The Pathogenesis of Hepatitis C Virus 
Is Influenced by Cytomegalovirus

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We investigated the effect of β-herpesviruses on allograft failure and mortality, hepatitis C virus (HCV) replication, and liver histologic characteristics among 92 HCV-infected liver transplant recipients. Reactivation of cytomegalovirus (CMV) but not of human herpesvirus 6 (HHV-6) was independently associated with allograft failure and mortality (risk ratio, 3.71; 95% confidence interval, 1.64–8.39); allograft failure and mortality was observed in 48% of patients with CMV disease, 35% of patients with subclinical CMV infection, and 17% of patients without CMV infection (P = .0275). CMV reactivation was highly predictive of mortality (P < .001), regardless of whether it remained subclinical or evolved into CMV disease. Patients with CMV disease had a higher fibrosis stage (P = .05) and had a trend toward a higher hepatitis activity index (P = .10) and HCV load (P = .10) at 16 weeks after liver transplantation. The pathogenesis of HCV is influenced by its interaction with CMV but not with HHV-6.

Hepatitis C virus (HCV) infects an estimated 170 million people worldwide [1]. The majority of HCV-infected individuals develop chronic infection, which, in many patients, could lead to hepatic failure. With its pandemic magnitude, HCV infection is currently the leading indication for liver transplantation (LT) [1]. The course of HCV infection after LT is characterized by recurrence of HCV viremia in up to 95% of patients and of HCV-induced hepatitis in up to 70% of patients [2–5]. Within 5 years after LT, 10% of HCV-infected patients develop allograft damage that results in death or requires the patient to undergo retransplantation [2–5]. HCV-associated allograft failure is the most common cause of death during the first 5 years after HCV-indicated LT [6]. The factors that promote the accelerated course of HCV infection after LT are poorly defined; HCV load, HCV genotype, and immunosuppression [6–11] have been suggested, but the findings are inconclusive.

The impact of cytomegalovirus (CMV) infection on transplantation extends beyond CMV’s direct invasion in target organs (e.g., hepatitis) by triggering indirect effects [12], such as allograft dysfunction and increased opportunistic infections [13–18]. Accordingly, CMV could influence post-LT HCV infection in susceptible patients [19, 20]. In a preliminary study, we observed that CMV viremia was associated with allograft failure among HCV-infected persons who had undergone LT [21]. Whether this is mediated by CMV-enhanced immunosuppression [22, 23] and/or by directly increasing HCV replication is unknown. Whether this is the result of bursts of high levels of CMV replication, which usually lead to CMV disease [24], or to asymptomatic viral
replication remains unknown. Furthermore, human herpesviruses 6 (HHV-6) and 7 (HHV-7) may influence the direct and indirect effects of CMV [25]. Like CMV, HHV-6 and HHV-7 have immunomodulating and viral transactivating properties [26–28]. In fact, coinfecion with the β-herpesviruses is recognized to cause clinical syndromes after transplantation [25]. Collectively, these observations raise the hypothesis that HHV-6 and HHV-7 may influence HCV pathogenesis, either individually or in their interaction with CMV.

The small number of patients studied, the insensitive methods used for CMV detection, and the lack of investigations to have addressed the role of HHV-6 and HHV-7 in previous studies [19, 20] have hindered the ability to make definitive conclusions about the role of the β-herpesviruses on HCV pathogenesis. In the present study, we sought to determine the potential role that β-herpesviruses play in the course of HCV infection after LT. Moreover, we investigated whether subclinical CMV replication influences HCV pathogenesis.

PATIENTS AND METHODS

Study population. We evaluated 92 consecutive patients who first underwent LT for HCV-induced cirrhosis during the period of January 1991 through December 1999 and who had ≥4 months of follow-up after LT. Informed consent was obtained from the patients or their guardians. The guidelines for human experimentation of the US Department of Health and Human Services and the Mayo Clinic Institutional Review Board were followed in the conduct of this clinical research. The baseline demographic characteristics of our patient cohort are presented in table 1.

