Combined CMV Prophylaxis Improves Outcome and Reduces the Risk for Bronchiolitis Obliterans Syndrome (BOS) after Lung Transplantation

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Background. The benefit of cytomegalovirus (CMV) hyperimmune globuline in preventing CMV infection after lung transplantation still remains unclear. The aim of this study was to investigate the effect of combined prophylaxis using ganciclovir (GAN) and CMV hyperimmune globulin (CMV-IG) on CMV infection, CMV disease, survival and its role in preventing Bronchiolitis obliterans syndrome (BOS).

Methods. A consecutive series of 68 CMV high-risk lung transplant recipients (D+/R−, D+/R+), who had a minimum follow-up of 1 year posttransplant were analyzed. Thirty patients (44.1%) received single GAN prophylaxis for 3 months (control group) and 38 recipients (55.9%) received GAN together with CMV-IG 7 times during the first postoperative month (study group). Median follow-up was 16.5 months in the control and 23.8 months in the study group ($P=0.54$).

Results. Five CMV-related deaths (16.7%) occurred in the control group ($P=0.014$). Fifteen recipients suffered from CMV pneumonitis and three patients had CMV syndrome. In the control group, 13 recipients (43.3%) suffered from clinically manifested CMV disease compared to 5 (13.2%) in the study group ($P=0.007$). Additionally, recipient survival was significantly better in the study group ($P=0.01$). One year freedom from CMV affection was 52.1% in the control and 71.5% in the study group ($P=0.027$). Three-year freedom from BOS was significantly higher in the study group (54.3% vs. 82%, $P=0.024$).

Conclusions. In CMV high risk patients, additional CMV-IG administration seems to be effective to reduce CMV-related morbidity and to avoid CMV-related mortality. Reduced incidence of BOS may result from improved CMV prevention, although randomized trials are warranted.

Keywords: Cytomegalovirus, Lung transplantation, Bronchiolitis obliterans syndrome (BOS).

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Among solid organ recipients lung transplant recipients are at highest risk to be affected by cytomegalovirus infection (CMV) or to die from CMV disease (*1*).

Despite the introduction of potent antiviral drugs, CMV infection still remains a serious, profoundly life limiting problem after lung transplantation. Recently, we have demonstrated similar outcomes between CMV sero-negative donor heart and lung transplant recipients, but inferior outcomes in CMV mismatched lung transplant recipients although receiving Ganciclovir (GAN) prophylaxis (*2*). These results indicate that current prophylactic CMV regimens warrant improvement.

Donor-recipient CMV matching would be one way to avoid transmission via the lung allograft. However, due to the high prevalence of CMV in the population together with organ shortage, CMV related matching is inapplicable in the clinical setting.

Several experimental trials have provided evidence that posttransplant CMV infection is involved in the process of chronic allograft rejection in heart and lung transplantation via immune modulation (*3*, *4*).

Vaccination might be the ultimate goal of preventive strategies, its clinical application however is still far away from clinical application. Therefore, better antiviral prophylaxis is needed to avoid CMV-related death, a leading cause of death after lung transplantation (*5*, *6*).

Several study groups have intended to find the optimal preventive strategy to avoid CMV infection after lung transplantation. Zamora and colleagues demonstrated that prolonged Valganciclovir prophylaxis (at least 180 days) following combined prophylaxis together with GAN and CMV-IG is safe and effective. However, they compared the results to a group receiving Aciclovir (*7*).

Taking into consideration that neither GAN nor CMV-IG alone was able to sufficiently prevent CMV disease in CMV mismatched lung transplant recipients, as demonstrated by Kruger and Palmer, combined regimens require further investigation (*8*, *9*). Furthermore, based on the findings of animal studies, combined use of GAN and CMV-IG may act synergistically and are able to reduce CMV-related mortality (*10*). However, striking costs of such therapies merit further studies (*11*, *12*).

Valantine and Weill described a beneficial effect of

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combined prophylaxis in cardiothoracic transplantation (heart, heart-lung and lung transplantation), however they used an extensive therapeutic regimen of CMV-IG administration lasting for at least 3 and 4 posttransplant months (*13*, *14*).

