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ORIGINAL ARTICLE

Changing impact of cytomegalovirus in liver transplantation – a single centre experience of more than 1000 transplantations without ganciclovir prophylaxis

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Summary

As cytomegalovirus (CMV) disease was a leading cause of death following liver transplantation in earlier reports, general CMV prophylaxis is widely used. We re-evaluated the impact of CMV in a recent time period under balanced immunosuppression and effective CMV diagnostics and therapy. A retrospective analysis of 1200 liver transplantations between 1988 and 2000 was performed comparing the incidence of CMV infection and disease and patient survival rates in two different time periods (before and after availability of the pp65-antigenaemia assay). In addition, risk factors for CMV in the recent time period were analysed. No ganciclovir prophylaxis was administered during the whole study period. The incidence of CMV tissue invasive disease decreased from 9.4% in period I to 2.7% in period II, whereas the incidence of viral syndrome was about 6% in both periods. Especially CMV pneumonia and generalized disease were almost abandoned in period II. Patients with tissue invasive disease, but not with infection or viral syndrome had reduced survival rates in both periods. However, the disease-specific mortality was 10% and 0% respectively. The overall rate of CMV infection in period II was low (25.9%). Risk factors for CMV infection in the univariate analysis were: Initial nonfunction, D+R− seroconstellation, acute liver failure, triple or quadruple immunosuppression, OKT3 or ATG treatment, transfusion of >10 packed red cells, steroid boluses, postoperative mechanical ventilation and retransplantation. In the multivariate analysis only quadruple or triple immunosuppression, OKT3-treatment, transplantation for acute liver failure and initial nonfunction. The incidence of CMV tissue invasive disease as well as the disease-specific mortality has markedly decreased during the last years. Using routine surveillance with the pp65-antigenaemia assay, CMV infection and disease rates compare well to data with long-term ganciclovir prophylaxis. As D+R− patients still more often develop symptomatic disease, pre-emptive therapy could be useful in this patient group.

Introduction

Cytomegalovirus (CMV) infection represents one of the most frequent opportunistic infections following solid-organ transplantation. Incidence and severity of CMV infection depend on the immunosuppressive regimen, CMV serostatus of donor and recipient and the type of transplanted organ [1,2]. After orthotopic liver

transplantation (OLT), the incidence of CMV infection ranges between 25% and 80% [3–5], but most infections have a relatively mild course. Before introduction of the pp65-antigenaemia assay and ganciclovir, CMV infection was correlated with increased morbidity and mortality [5–7]. Universal CMV prophylaxis resulted in reduced infection rates [8,9]. Since several years improved diagnostic tools for the early and specific diagnosis of CMV infection [1,10–12], and ganciclovir as an effective antiviral agent are available. Therefore, universal prophylaxis could be replaced by more targeted approaches like preemptive treatment, i.e. antiviral treatment of asymptomatic patients with positive pp65 testing [1,16,13]. In parallel, modern immunosuppressive regimen reduced the incidence of CMV infection. Nevertheless, there is still a controversy about the impact of CMV on the long-term outcome after liver transplantation and the necessity of general CMV prophylaxis.

In the present analysis, we compared the incidence, and mortality of CMV disease as well as long-term patient survival rates in a large patient cohort during two periods (before and after the availability of the pp65-antigenaemia assay) without application of CMV prophylaxis. In addition, we analysed risk factors for CMV in the more recent period.

Patients and methods

Patient population

Between September 1988 and April 2000, a total of 1200 liver transplantations were performed at our centre. A total of 60 grafts in 54 patients under 18 years of age and 50 grafts surviving <30 days were excluded from the analysis. Thus, 1090 liver transplantations in 1007 patients (598 male and 409 female patients) were retrospectively analysed. Indications for primary liver transplantation were viral hepatitis ($n = 370$), alcohol cirrhosis ($n = 223$), cholestatic liver disease ($n = 139$), autoimmune cirrhosis ($n = 44$), cryptogenic liver cirrhosis ($n = 77$), Budd–Chiari syndrome ($n = 24$), cryptogenic acute liver failure ($n = 20$), bile-duct cancer ($n = 19$) and other less common causes ($n = 91$). In 94 patients a hepatocellular carcinoma was found in the explanted liver.

