

Cytomegalovirus Serology and Replication Remain Associated With Solid Organ Graft Rejection and Graft Loss in the Era of Prophylactic Treatment

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and on behalf of all members of the Swiss Transplant Cohort Study

Background. Cytomegalovirus (CMV) replication has been associated with more risk for solid organ graft rejection. We wondered whether this association still holds when patients at risk receive prophylactic treatment for CMV.

Methods. We correlated CMV infection, biopsy-proven graft rejection, and graft loss in 1,414 patients receiving heart (n=97), kidney (n=917), liver (n=237), or lung (n=163) allografts reported to the Swiss Transplant Cohort Study.

Results. Recipients of all organs were at an increased risk for biopsy-proven graft rejection within 4 weeks after detection of CMV replication (hazard ratio [HR] after heart transplantation, 2.60; 95% confidence interval [CI], 1.34–4.94, $P<0.001$; HR after kidney transplantation, 1.58; 95% CI, 1.16–2.16, $P=0.02$; HR after liver transplantation, 2.21; 95% CI, 1.53–3.17, $P<0.001$; HR after lung transplantation, 5.83; 95% CI, 3.12–10.9, $P<0.001$). Relative hazards were comparable in patients with asymptomatic or symptomatic CMV infection. The CMV donor or recipient serological constellation also predicted the incidence of graft rejection after liver and lung transplantation, with significantly higher rates of rejection in transplants in which donor or recipient were CMV seropositive (non-D⁺/R⁺), compared with D[−] transplant or R[−] transplant (HR, 3.05; $P=0.002$ for liver and HR, 2.42; $P=0.01$ for lung transplants). Finally, graft loss occurred more frequently in non-D[−] or non-R[−] compared with D[−] transplant or R[−] transplant in all organs analyzed. Valganciclovir prophylactic treatment seemed to delay, but not prevent, graft loss in non-D[−] or non-R[−] transplants.

Conclusion. Cytomegalovirus replication and donor or recipient seroconstellation remains associated with graft rejection and graft loss in the era of prophylactic CMV treatment.

Keywords: Organ transplantation, CMV, Infection, Rejection.

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Cytomegalovirus (CMV) infection is among the most frequent complications after solid organ transplantation (SOT) (1). De novo infection can occur if passenger leukocytes contained in the graft of a seropositive donor

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mediate primary infection in a seronegative patient. Secondary reactivation in seropositive recipients is also frequent and is caused by pharmacologically compromised T-cell immunity in patients with latent infection. Intensification of immunosuppression to prevent or treat graft rejection is therefore an established risk factor for CMV replication (2).

Several reports have suggested that the relationship between CMV and rejection is complex: not only can rejection (and its treatment) act as a risk factor for CMV replication but CMV infection can also trigger graft rejection. In a mouse heart transplant model, latent murine CMV infection was able to induce graft rejection (3). Similarly, an early single-center study found an almost sixfold increase in the risk of graft rejection in the month after CMV disease after kidney transplantation (4). In several studies, CMV disease was associated with an increase in graft loss after kidney or combined kidney and pancreas transplantation (5–7). Comparable data exist for patients receiving lung (8), heart (9), or liver (10) allografts. Pathophysiologically, the systemic inflammation induced by CMV replication might alter the fragile state of graft tolerance in the transplanted patient and trigger graft rejection (11). Reduction of immunosuppression in the context of CMV disease might be another contributing factor.

As a consequence of the risks associated with post-transplant CMV infection, CMV chemoprophylaxis and preemptive treatment have become a standard of care over the past decade (12). Typically, high-risk patients (donor seropositive, patient seronegative) receive valganciclovir or ganciclovir prophylaxis, whereas intermediate-risk patients (recipient seropositive) are monitored by pp65 antigenemia or nucleic acid testing and are treated preemptively. The incidences of posttransplant CMV infection and disease have as a consequence substantially decreased, and most CMV infections occurring nowadays are asymptomatic replication events. Whether CMV is still a risk factor for graft rejection in the era of prophylactic or preemptive treatment has not been systematically analyzed. Small studies in lung and kidney transplant recipients treated prophylactically failed to find an association between CMV replication and graft rejection (13, 14). We therefore aimed to study the effect of CMV replication—*asymptomatic and symptomatic*—on the incidence of rejection and graft failure in a large cohort of patients prospectively followed within the Swiss Transplant Cohort Study (STCS).