CMV-IG has been used in transplantation for more than a decade. However, this substance has never been evaluated by a prospective randomized clinical trial in lung transplant recipients. Most immunosuppressive and anti-infective drugs have only been proven for safety and efficacy in kidney or liver transplant recipients. Therefore, no clear recommendations concerning prophylactic regimen and dosage in cardiothoracic transplantation are available from the companies distributing CMV-IG.

The aim of this study was to evaluate the effect of combined CMV prophylaxis using CMV-IG in addition to GAN administration on clinical apparent CMV infection, CMV-related death, overall survival, acute rejection episodes, and the development of BOS in high-risk lung transplant recipients.

MATERIALS AND METHODS

A consecutive series of 68 lung transplant recipients receiving a CMV sero-positive allograft (sero-status D+/R−, D+/R+) was analyzed retrospectively.

Patients were classified regarding the regimen of CMV prophylaxis used. Thirty patients (control group transplanted from 1994 to 2000) received GAN alone for the first 3 postoperative months and 38 recipients (study group transplanted from 2000 to 2004) received additional treatment with CMV-IG (Cytotect Biotest Pharmazeutika GmbH, Vienna, Austria) (GAN+CMV-IG) in 7 doses (1 ml/kg body weight, 50 Paul Ehrlich units/ml) within the first posttransplant month. Only patients who were at risk for at least 1 year were included into the study.

Immunosuppressive Protocol

Intraoperatively, 1 gram of methyl-prednisolone (Aprednisolon, Nycomed GmbH, Austria) was administered before finishing the atrial anastomosis and another 3 doses of 125 mg were given every 8 hr at day 1 and were tapered down to 20 to 25 mg per day within the first week and further reduced to 10 to 15 mg per day within the first 3 to 6 months posttransplant.

Beside corticosteroids, maintenance immunosuppression consisted of standard triple therapy including cyclosporine (Sandimmun, Novartis, Basel, Switzerland), azathioprine (Imurek, Glaxo Wellcome Operations, UK) and from 1998 onwards mycophenolate mofetil (Cellcept, Roche, Basel, Switzerland) as initial immunosuppression. Initial Cyclosporin trough levels of 300 to 400 ng/ml were aimed for.

Antithymocyte globulin (Fresenius Kabi, Graz, Austria) was administered in 19 recipients of the control group, starting on the first posttransplant day (2 mg/kg) and was administered for 5 to 7 days. Induction therapy using an interleukin-2 receptor antibody (IL-2) (daclizumab, Zenapax, Roche, Basel, Switzerland) was given in the remaining recipients (49 patients). IL-2 receptor antibody therapy was started intra-operatively after induction of anesthesia and was repeated on day 14 at a dose of 2 mg/kg body weight.

CMV Prophylaxis Regimen

All patients received CMV prophylaxis consisting of GAN intravenously (Cymevene, Roche Pharmaceutical, Basel, Switzerland) starting at day 1 with a daily dose of 10 mg per kg body weight until day 14. Afterwards, either oral GAN prophylaxis containing 3 grams daily (until year 2003) or valganciclovir 900 mg twice daily (from 2003 onwards) for the first 100 days posttransplant was given.

In the study group (from year 2000 onwards) additional CMV-IG (1 ml/kg body weight, 100 mg/ml, 50 Paul-Ehrlich units per ml) was administered at days 1, 3, 5, 7, 14, 21 and day 28 posttransplant.

CMV surveillance was performed by using the pp65 CMV antigenemia test three times a week during the initial hospital stay, on every visit or in the case that CMV infection or disease were suspected. If clinical CMV infection was suspected, transbronchial biopsy (TBB) and bronchoalveolar lavage (BAL) was performed. BAL samples were analyzed by PCR methods and biopsy specimen for histopathologic evidence of CMV to confirm clinical infection.

In the case of CMV affection or clinical disease, recipients were hospitalized and intravenous GAN was administered until pp65 testing became negative. Again oral GAN therapy was given for another month.