Orthotopic liver transplantation was performed using standard techniques. Immunosuppression consisted of tacrolimus ($n = 527$) or cyclosporine ($n = 563$) plus prednisolone. In addition, azathioprine ($n = 541$) and mycophenolate mofetil ($n = 99$) were part of the primary immunosuppressive regimen. An induction therapy with ATG or IL2-receptor antibodies was performed in 358 and 208 transplants respectively. Histologically confirmed rejection episodes were treated with 500 mg of intravenous methylprednisolone for three consecutive days. In case of steroid resistant rejection, patients were treated with 5 mg/day of OKT3 monoclonal antibody (Orthoclone®; Janssen Cilag, Neuss, Germany) for 5–7 days.

CMV-surveillance

Cytomegalovirus serostatus of donors and recipients was determined preoperatively by detection of CMV-immunoglobulin-G (IgG) and CMV-IgM with commercially available enzyme-linked immunosorbent assay (ELISA) (ETI Cytok G; Byk & DiaSorin Diagnostics, Dietzenbach, Germany). Before 1993, viral cultures were performed in case of suspected CMV infection. Since 1993, CMV pp65-antigenaemia in leucocytes was monitored with the APAAP technique (Clonab®; Biotest, Dreieich, Germany) as described previously [11]. CMV assays were performed weekly during primary hospitalization after OLT and additionally if CMV infection was suspected. Afterwards, patients were followed by our outpatients clinic and assays were performed only in case of suspected infection.

Definitions

In the following, definitions of CMV infection, syndrome and disease were used as suggested by Ljungman *et al.* [14]. Briefly, 'CMV infection' was defined as positivity of the pp65 antigen assay (pp65-antigenaemia with at least one positive cell per 10 000 leucocytes). CMV viral syndrome was used for patients with CMV infection plus CMV-specific symptoms (antigenaemia plus fever, leucopenia or thrombocytopenia), CMV tissue invasive disease for patients with CMV infection plus detection of organ invasion (hepatitis, pneumonia, gastroenteritis or involvement of other organs).

As no pp65-Ag assay was available before 1993 (period I), asymptomatic infections were only analysed in patients transplanted after March 1993 (period II). Therefore, patients of period I were only divided in patients with or without CMV disease. In both periods, CMV disease was classified as CMV-syndrome or tissue invasive disease. In case of elevated liver enzymes, a percutaneous liver biopsy was initiated and investigated histomorphologically and immunohistochemically for CMV-hepatitis. In case of suspected involvement of other organs, respective biopsies were taken. Regarding the manifestation of CMV (no CMV, CMV infection, CMV syndrome and CMV tissue invasive disease) and the period of transplantation (periods I and II), the whole population was divided in to seven groups. If one patient had more than one episode of CMV with different manifestations, he was assigned to the group with the most severe manifestation.

CMV – prophylaxis and treatment

All patients received oral low-dose acyclovir (200 mg/tds or less, adapted to renal function) as herpes simplex prophylaxis for 6 weeks. No ganciclovir prophylaxis was given, neither in low nor in high-risk patients. CMV prophylaxis with CMV-hyperimmunoglobulin (Cytotect®, 1 ml/kg BW; Biotest) at postoperative days 1 and 14 was used inconsistently until 1996. After 1996, no CMV prophylaxis was applied. Between 1993 and 1996, pp65-Ag positive asymptomatic patients were partially (50%) treated pre-emptively with intravenous ganciclovir [15], from 1996 to 2000 partially (50%) pre-emptively with oral ganciclovir [16], both within randomized studies. Treatment of CMV disease consisted of intravenous ganciclovir (5 mg/kg BW twice daily or adapted to renal function, Cymeven®; Roche, Grenzach-Wyhlen, Germany) for a minimum of 14 days. Until 1996 CMV hyperimmunoglobulin was given additionally at a dosage of 1 ml/kg BW every other day.

Statistical analysis

All values are depicted as mean, median, range and SEM. Differences between patient groups were compared by Mann–Whitney *U*-test or by Kruskal–Wallis test if more than two groups were compared. Comparison of categorical variables was performed by chi-square test. Multivariate analysis of risk factors for CMV infection and disease was performed by binary logistic regression analysis. Actuarial patient survival rates were calculated using the Kaplan–Meier estimation. Differences between groups were evaluated by log-rank test. Patients were followed up until death or last visit at which time point the event was classified as censored. All differences were considered significant at *P*-values of <0.05. Statistical analyses were performed with SPSS 10.0 (SPSS Inc., Chicago, IL, USA).