RESULTS

Incidence of CMV Replication and Acute Rejection

The 2-year cumulative incidence of CMV replication amounted to 46%±6% in heart, 42%±2% in kidney, 41%±3% in liver, and 31%±4% in lung allograft recipients (Figure S1A, SDC, <http://links.lww.com/TP/A976>). The distribution between patients grouped by donor recipient serostatus was similar in all organ groups, with overall CMV replication rates of 3%±1% in D⁻/R⁻, 41%±3% in D⁻/R⁺, 47%±3% in D⁺/R⁻, and 56%±2% in D⁺/R⁺ transplants, respectively. Cytomegalovirus replication rates were not significantly influenced by the type of induction treatment (anti-lymphocyte

globulins vs. CD25 antibody) or by the type of maintenance immunosuppression (cyclosporine vs. tacrolimus based). Of the 487 first episodes of CMV replication, 52 (11%) were symptomatic, whereas the remaining 435 (89%) were asymptomatic. Of the asymptomatic episodes, 275 (63%) were treated, whereas the remaining 160 (37%) were observed. The number of patients developing a second, third, and fourth episode of CMV replication were 142, 71, and 8, respectively, with distributions between symptomatic and asymptomatic replication similar to first episodes (data not shown).

Prophylaxis with valganciclovir was administered to 47% of the patients after transplantation with significant differences between the types of organ transplanted (Table 1). Most D⁺/R⁻ patients received CMV prophylaxis (79%), whereas only half of the CMV seropositive recipients received prophylactic treatment (50% and 49% for D⁻/R⁺ and D⁺/R⁺, respectively). The median duration of CMV prophylactic treatment was 3.6 months (range, 0–19 months). At 4 years, the cumulative incidence of biopsy proven graft rejection was 67%±5% in heart, 29%±2% in kidney, 41%±4% in liver, and 34%±4% in lung transplant patients, respectively (Figure S1B, SDC, <http://links.lww.com/TP/A976>).

CMV Replication and Rejection

Hazard ratios for the development of graft rejection within 4 weeks after detection of CMV replication are shown in Figure 1 for patients grouped by type of organ transplanted. A significant increase in the risk for graft rejection was detected in all organs. Substantial differences were noted between different organs, with the highest risk in lung transplants and the lowest risk in kidney grafts (hazard ratio (HR) for graft rejection after any type of CMV infection event after heart transplantation, 2.60; 95% confidence interval (CI), 1.34–4.94; *P*<0.001; HR after kidney transplantation, 1.58; 95% CI, 1.16–2.16; *P*=0.02; HR after liver transplantation, 2.21; 95% CI, 1.53–3.17; *P*<0.001; HR after lung transplantation, 5.83; 95% CI, 3.12–10.9; *P*<0.001). Interaction analysis revealed that the differences in hazard ratios between organs were significant (*P*=0.003), whereas when patients were grouped by transplanted organ, no significant difference in the risk for graft rejection was evident between patients with asymptomatic untreated, asymptomatic treated, and symptomatic CMV replication, respectively (all interaction *P* values >0.1; Fig. 1).

Treatment of a rejection episode with escalation of immunosuppressive treatment might lead to CMV replication and thereby lead to an overestimation of the effect of CMV on graft rejection because patients with previous rejection episodes are at an increased risk for further rejections. We therefore next restricted the analysis to first episodes of CMV replication, and this analysis showed a similar picture (Figure S2, SDC, <http://links.lww.com/TP/A976>), albeit with larger confidence intervals caused by the smaller number of CMV replication events analyzed.