Since the year 2000, additional CMV-IG was given daily at a standard dosage of 1 ml/kg body weight daily if an infection had occurred.

Monitoring for Acute Rejection and BOS

Acute rejection was diagnosed by transbronchial biopsy and graded according to the ISHLT (International Society of Heart and Lung Transplantation) classification (*15*) or if clinically suspected and successfully treated with a 3-days course of intravenous corticosteroids (500 to 1000 mg daily).

The staging of BOS was based on pulmonary function decline and histopathological findings from transbronchial biopsy. Standard criteria for the definition of BOS were used according to the guidelines by Cooper and Yousem (*15*, *16*).

Statistical Analysis

Fisher's exact test was applied to test for univariate differences in categorical variables. Continuous variables were tested by use of the Student´s *t* test or Mann-Whitney *U* test. To evaluate differences in the incidence of clinically apparent CMV disease and CMV related mortality within the follow-up (length comparable in both groups), 2×2 tables were used together with the Fisher's exact. A Kaplan-Meier analysis was applied to investigate recipient survival and freedom from CMV reactivation or de novo infection, acute rejection episodes and BOS. The log-rank test was applied to evaluate differences within the groups in the Kaplan-Meier analyses. *P*-values less than 0.05 were considered to indicate statistical significance. Data documentation as well as statistical analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The median follow-up period was 16.5 months in the control group (5.3 to 69.5 months) and 23.8 months in the study group (11.9 to 35 months, $P=0.54$). The mean age was

significantly higher in the study group (55.8 vs. 49.2 years, $P=0.025$).

A detailed recipient characteristics are summarized in Table 1.

One-year patient survival was 63.3% in the control group and 81.6% in the study group and 3 year survival was 40% in the control and 71.5% in the study group (log-rank: $P=0.013$, Figure 1).

One-year freedom from CMV reactivation or de novo infection was 51.1% in the control group and 71.5% in the study group, whereas 3-year freedom was 30% in the control and 66.4% in the study group (log-rank: $P=0.027$, Figure 2).

During the follow-up, a total of 18 recipients developed CMV disease, 13 of these patients (43.3%) in the control group and 5 patients (13.2%) in the study group ($P=0.007$).

CMV pneumonitis occurred in 15 patients (10 of them in the control group) and 3 patients suffered from CMV syndrome (none of them in the study group). CMV related death occurred in a total of 5 patients in the control group only (16.7% vs. 0%, $P=0.014$).

No significant difference was found in freedom from acute rejection (Fig. 3). One-year freedom from acute rejection was 41.7% in the control group and 52.5% in the study group and 3-year freedom was 35.8% in the control and 49.0% in the study group (log-rank: $P=0.33$).

There was a significantly higher freedom from BOS in the study group compared to the control group. One-year freedom from BOS was 69.7% in the control group and 91.0% in the study group and 3-year freedom was 54.3% vs. 82.0% in the study group (log-rank: $P=0.024$, Figure 4).

To evaluate a possible influence of the use of either ATG or IL-2 receptor antibody induction therapy, a subanalysis of the patients in the control group was performed.

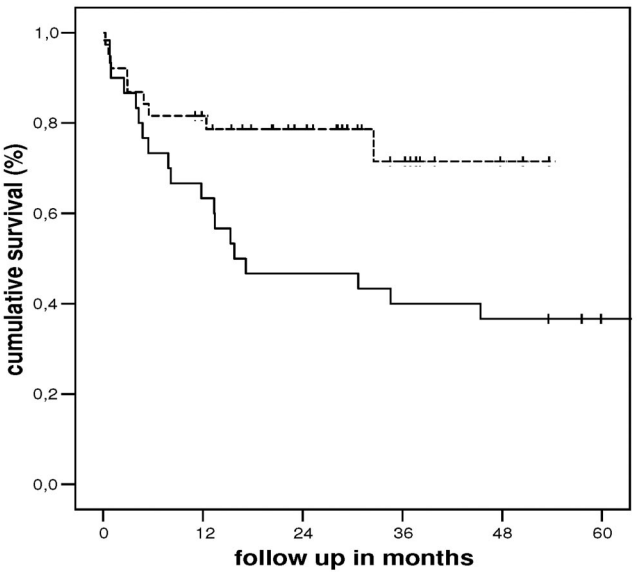

FIGURE 1. Recipient survival in months (Kaplan-Meier survival analysis) in patients receiving augmented CMV prophylaxis with ganciclovir and CMV-IG (dashed line) compared to patients only receiving ganciclovir (solid line); log rank: $P=0.013$.