Results

CMV seroconstellation

In 713 transplantations (65%) the recipients were CMV-IgG seropositive (R+), in 335 (31%) were negative (R−). In 42 cases (4%) the pretransplant serostatus was not available. In 538 organ donors (49%) were CMV seropositive (D+), 510 (47%) were seronegative (CMV IgG negative donor, D−) and in 42 (4%) no CMV serostatus was performed. CMV seroconstellation of donors and recipients in both periods were not significantly different ($P = 0.15$, see Table 1).

CMV infection and disease

Cytomegalovirus tissue invasive disease occurred after 33 of 352 (9.4%) transplantations in period I (1988–1993); additional 22 patients suffered from CMV viral syndrome (6.3%). The incidence of CMV tissue invasive disease was significantly higher in the high-risk group (D+R−, 17%) than in the low-risk groups (7%, $P < 0.05$). Since the pp65 antigenaemia assay was not available at that time, no comparable 'asymptomatic infections' were definable during this period in the 297 patients without CMV disease.

During period II, CMV infection occurred at a mean time of 55 ± 13 days (range 0–2203, median 29 days) after transplantation. No significant differences were observed between patients with asymptomatic infection (44 ± 7 days, median 29 days), CMV viral syndrome (94 ± 48 days, median 28 days) and CMV tissue invasive

Table 1. CMV-seroconstellation and incidence of CMV infection with the respective clinical manifestation.

	Period I (September 1988 to April 1993)	Period II (May 1993 to April 2000)	*P*-value
Number of transplantations	352	738	
CMV seroconstellation (%)			
D−R−	60 (17)	103 (14)	NS
D−R+	107 (30)	224 (30)	NS
D+R+	106 (30)	244 (33)	NS
D+R−	66 (19)	101 (14)	NS
D or R unknown	13 (4)	66 (9)	NS
CMV-infection (%)			
No pp65 antigenaemia	No pp65 testing*	547 (74.1)	–*
Asymptomatic CMV-infection	No pp65 testing*	123 (16.7)	–*
CMV-syndrome	22 (6.3%)	48 (6.5)	NS
CMV-tissue invasive disease	33 (9.4%)	20 (2.7)	<0.01

CMV, cytomegalovirus; NS, not significant.

*The relatively high number of patients without CMV-infection in period I is caused by the definition of asymptomatic CMV-infection by pp65 antigenaemia, which was not available in period I, therefore no statistical analysis was performed for these groups.

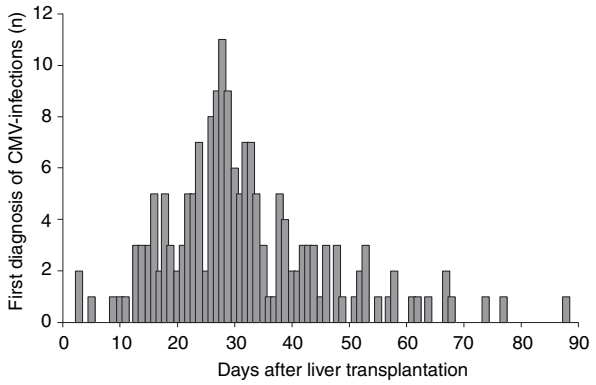

Figure 1 Timing of first cytomegalovirus infection after liver transplantation. The maximum incidence was observed at postoperative day 28, infections within the first 2 weeks were rarely observed.

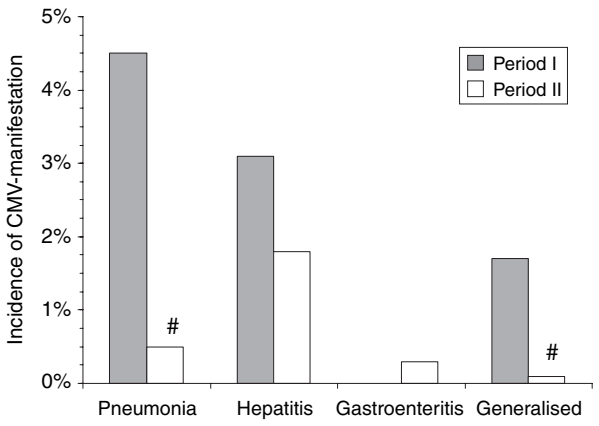

Figure 2 Manifestation of cytomegalovirus (CMV) disease in periods I and II: CMV-pneumonia and generalized disease were rarely observed in period II (#$P < 0.01$ versus period I by chi-square test).