Immunosuppression. Before 1994, the immunosuppressive regimen administered to patients undergoing LT consisted of cyclosporine, prednisone, and azathioprine. Thereafter, tacrolimus was introduced. In 1997, a trial comparing mycophenolate mofetil (MMF) and azathioprine was undertaken. Beginning in 1999, the immunosuppressive regimen consisted of tacrolimus, MMF, and prednisone. Overall, our patients received cyclosporine (38% of patients), tacrolimus (72% of patients), azathioprine (55% of patients), MMF (14% of patients), and prednisone (100% of patients). Three intravenous boluses of methylprednisolone (1 g per day given on alternate days) were administered to treat graft rejection; OKT3 was reserved to treat episodes of steroid-resistant rejection.

End points. The primary end point of this study was the composite of HCV-induced allograft failure and mortality. Allograft failure was defined as cirrhosis (fibrosis stage 4) or the need for retransplantation. HCV replication and liver histologic characteristics were assessed as secondary end points. HCV RNA concentrations were measured using serum samples obtained before LT and during weeks 16 and 52 after LT by use of the bDNA assay 2.0 (Quantriplex HCV RNA; Chiron). Needle liver biopsies were performed, in accordance with a fixed protocol, on weeks 16 and 52 after LT and when clinically indicated; the histologic findings were reviewed by a single pathologist in a blinded fashion by means of the fibrosis stage and modified hepatitis activity index [29, 30].

Antiviral prophylaxis. Decisions regarding antiviral prophylaxis were influenced by the CMV serostatus of the donor and the recipient (positive donor/negative recipient [n = 14], positive donor/positive recipient [n = 46], negative donor/positive recipient [n = 24], and negative donor/negative recipient [n = 6]). Patients received either acyclovir (200 mg po t.i.d. for 4 weeks) or ganciclovir (1 g po t.i.d. for 8 weeks preemptively), both adjusted according to renal function, depending on risk. During the period from 1 January 1991 through 30 June 1994, 16 patients were enrolled into the study to receive acyclovir (800 mg po q.i.d.) for 4 months or intravenous ganciclovir (5 mg/kg q12h) for 2 weeks, followed by acyclovir (800 mg po q.i.d.) for 4 months. During 1997–1999, patients were randomized to receive preemptive oral ganciclovir therapy (1 g po t.i.d. for 8 weeks or placebo for CMV reactivation (determined by use of qualitative PCR). Patients received intravenous ganciclovir (5 mg/kg q.d.) during OKT3 administration.

Detection of β-herpesvirus infection and CMV disease. CMV infection, defined as the detection of CMV in clinical specimens, was identified by use of the Transplant Infectious Diseases database (which contains prospectively collected data about clinical events beginning at the time of transplantation until the last day of follow-up), a review of the medical and microbiology records, and detection of viral DNA in serum

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age, mean years (range)</td>
<td>49.64 (31–69)</td>
</tr>
<tr>
<td>Male sex</td>
<td>59.78</td>
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<tr>
<td>White race</td>
<td>83.70</td>
</tr>
<tr>
<td>CMV-positive donor/CMV-negative recipient status</td>
<td>15.21</td>
</tr>
<tr>
<td>Donor age, mean years (range)</td>
<td>42.58 (11–77)</td>
</tr>
<tr>
<td>Body mass index, mean ± SD</td>
<td>29.23 ± 5.93</td>
</tr>
<tr>
<td>MELD score, mean ± SD</td>
<td>14.30 ± 5.57</td>
</tr>
<tr>
<td>Child-Turcotte-Pugh score, mean ± SD</td>
<td>8.72 ± 1.88</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>23.91</td>
</tr>
<tr>
<td>Pretransplantation alcohol use</td>
<td>22.82</td>
</tr>
<tr>
<td>HCV load</td>
<td></td>
</tr>
<tr>
<td>&gt;1 mEq/mL</td>
<td>60.00</td>
</tr>
<tr>
<td>Mean mEq/mL (range)</td>
<td>3.29 (0–24.64)</td>
</tr>
<tr>
<td>HCV genotype 1</td>
<td>74.67</td>
</tr>
</tbody>
</table>

NOTE. Data are percentage of patients, unless otherwise indicated. CMV, cytomegalovirus; MELD, Model for End-Stage Liver Disease.