Nineteen patients received ATG and 11 patients of the control group received daclizumab. There were no statistical differences regarding survival (log rank $P=0.84$), freedom from CMV reactivation (log-rank: $P=0.12$), freedom from acute rejection (log-rank: $P=0.9$) or the freedom from BOS (log-rank: $P=0.54$). Additionally, there were no differences in the

TABLE 1. Clinical characteristics of the recipients

	GanC alone	GanC + CMV-IG	*P* value
n	30	38	
Age, years	49.2±15.6	55.8±7.0	0.025
Sex, male	18 (60%)	17 (44.7%)	0.21
Bilateral lung transplantation	18 (60%)	26 (68.4%)	0.47
Previous pulmonary surgery	8 (26.7%)	10 (26.3%)	0.97
Extracorporal circulation used	6 (20%)	14 (36.8%)	0.13
Perfusion solution			
Eurocollins	23 (76.7%)	0 (0%)	
Perfadex	7 (23.3%)	38 (100%)	
Induction therapy			
Anti-thymocyte globuline	19 (63.3%)	0 (0%)	
IL-2 receptor antibody (daclizumab)	11 (36.7%)	38 (100%)	
Underlying disease			
COPD	12 (40%)	27 (71.1%)	
α1-ATD emphysema	5 (16.7%)	7 (18.4%)	
Fibrosis	4 (13.3%)	2 (5.3%)	
Cystic fibrosis	5 (16.7%)	1 (2.6%)	
Chronic thromboembolic pulmonary hypertension	1 (4.4%)	0 (0%)	
Cardiac (Eisenmenger)	1 (4.4%)	0 (0%)	
Other	1 (4.4%)	1 (2.6%)	
CMV status			
Donor positive/recipient negative	10 (33.4%)	13 (34.2%)	
Donor positive/recipient positive	20 (66.6%)	25 (65.8%)	0.939
Median follow-up	16.5 months	23.8 months	0.54

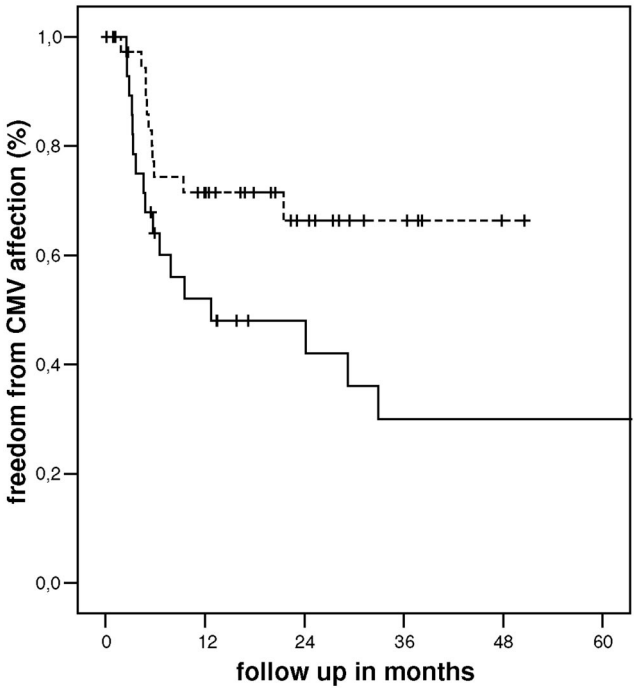

FIGURE 2. Freedom from CMV reactivation or de-novo infection in months using Kaplan-Meier survival analysis in patients receiving either augmented CMV prophylaxis (ganciclovir and CMV-IG, dashed line) or patients receiving single ganciclovir (solid line); log rank: $P=0.027$.