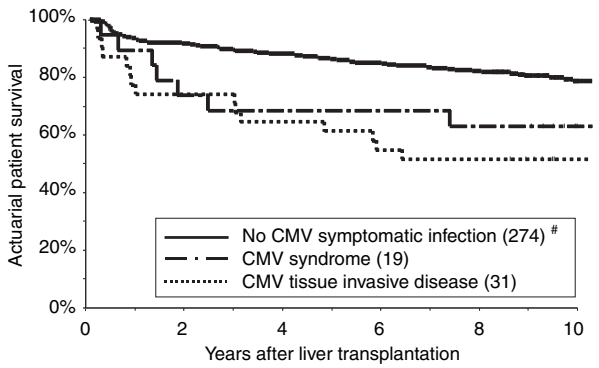

Figure 3 Kaplan–Meier estimation of patient survival related to manifestation of cytomegalovirus (CMV) in 324 patients transplanted in period I (orthotopic liver transplantation before 1993). Patients with CMV tissue invasive disease had a significantly impaired survival rate ($P < 0.01$), whereas survival of patients with CMV syndrome was not significantly lower ($P = 0.073$, all by log-rank test) (#no definition of CMV infection comparable with period II because of different diagnostic parameters for CMV).

disease (33 ± 3 days, median 29 days). The maximum of CMV infection was found at postoperative day 28 (Fig. 1). In period II, 547 of 738 liver transplant recipients (74.1%) had no episode of CMV infection whereas in 191 liver transplant recipients (25.9%), the pp65-Ag assay was positive at least once (Table 1). Of these 191 patients, 123 remained asymptomatic (16.7%), 48 developed CMV viral syndrome (6.5%) and 20 developed tissue invasive disease (2.7%). The incidence of asymptomatic CMV infection, CMV viral syndrome and tissue invasive disease were 24%, 14% and 12% in the D+R− group and significantly higher than 14%, 6% and 1% in the other groups ($P < 0.01$). The overall incidence of CMV infection in periods I and II was not compared statistically because of different diagnostic assays in the two periods. The incidence of CMV tissue invasive disease was significantly lower in period II (2.7%) compared with period I (9.4%, $P < 0.01$), whereas the incidence of CMV viral syndrome revealed no significant differences between the two periods (6.3% vs. 6.5%, $P = 0.43$). Differences in the manifestation of tissue invasive disease in periods I and II are shown in Fig. 2. CMV pneumonia and generalized disease was rarely observed in the second period, and the most frequent manifestation in this period was CMV hepatitis.

Patient and graft survival rates

In period I the overall 1, 3 and 5-year patient survival rates were 91%, 85% and 82% respectively. Period I patients with tissue invasive disease had significantly lower survival rates than patients without CMV infection (Fig. 3), whereas in patients with CMV viral syndrome the difference was not statistically significant.

In period II, patient survival in all patients with pp65-antigenaemia was not significantly different from patients without CMV infection ($P = 0.46$ by log-rank test, Fig. 4). Overall 1, 3 and 5-year patient survival rates in the 547 patients without CMV infection were 94%, 87% and 85%, respectively, which was not significantly different from 93%, 90% and 86% in patients with asymptomatic CMV infection ($P = 0.89$, Fig. 4). The survival rate of patients with CMV viral syndrome was also not impaired, whereas patients with tissue invasive disease had slightly but not significantly lower survival rates than patients without CMV infection. Five of the 20 patients with CMV tissue invasive disease died during the follow-up period. However, the cause of death in the five patients were not directly related to CMV infection: recurrent malignant tumour ($n = 3$), graft versus host

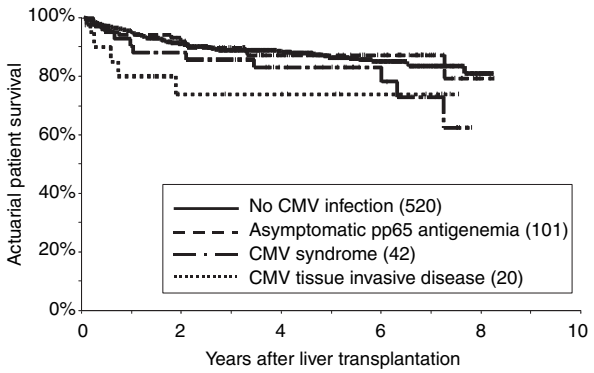

Figure 4 Kaplan–Meier estimation of patient survival related to manifestation of cytomegalovirus in the 683 patients transplanted in period II (orthotopic liver transplantation after 1993), all differences were not statistically significant ($P = 0.15$ by log-rank test).