CMV Serology and Rejection

Having established that CMV replication increases the relative risk of graft rejection, we were also interested in quantifying whether CMV influences the absolute risk of graft rejection. Although the risk of graft rejection was clearly elevated after CMV replication, the time at risk accounted for only 2% of total follow-up in this study (59

TABLE 1. Patient characteristics

Organ transplanted	Heart (n=97)	Kidney (n=917)	Liver (n=237)	Lung (n=163)
Patient age at transplantation				
Median (range)	50 (0–70)	53 (0–79)	54 (0–71)	54 (9–70)
Sex, n (%)				
Men	72 (74)	599 (65)	153 (65)	79 (49)
Women	25 (26)	318 (35)	84 (35)	84 (52)
CMV serology, n (%)				
D–/R–	21 (22)	190 (21)	36 (15)	36 (22)
D–/R+	20 (21)	198 (22)	63 (27)	35 (22)
D+/R–	21 (22)	183 (20)	39 (17)	44 (27)
D+/R+	32 (33)	333 (36)	91 (38)	47 (29)
Missing	3 (3)	13 (1)	8 (3)	1 (1)
No HLA-A/B/DR-mismatches, n (%)				
0–2	2 (2)	143 (16)	5 (2)	7 (4)
3–4	27 (28)	399 (44)	160 (68)	48 (29)
5–6	68 (70)	375 (41)	72 (30)	108 (66)
Antibody induction, n (%)				
Anti-CD25 mAb	11 (11)	578 (63)	132 (60)	147 (90)
ATG	84 (87)	224 (24)	1 (0)	15 (9)
None	2 (2)	115 (13)	93 (39)	1 (1)
Maintenance immunosuppression, n (%)				
Tacrolimus, mycophenolate, prednisone	35 (36)	626 (68)	140 (59)	58 (36)
Cyclosporine, mycophenolate, prednisone	55 (57)	274 (30)	57 (24)	102 (63)
Other	7 (7)	17 (2)	40 (17)	3 (2)
Valganciclovir prophylaxis, n (%)				
No	48 (50)	546 (60)	192 (81)	38 (23)
Yes	48 (50)	371 (40)	45 (19)	125 (77)

CMV, cytomegalovirus; D, donor; R, recipient; HLA, human leukocyte antigen; mAb, monoclonal antibody; ATG, anti-lymphocyte globulins.

person-years of a total of 2,976 person-years of follow-up). The number of rejection episodes occurring within 4 weeks after detection of CMV replication was 66 (9% of a total of 708 episodes).

As CMV replication was almost nonexistent in the D– and R– populations, we compared total rates of graft rejection in this population compared with the pooled population of D+ or R+ transplants. This analysis revealed that recipients of liver and lung, but not kidney or heart allografts, were at increased absolute risk of graft rejection if donor or recipient were CMV seropositive at the time of transplant (Fig. 2). In agreement with this, adjusted hazard ratios for graft rejection between D+ and R+ patients and D–/R– patients were 1.13 (95% CI, 0.68–1.90; $P=0.62$) for heart; 0.92 (95% CI, 0.72–1.18; $P=0.52$) for kidney; 3.05 (95% CI, 1.49–6.23; $P=0.002$) for liver; and 2.42 (95% CI, 1.19–4.92; $P=0.01$) for lung allografts.

CMV Serology and Graft Loss

To address whether the increased risk of graft rejection after CMV replication and in CMV D+ or R+ patients also translated into more risk of graft loss, we compared the incidence of graft loss in CMV D–/R– to D+ or R+ patients. For all organs, graft loss occurred more frequently in transplants involving a CMV seropositive donor or patients (heart, 1% vs. 0%; kidney 6% vs. 2%; liver, 8% vs. 3%; lung, 11% vs. 0%; in CMV D+ or R+ vs. D–/R–, respectively;