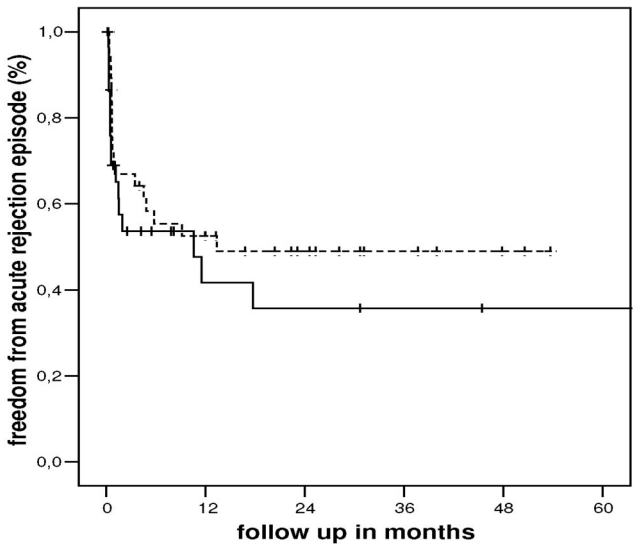

FIGURE 3. Freedom from acute rejection episodes in months (Kaplan-Meier analysis) in patients receiving augmented CMV prophylaxis with ganciclovir and CMV-IG (dashed line) compared to patients only receiving ganciclovir (solid line); log rank: $P=0.33$.

incidence of clinical CMV disease ($P=0.5$) or CMV related deaths ($P=1.0$) within this subgroup.

Azathioprine was given as initial immunosuppressive medication in 16 patients until the year 1998. In a subgroup

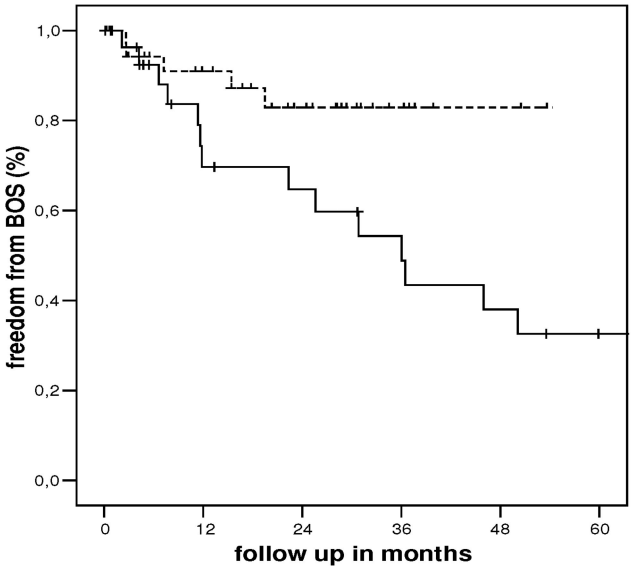

FIGURE 4. Freedom from Bronchiolitis obliterans (BOS) in months (Kaplan-Meier analysis) in patients receiving augmented CMV prophylaxis with ganciclovir and CMV-IG (dashed line) compared to patients only receiving ganciclovir (solid line); log rank: $P=0.024$.

analysis within the control group, we could not identify a difference concerning survival (log-rank: $P=0.81$), freedom from CMV affection (log-rank: $P=0.39$), CMV disease ($P=0.89$), CMV related death ($P=0.89$), acute rejection episodes (log-rank: $P=0.52$) or freedom from BOS (log-rank: $P=0.65$) in recipients receiving azathioprine instead of mycophenolate-mofetil.

In recipients who suffered from clinical CMV infection (either pneumonia or syndrome), one-year freedom from BOS was 75.4% in patients suffering from clinical manifest CMV infection versus 84.7% in patients without, whereas 3-year freedom from BOS was 53.3% vs. 75.7% (log-rank: $P=0.06$). There was a trend towards higher risk for BOS in patients who suffered from previous clinical CMV infection.