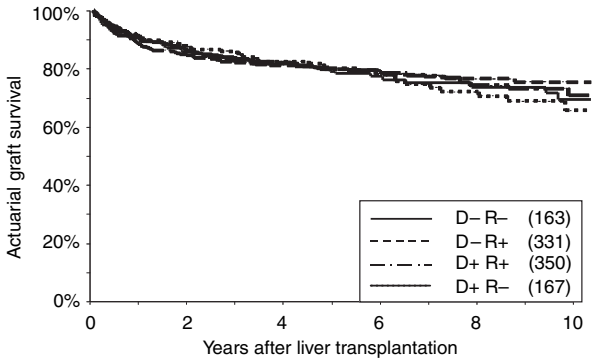

Figure 5 Kaplan–Meier estimation of graft survival related to donor and recipient cytomegalovirus serostatus for both periods together ($n = 1011$ grafts with known donor–recipient constellation of 1090 transplantations with a graft survival >30 days). No significant differences were found for all transplantations ($P = 0.91$ by log-rank test) and also for both periods separately although D+R– constellation had a trend lower graft survival in period I ($P = 0.22$).

disease and aspergillosis. In parallel, none of the patients in the other groups of period II died because of CMV related courses (Table 2). In contrast, three of 33 patients with CMV tissue invasive disease in period I died because of CMV infection (CMV-pneumonia $n = 2$, disseminated CMV disease $n = 1$).

The CMV seroconstellation of donor and recipient did not influence long-term survival rates in both periods. The 1, 5 and 10-year patient survival rates in 167 patients of the high-risk group D+R– were 93%, 84% and 69% and did not significantly differ from 91%, 85% and 77% in the D–R– group ($P = 0.30$; Fig. 5).

Risk factors for CMV infection and disease

Risk factors for CMV infection and disease were analysed in period II, because a standardized definition of CMV infection was only available in this period. In addition these more recent data are representative for the actual management (Table 3). In the univariate analysis, the following parameters were associated with a significantly increased relative risk for CMV infection: transplantation for cryptogenic ALF or cryptogenic cirrhosis, interferon (INF), triple and quadruple immunosuppression, cyclosporine as primary immunosuppressant, OKT3 treatment for rejection, ATG or ALG treatment, azathioprine, retransplantation, D+R–, CMV seropositive donor or seronegative recipient, postoperative ventilation >24 h and transfusion of more than 10 packed red cells. In contrast, tacrolimus as primary immunosuppressive drug, dual immunosuppression and OLT for hepatitis B significantly reduced the relative risk for CMV infection. In the multivariate analysis, only INF, cryptogenic liver failure, triple or quadruple immunosuppression and OKT3

Table 2. Reasons of death in 324 and 683 patients with primary liver transplantation during periods I and II respectively.

	Period I		Period II		
Reason of death	No symptomatic CMV infection	Symptomatic CMV infection	No CMV infection	Asymptomatic pp65 antigenaemia	Symptomatic CMV infection
CMV disease	–	3	–	–	–
Fungal/PCP# infection	2	4	3	2	–
Sepsis/bacterial infections	2	–	7	1	2
Recurrent primary disease*	19	7	27	4	6
De novo malignant tumor	12	2	12	1	–
Chronic rejection	2	1	–	–	1
Others	20	4	20	5	6
Total deaths (97)	57/274 (20.8%)	22/50 (44.0%)	69/520 (13.3%)	13/101 (12.9%)	15/62 (24.2%)

CMV, cytomegalovirus.
*Including recurrent viral hepatitis, alcoholic liver disease and malignant tumours.
#Pneumocystis carinii pneumonia.

Table 3. Relative risk of CMV infection (symptomatic + asymptomatic, era II, $n = 738$ OLT).