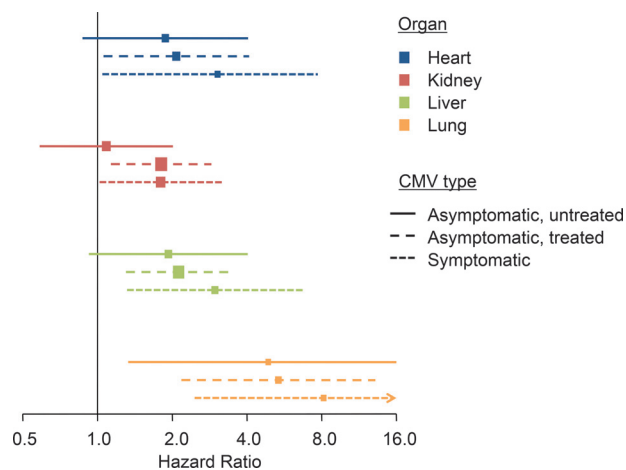


FIGURE 1. Forest plot of hazard ratios derived from time-dependent Cox models analyzing the impact of CMV replication on the incidence of biopsy proven graft rejection in recipients of heart (n=97), kidney (n=917), liver (n=237), or lung (n=163) allografts. Cox models included induction and maintenance immunosuppression, number of HLA mismatched between recipient and graft, and incidence of previous rejection episodes as covariables. CMV, cytomegalovirus; HLA, human leukocyte antigen.

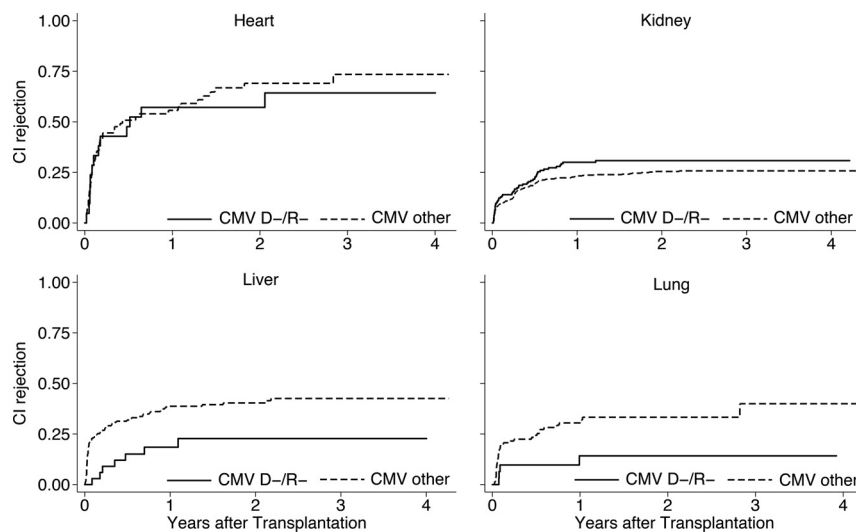


FIGURE 2. Cumulative incidence of graft rejection in patients grouped by transplanted organ and by donor recipient CMV IgG serostatus at the time of transplantation. Transplants from D⁻/R⁻ are compared with all other combinations (D⁻/R⁺, D⁺/R⁻, D⁺/R⁺) combined (heart, n=97, *P*=0.69; kidney, n=917, *P*=0.14; liver, n=237, *P*=0.03; lung, n=163, *P*=0.03; all *P* values by log-rank test). CMV, cytomegalovirus; IgG, immunoglobulin G; D, donor; R, recipient.

Fig. 3A). As prophylactic treatment with valganciclovir efficiently suppresses CMV replication during the time of prophylactic administration (Fig. 3B), we wondered whether valganciclovir treatment had any effect on graft survival. Analysis of graft loss over time revealed that indeed, non-D⁻/R⁻ patients receiving valganciclovir showed rates of graft loss comparable to D⁻/R⁻ patients in the first 6 months after transplantation. In contrast, non-D⁻/R⁻ patients not receiving CMV prophylaxis were at an increased risk of graft loss in the first months after transplantation. After 2 years, however, rates of graft loss were no longer lower in patients receiving valganciclovir (CMV D⁺ or R⁺ with valganciclovir, 6%±1%; without valganciclovir, 5%±1%; D⁻/R⁻, 2%±0%; Fig. 3C), suggesting that valganciclovir delays rather than prevents graft rejection.