DISCUSSION

The results of this study suggest that CMV-IG in addition to GAN within the first postoperative month is highly effective in reducing CMV infection and in preventing CMV-related mortality in high risk lung transplant recipients. In addition, we observed a beneficial effect of the combined CMV prophylaxis on the development of BOS, which has not been shown in previous studies (*14*). Neither the use of IL-2 receptor antibody induction therapy nor the use of mycophenolate-mofetil had an impact on recipient survival and CMV outcome. The additional use of CMV-IG seems to be responsible for the reduction of BOS in long term follow-up.

There is a wealth of clinical and experimental evidence indicating the interaction of CMV infection and rejection in cardiac and other solid organ allografts by activating the release of TNF-α and thereby enhancing chronic rejection (*17–19*). In a study by Kroshus, CMV pneumonitis was identified to be the strongest independent predictive factor for the later

development of BOS (*20*). In contrast to these studies, Tamm and colleagues demonstrated that patients with CMV pneumonia were not at higher risk of developing BOS (*21*). However, they argued that CMV pneumonia often follows acute rejection episodes as a result of intensified immunosuppression. In our study, we could find a trend towards higher rates of BOS in patients suffering previous clinical CMV infection.

The results of our study are in line with reports that proposed combined regimens in order to prevent or treat CMV in high risk lung transplant recipients, as the use of single GAN or CMV-IG alone was not effective (*8*, *9*).

The recent studies by Valantine and Weill (*13*, *14*) used CMV-IG lasting for 3 to 4 months postoperatively. In contrast to these studies, our data underline that effective CMV prevention is also provided if CMV-IG is only given for the first posttransplant month.

According to the study by Goldfarb et al., who reported a hypogammaglobulinemia rate of 70% after lung transplantation, the administration of CMV-IG may be of additional benefit in preventing other infections (such as aspergillosis or bacterial) as well (*22*).

Another study by Bhorade and colleagues described GAN resistance of CMV strains to be up to 12% and found that IL-2 induction therapy might be associated with a 7 fold greater likelihood to develop GAN resistance (*23*). In contrast to their results, we have never observed GAN resistance in patients receiving IL-2 induction therapy.

Prospective randomized trials to prove the efficacy of CMV-IG for the prevention of CMV have only been performed in kidney and liver transplantation (*24*, *25*). However, CMV has the most significant impact on survival in heart-lung and lung transplant recipients, owing to the deleterious consequences of CMV affecting the allograft. Furthermore, up to now, there are no recommendations available regarding dosage and treatment duration of GAN or CMV-IG. Recent other studies have demonstrated good results in reducing the incidence of CMV disease using long time protocols of intravenous GAN (*12*) or CMV-IG for the first 3 to 4 months postoperatively (*13*, *14*). Since we know that transplant recipients are at highest risk for systemic infections, short time i.v. protocols should be favored, as central venous catheters might be a potential infective source (*26*).

The main limitations are the non-prospective and non-randomized nature of this current study. Additionally, the use of a historical control rather than a contemporary one is a major limitation in interpreting the findings.

During the study period, we have switched the organ preservation solution from Eurocollins to Perfadex and therefore cannot fully adjust for this factor either of the groups. A previous study reported that Perfadex may have an impact on early reperfusion edema (*27*); however, there are no long-term studies available that have shown any beneficial long term effect after lung transplantation.

Although we have tried to assess the possible effects of various immunosuppression regimens and other changes such as preservation solution, we cannot neglect the fact that this is not a randomized trial. Survival and other outcomes in lung transplantation have improved over time, probably due to a whole host of factors that are difficult to assess in a study like this. However, as we have not changed the GAN regimen within the groups, our findings suggest such an effect and might therefore add to the current knowledge of CMV prophylaxis. For the future, prospective randomized clinical trials are still needed to evaluate the benefit of either combined CMV prophylaxis compared to prolonged application of ganciclovir or val-ganciclovir to elaborate the most effective and cost-saving protocol for sufficient CMV prevention.

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