avoidable supplementary CMV infections and their treatment. Compared with shorter regimens, a proportional increase in costs is to be expected with a prolonged prophylaxis scheme. As pointed out by Kelly and colleagues, this not insignificant increment in the expenses of an already costly intervention needs to be justified by the number of patients spared infections and their consequent treatments. In our study, a substantial number of CMV infections were avoided with the additional weeks of prophylaxis compared with the number of infections reported with shorter protocols. However, the differential costs generated by the 12- and the 20-week prophylaxis protocols to prevent and treat infections were estimated to be 188,848 SFR ($132,220) and 25,120 SFR ($17,585), respectively. In other words, there is a cost difference of approximately seven times that of treating excessive infections, assuming that they were managed on an ambulatory basis, as were our patients. Thus, we postulate that the excessive number of CMV infections that may arise after a shorter prophylaxis scheme, when identified and treated early, are far less expensive than the extension of prophylaxis, which has no clear long-term effects on outcomes.

In conclusion, the data presented here suggest additional benefits with extended ganciclovir prophylaxis during the period of maximal immunosuppression, which both decreases short-term rates of CMV infection and delays their onset. However, prolonging the duration of prophylaxis markedly increases the global costs of the intervention without clear changes in long-term outcomes. Preemptive treatment according to levels of CMV antigenemia may be a cost-effective alternative, but the accuracy of the test in predicting disease, and therefore in restricting therapy only to patients who are at risk for disease, is still suboptimal. Intermittent vs daily IV ganciclovir therapy has been tested, but the occurrence of CMV disease and adverse events remained substantial and mortality was significantly higher in the group that was given therapy three times per week. Finally, by the time of this writing, oral ganciclovir had been reported for CMV prophylaxis in five patients. Unfortunately, the occurrence of a severe CMV pneumonia in this small group of patients, the elevated costs of therapy, and the cumbersome number of daily capsules to be taken in order to achieve the recommended dosage may limit oral ganciclovir use, notably in the early phase following transplant. Nevertheless, the efficacy of oral ganciclovir in completing the extended prophylaxis regimen or in preemptively treating intermittent infections remains to be tested. Further studies are required to evaluate other therapeutic strategies in development that are based on new viral replication inhibitors or on techniques aimed at the restoration of CMV-specific immunity using T-cell clones, which may provide a better, safer, and longer lasting protection against CMV.

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REFERENCES