DISCUSSION

Previous studies have correlated CMV replication and disease after SOT with transplant outcome and have in their majority shown that CMV replication is associated with poor transplant outcome in graft rejection, graft survival, and patient survival. These data, along with the availability of valganciclovir, a highly efficient substance available for oral treatment of CMV, has led to the widespread use of CMV prophylaxis after SOT. Introduction of CMV prophylaxis—along with monitoring and preemptive treatment—has reduced the incidence of symptomatic CMV disease and has also significantly reduced the number of patients with asymptomatic replication. Cytomegalovirus replication in patients receiving prophylaxis is also typically delayed until prophylaxis is discontinued, a period when patients are potentially at lower risk for graft rejection events. The significance of CMV replication and disease in triggering graft rejection in patients receiving transplants in the era of CMV prophylaxis is therefore unclear.

We analyzed the correlation of CMV replication and donor or recipient seroconstellation in a large cohort of patients receiving solid organ allografts between 2008 and 2012 in any of the six transplant centers in Switzerland. We found that, similar to earlier studies, CMV replication was associated with more risk for graft rejection after heart, kidney, liver, or lung transplantation. Although differences in the relative risks were apparent between organ type (lowest in kidney, highest in lung), we found no significant difference between patients with asymptomatic and symptomatic CMV infection. Further correlation between CMV serostatus and transplant outcome showed more rate of graft rejection in non-low-risk patients (i.e., non-D⁻/R⁻) receiving liver or lung allografts, but not heart or kidney allografts. In contrast, the incidence of graft loss was higher in non-D⁻/R⁻ patients compared with D⁻/R⁻ controls in all organs analyzed. Time to event analyses suggested that prophylactic treatment with valganciclovir is able to delay rather than prevent graft loss in non-D⁻/R⁻ transplants. These results extend a recently reported STCS analysis, which had analyzed the effect of valganciclovir prophylaxis on graft failure-free survival (a composite endpoint of graft failure and death) (11). In line with this previous study, we confirmed in this cohort that prophylactic treatment of CMV increases graft failure-free survival (Figure S3, SDC, <http://links.lww.com/TP/A976>). The rates of graft failure analyzed as a separate endpoint in this study suggest that prophylactic valganciclovir treatment may reduce the incidence of death without preceding graft failure, and that this effect may be largely responsible for the effect on graft failure-free survival.

The data shown here argue that despite prophylaxis, CMV replication continues to be significantly associated with graft rejection. This finding is corroborated by the analysis of patients grouped by donor or recipient serology. The data pose the question, whether prophylactic treatment should be prolonged with the goal to prevent graft rejection