	CMV-infection relative risk	Univariate P = chi-squared test	Symptomatic CMV relative risk	Univariate P = chi-squared test
INF	3.08	<0.001*	4.73	<0.001*
D+R−	2.40	<0.001	3.90	<0.001
Cryptogenic acute liver failure	1.97	0.037*	3.42	0.007*
Triple/quadruple immunosuppression	1.77	<0.001*	2.20	0.010*
OKT treatment (rejection)	1.73	0.005*	2.05	0.037
Retransplantation (first/second)	1.70	0.005	1.73	NS
Donor CMV seropositive	1.64	<0.001	1.82	0.017
Postoperative ventilation >24 h	1.59	0.046	2.01	0.044
Recipient CMV seronegative	1.56	0.003	3.44	<0.001
Cryptogenic cirrhosis	1.52	0.043	1.34	NS
ATG/ALG induction	1.44	0.008	1.36	NS
Intraoperative >10 packed red cells	1.40	0.034	1.85	0.020*
Steroid boluses (rejection)	1.39	0.018	1.03	0.899
Azathioprin	1.38	0.010	2.00	0.002
Cyclosporine	1.30	0.037	1.71	0.023
Child C pretransplant	1.26	NS	1.25	NS
Female gender	1.25	NS	1.11	NS
CIT >12 h	1.22	NS	0.96	NS
BT 563	1.20	NS	1.46	NS
No HLA C matches	1.18	NS	1.12	NS
Liver shipped	1.11	NS	1.15	NS
Mycophenolate mofetil	1.07	NS	0.87	NS
No HLA DQ matches	1.05	NS	1.05	NS
No HLA A matches	1.05	NS	1.05	NS
No HLA B matches	1.04	NS	1.04	NS
HCV infection	1.04	NS	1.09	NS
HCC	0.99	NS	1.03	NS
No HLA DR matches	0.91	NS	1.11	NS
Tacrolimus	0.77	0.037	0.59	0.023
Hepatitis B	0.58	0.011	0.28	0.013*
Dual immunosuppression	0.56	<0.001	0.45	0.10

CMV, cytomegalovirus; INF, interferon; HLA, human leucocyte antigen; HCV, hepatitis C virus; NS, not significant; CIT, cold ischemia time.
*Significant by multivariate analysis.

treatment remained significant. Regarding CMV disease (viral syndrome plus tissue invasive disease), the following parameters increased the relative risk in the univariate analysis: cryptogenic ALF, INF, triple and quadruple immunosuppression, cyclosporine, OKT3, azathioprine, D+R−, CMV seropositive donor or a seronegative recipient, postoperative ventilation >24 h and transfusion >10 packed red cells. Tacrolimus and hepatitis B reduced the risk for CMV disease. In the multivariate analysis, cryptogenic ALF, INF, triple and quadruple immunosuppression, transfusion >10 packed red cells and hepatitis B had an influence on the incidence of CMV disease (Table 2). The relative risk of developing CMV infection compared with patients with alcoholic liver disease for patients with different underlying diseases are shown in Fig. 6. The highest risk was observed for patients retransplanted because of initial nonfunction of the liver graft (rr = 4.39) and for patient with acute liver failure (rr = 2.80).

Discussion

The present large single centre experience demonstrates, that incidence and severity of CMV disease have decreased recently. Early reports identified CMV disease as a predictor of impaired survival rates [6,7]. Analysis of our data revealed a very low disease-specific mortality of CMV (0.9%). In the study of Otero *et al.* [7], CMV disease was a risk factor for graft loss and decreased patient survival, but no graft was lost and no patient died because of CMV. In the second report by Falagas *et al.* [6] no disease-specific mortality is indicated. Therefore, it remains unclear if CMV was in fact responsible for the impaired survival or rather an epi-phenomenon in critically ill patients. Nevertheless, there was a strong need for protection against CMV at this time.

In the recent period, the incidence of tissue invasive disease markedly decreased in our patients, whereas the

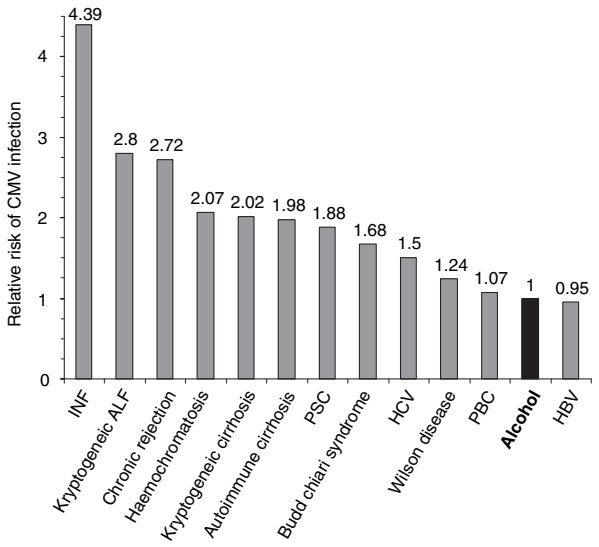

Figure 6 Relative risk of cytomegalovirus infection in all patients (periods I and II) according to the indication for liver transplantation compared with patients with alcoholic liver disease defined as rr = 1.

incidence of viral syndrome remained similar. In accordance with Stratta *et al.* [3] we found no significant different survival rates in patients with and without CMV infection. In parallel, D+R− patients did not reveal impaired survival rates despite and increased risk for CMV disease.