Table 1. Demographic data for 92 hepatitis C virus (HCV)–infected liver transplant recipients.
samples obtained weekly (see below). CMV disease was defined as the occurrence of accepted clinical symptoms (e.g., fever) or signs (e.g., leukopenia) in the presence of CMV infection [31].

In all patients, CMV reactivation in blood was assessed on a weekly basis by use of shell-vial assay during the first 6 weeks after LT and thereafter when clinically indicated. During this study, β-herpesvirus replication was further assessed (to identify CMV reactivation that was not detected by shell-vial assay and to determine HHV-6 and HHV-7 reactivation) with the quantitative LightCycler PCR assay (Roche Molecular Biochemicals) [32, 33] with use of stored serum specimens that were obtained weekly during the first 6 weeks after LT.

The analytical performance of the LightCycler PCR assays has been assessed elsewhere [32, 33]. In brief, viral nucleic acid was extracted from 200 µL of serum by the Isoquick Method (ORCA Research), in accordance with the manufacturer’s specifications, and was eluted in 100 µL of DNase-free and RNase-free water. From this, 5 µL was used each for CMV, HHV-6, and HHV-7 detection and was added to 15 µL of PCR mastermix solution. The PCR mixture was subjected to an automated LightCycler PCR system. The CMV PCR amplified and detected a 291-bp product contained at position 2500–2791 of the CMV genome, the HHV-6 PCR amplified and detected a 175-bp product located in the immediate early gene of HHV-6, and the HHV-7 PCR amplified and detected a 203-bp product located in the U10 and U11 genes of HHV-7. These assays can detect as few as 1 HHV-6 or HHV-7 genomic copy and 5 CMV genomic copies per PCR input.

Other risk factors. In addition to β-herpesvirus reactivation [13, 19, 20], we analyzed the data as factors that may predispose patients to cirrhosis, retransplantation, or death: the age, sex, and race of the patient and donor [34]; date of LT; body mass index; cold ischemia time [35]; underlying hepatocellular carcinoma and alcohol use [1]; Model for End-Stage Liver Disease scale [36]; Child-Turcotte-Pugh score [37]; immunosuppressive agents received [38]; occurrence of acute cellular rejection [10, 39]; and HCV load and genotype [7, 8].

Statistical analysis. Kaplan-Meier estimation was used to describe survival curves. Proportional hazard regression and frequency tables were used to analyze the impact of β-herpesvirus infection on the primary end point. This was performed first individually for baseline covariates in the proportional hazards model. Then, stepwise regression that included significant baseline covariates was used to assess the significance of CMV as an independent predictor. When applicable, exact P values were derived from the frequency tables. The secondary end points and the baseline and demographic variables were described in terms of mean and SD and compared using the Student’s t test or F test, as appropriate. The level of significance was set at .05.

RESULTS

β-herpesvirus Reactivation

β-Herpesvirus reactivation was observed in 66% of patients. CMV, HHV-6, and HHV-7 infection were documented in 40 (43%) of 92, 36 (40%) of 90, and 0 (0%) of 90 patients, respectively. Sequential HHV-6 then CMV coinfection occurred in 16% of patients, but no significant correlation was observed on the level of replication between these viruses.

CMV reactivation during the first 6 weeks after LT was demonstrated in 32 patients (35%) and was highly predictive of subsequent CMV disease (P < .001). Fifteen (47%) of 32 patients who had CMV reactivation during the first 6 weeks after LT subsequently developed CMV disease. Conversely, 17 (53%) had CMV reactivation that did not manifest clinically. A trend toward a higher peak CMV load was observed among patients who developed CMV disease, compared with patients who had subclinical CMV replication (mean peak CMV load, 27,651 vs. 3638 copies/mL). During the conduct of the study, 23 (58%) of 40 CMV-infected patients developed CMV disease (8 patients had end-organ involvement and 15 patients had nonspecific febrile illness).