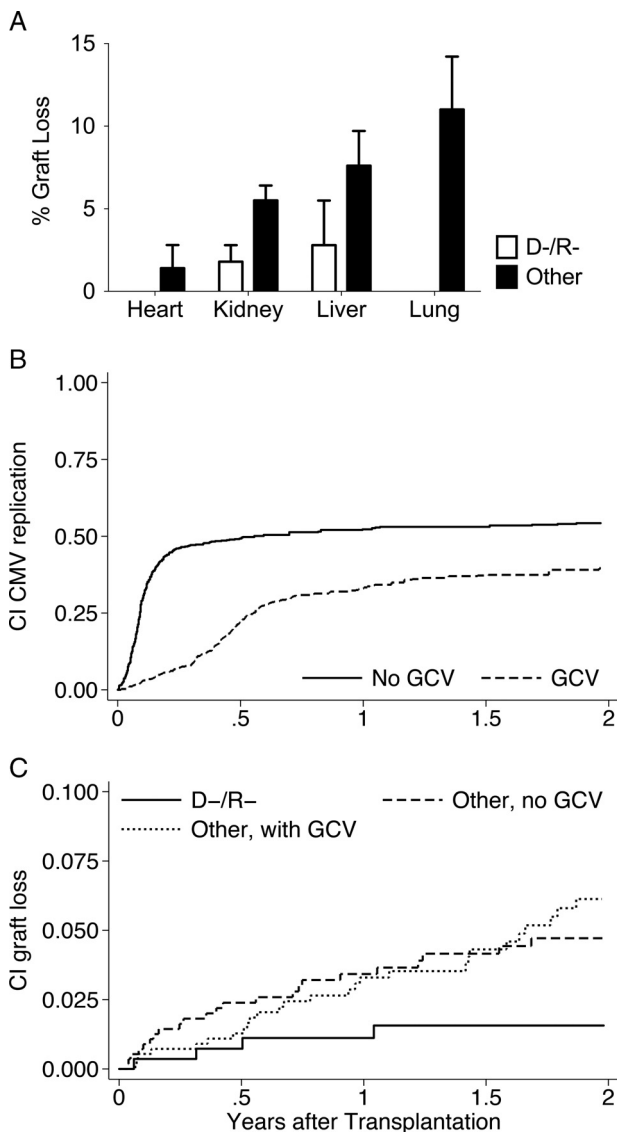


FIGURE 3. Rates of graft loss in D-/R- (white bars) versus non-D-/R- (black bars) in recipients of heart (0% vs. 1.4%; $P=1.0$), kidney (1.8% vs. 5.5%; $P=0.02$), liver (2.8% vs. 7.6%; $P=0.48$), or lung (0% vs. 11%; $P=0.08$) allografts (A). Cumulative incidence of CMV replication in patients receiving (dashed line) or not (solid line) valganciclovir (GCV) prophylaxis (B, all organs combined). Cumulative incidence of graft loss in D-/R- allografts (solid line, $n=278$), and in non-D-/R- allografts receiving (dotted line; $n=555$) or not (dashed line; $n=560$) valganciclovir prophylaxis ($P=0.16$). D, donor; R, recipient; CMV, cytomegalovirus.

and graft failure. Prolongation of valganciclovir administration from 3 months to 12 months has recently been shown to be feasible in a small study and led to reduced rates of both CMV infection and acute rejection in lung transplant recipients (15), although this could not be replicated in a similar study (16). A significant reduction of CMV disease was achieved by prolonging valganciclovir prophylaxis from 100 to 200 days after kidney transplantation, with

a nonsignificant reduction in rejection episodes occurring in this study (17).

The data in the current cohort suggest that valganciclovir administration for approximately 4 months may be too short to have an impact on long-term graft survival. Whether longer-term administration of CMV prophylaxis is indeed able to prevent rejections, or just further delays rejection events, would need to be studied prospectively. A potential limitation of this study is that monitoring for CMV was only performed regularly in the first months after transplantation. Late rejections may therefore have been preceded by undocumented CMV replication events. However, most rejections occurred during the period in which CMV replication was monitored. Despite this, the true risk of rejection associated with CMV replication events may be underestimated because of incomplete monitoring throughout the study period.

In conclusion, we show that in solid organ transplant recipients receiving prophylactic or preemptive treatment of CMV, infection with CMV—asymptomatic or symptomatic—remains to be a risk factor for biopsy-proven acute graft rejection. In line with this, despite attempts to prevent CMV replication or treat it early, CMV donor or recipient seroconstellation remains associated with graft rejection in patients receiving liver or lung allografts, and with graft loss in all organs analyzed.

MATERIALS AND METHODS

Study Design

The STCS is a prospective multicenter cohort study, enrolling patients treated with SOT in six transplant centers in Switzerland since May 2008 (18). Data are collected on demographic parameters, transplant type, comorbidities, immunosuppressive treatment, antimicrobial drugs, rejection, and infectious and noninfectious events at enrollment, at 6 months, and every 12 months on standardized data forms. Specific data on CMV infection available in the STCS database include the use of antiviral drugs and the type classified as asymptomatic replication, viral syndrome, and probable and proven end-organ disease.