The overall incidence of CMV-infection (25.9%) in period II was relatively low without application of CMV prophylaxis. These data compare well with other recent series: even prophylactic application of ganciclovir resulted in 30% CMV infection rate [17]. And even under oral ganciclovir prophylaxis for 100 days, 25% of patients developed CMV infection and 4.8% CMV-disease in a study by Gane *et al.* [18]. A lower incidence of CMV infection (13% of patients in the high-risk group and 7% in the other groups) could be achieved by using combination prophylaxis with oral ganciclovir plus CMV-Ig [19]. Winston and Busuttil [20] reported a 7.3% rate of CMV disease in seropositive recipients using sequential intravenous ganciclovir and oral acyclovir prophylaxis. In contrast, a comparable study using CMV Ig plus (mainly oral) ganciclovir prophylaxis for 100 days post-transplant showed a 55% incidence of CMV disease in D+R− patients [21]. These obvious differences despite similar prophylactic regimens point out the importance of other factors. One important factor in the mentioned trials and in our two study periods is the kind of immunosuppression. In some studies, a relatively high net immunosuppression was given using a quadruple regimen including ALG induction therapy or azathioprine [20,21]. In the present study, the use of triple or double immunosuppression without azathioprine and with lower serum trough levels of cyclosporine or tacrolimus in the second period resulted in a low rate of CMV infection. In addition, during the period II, around 50% of patients were treated pre-emptively, guided by the pp65-antigenaemia assay, within randomized studies. Results of these two studies [15,16] point out, that in CMV seropositive recipients, the positive predictive value for CMV disease of the assay is low and symptom triggered treatment is equally effective. In contrast, in the high-risk group intravenous pre-emptive treatment might be beneficial in terms of lowering the incidence of tissue invasive disease [15,16]. Similarly, the pre-emptive approach guided by PCR led to a significant decrease of CMV disease [22].

Centres which have abandoned routine surveillance use either long-term prophylaxis [20] or treat only in case of symptomatic CMV disease [23]. Long-term ganciclovir prophylaxis often postpones the occurrence of CMV disease instead of avoiding it [24]. In a study with symptom-triggered treatment and without routine surveillance, two of 116 patients died of CMV tissue invasive disease [23]. These deaths might have been prevented by earlier diagnosis of CMV infection.

As most infection rates in studies using ganciclovir prophylaxis are not markedly lower than in the present series and survival rates do not differ, a general CMV prophylaxis seems not to be necessary, if a balanced immunosuppressive regimen and an adequate monitoring of CMV-infection is performed. Whereas in D+R− patients pre-emptive treatment is superior, in low-risk patients either pre-emptive or symptom triggered treatment seem to be feasible.

Risk factors for CMV infection and disease have already been analysed extensively in the literature [1,25–27]. The fact that an intensified immunosuppression was associated with an increased incidence of CMV infection and disease emphasizes the central role of a balanced immunosuppression. Patients transplanted for HBV cirrhosis received lamivudine or famciclovir, agents with anti-HBV and anti-CMV activity. This might explain the lower risk of CMV disease in HBV patients. In contrast to most other published data, the CMV serostatus was found as risk factor only in the univariate, but not in the multivariate analysis.

In summary, a comparison of studies evaluating the impact of CMV is difficult because of several influence factors. The immunosuppressive regimen and the surveillance of CMV differ between centres, therefore each centre has to analyse its own experience and to find the optimal CMV regimen. No general recommendations can be given. Nevertheless, the present study without ganciclovir prophylaxis demonstrates a very low incidence of

CMV infection and disease by using a balanced immunosuppression avoiding ATG/ALG induction therapy. CMV-infection and CMV-viral syndrome did not significantly influence patient survival rates in the present series. Therefore, a general prophylaxis seems to be no longer mandatory nowadays.

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