Patients

Of 2,119 solid organ transplants reported to SCTS within the timeframe of the study, 1,414 patients undergoing first single SOT in Switzerland between May 2008 and August 2012 were combined in this analysis (Inselspital Bern, $n=201$; Centre Hospitalier Universitaire Vaudois, Lausanne, $n=228$; Hôpitaux Universitaires de Genève, $n=158$; Kantonsspital St. Gallen, $n=69$; Universitätsspital Basel, $n=222$; Universitätsspital Zürich, $n=536$). We selected patients receiving a first single heart, kidney, liver, or lung allograft. Seven hundred and nine patients receiving solid organ transplants during the time frame of this study were excluded. Reasons for exclusion were: transplantation of more than one organ ($n=192$), transplantation of small bowel, pancreas, or pancreas islets ($n=42$), patients with ABO blood group barrier ($n=20$), patients with donor-specific antibodies ($n=52$), non-first transplants ($n=42$), or missing data ($n=361$). Induction and maintenance immunosuppressive regimens are summarized in Table 1 along with demographic characteristics.

Cytomegalovirus serologic constellation was assessed by detecting anti-CMV immunoglobulin G antibodies in donors and recipients at the time of transplant. Screening for CMV replication by polymerase chain reaction was performed at each transplant center every 1 to 2 weeks during the first 6 months after transplantation. Data on transplant characteristics and transplant outcome including infectious complications were prospectively collected using an electronic database. Written informed consent was

obtained from all study participants, and the study was institutional review board approved at all centers.

Classification of CMV Replication and Rejection Episodes

In general, only biopsy-proven rejection episodes were considered in this study. Cardiac biopsies were classified according to the International Society for Heart and Lung Transplantation guidelines (19), and any grade II or higher histology was considered a rejection event. Renal biopsies were classified according to the Banff classification (20), and rejection episodes of grade IA and higher were classified as acute rejections. Pure humoral rejections defined as C4d deposition without any cellular involvement were not considered in this study because the definition and the criteria to diagnose a pure acute humoral rejection differ from organ to organ. Liver biopsies were categorized according to Banff Rejection Activity Index (21), and scores of 3 or higher were considered acute rejection episodes. Lung biopsies were classified according to the revised International Society for Heart and Lung Transplantation guidelines (22), and grade II or higher episodes were classified as acute rejection.

Cytomegalovirus replication was classified as asymptomatic (evidence of CMV replication without symptoms) and symptomatic (viral syndrome or tissue invasive disease). Asymptomatic replications were further classified into those that resulted in anti-CMV treatment and into those observed only.

Statistical Analysis

Recipients of heart, kidney, liver, and lung allografts were analyzed separately. Cumulative incidences of CMV replication and of graft rejection episodes were estimated using death and graft loss as competing risks. Cox regression was used for multivariable analyses with graft rejection as an endpoint, adjusting for type of induction and maintenance immunosuppression, number of human leukocyte antigen mismatches between donor and graft and—in models that looked at more than one rejection episode—number of previous rejection events. Episodes of CMV replication were coded as a time-dependent covariate. Because we did not have data on the duration of CMV replication, we considered patients to be at risk for rejection for 4 weeks after first detection of CMV replication. In a subset of analyses, multiple rejection events were considered, with the number of previous rejections included in models as a stratification variable to account for the increased risk of rejections in patients with a history of previous rejections.

For the analysis of the effect of CMV prophylaxis on graft survival, all patients experiencing early graft loss or death (occurring in the first 2 weeks after transplantation) were excluded because follow-up in these patients may have been too short to start a planned prophylactic treatment. Prophylactic treatment was assumed if treatment with valganciclovir was initiated within 3 months after transplantation without a preceding CMV replication event. Death without preceding graft failure was considered a competing event in this analysis.

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