Patients with CMV reactivation were observed to be older (P = .0444), and patients with HHV-6 reactivation were observed to have received higher doses of steroids (P = .0320). The characteristics of patients with or without CMV (or HHV-6) reactivation are presented in table 2. Patients with CMV-positive donor/CMV-negative recipient serostatus (P = .0188) and those who developed acute rejection (P = .0102) were at higher risk of developing CMV disease.

Primary End Points

During the median follow-up period of 24 months (range, 4–103 months), the primary end points of allograft failure (18 [19.6%] of 92 patients developed allograft failure) and mortality (8 [8.7%] of 92 patients died) occurred in 28% of patients. By use of a univariate model, clinical and subclinical CMV reactivation (P = .0224; table 3) were significantly associated with the primary end point, which was observed in 11 (48%) of 23 patients with CMV disease, 6 (35%) of 17 patients with subclinical CMV reactivation, and 9 (17%) of 52 patients without CMV infection (P = .0275).

Likewise, on univariate analysis, HHV-6 was associated with the primary end point (P = .0254; table 3). However, data to support this association are less convincing. HHV-6 reactivation, when analyzed irrespective of the degree of replication, was not associated with the primary end point (P = .5251), but a nonsignificant trend (P = .1236) and significant association (P = .0254) were observed when the degree of replication and the geometric mean HHV-6 levels, respectively, were considered.

In addition to CMV and HHV-6 status, the age of the donor
Reactivation during this period ( ). Mortality was not compared with 0 (0%) of 60 patients who did not have CMV, and progression of hepatocellular carcinoma (25%) of 32 patients who had CMV replication during the first 6 weeks after LT died of HCV-related causes (hepatic failure, regardless of whether it evolved into clinical disease. Eight (25%) of 32 patients who had CMV replication during the first 6 weeks after LT died of HCV-related causes (hepatic failure, with or without hepatorenal syndrome or multiorgan failure [n = 6], and progression of hepatocellular carcinoma [n = 2]), compared with 0 (0%) of 60 patients who did not have CMV reactivation during this period (P < .0001). Mortality was not associated with the degree of CMV replication; 5 of 8 patients who died had subclinical CMV reactivation that did not evolve into clinical disease.

Secondary End Points

Histologic outcome. Clinical and subclinical CMV infection were associated with higher fibrosis stage at 16 but not at 52 weeks after LT (mean stage ± SD, 0.8750 ± 1.288 vs. 0.4286 ± 0.7373; P = .0436). A trend toward a higher hepatitis activity index score at 16 weeks was observed (mean score ± SD, 3.9375 ± 2.8048 vs. 2.7907 ± 2.3960; P = .0606; table 5).

HCV replication. Serum HCV RNA was demonstrated in all 84 patients who were tested 16 weeks after they underwent LT (median HCV RNA level, 23.01 mEq/mL). Moreover, a trend toward higher mean serum HCV RNA levels at 16 but not at 52 weeks after LT was observed among patients who developed CMV disease (mean HCV RNA level ± SD, 55.71 ± 50.47 mEq/mL vs. 33.52 ± 47.03 mEq/mL; P = .0343; table 5).

DISCUSSION

By use of a defined clinical setting such as that occurring after LT, our study demonstrates that CMV (but not HHV-6) is a key pathogen that influences HCV pathogenesis. Even after adjusting for significant variables, such as donor age, patient

### Table 2. Characteristics of 92 hepatitis C virus–infected liver transplant recipients with or without β-herpesvirus reactivation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CMV reactivation</th>
<th>HHV-6 reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMV-positive</td>
<td>CMV-negative</td>
</tr>
<tr>
<td></td>
<td>patients</td>
<td>patients</td>
</tr>
<tr>
<td></td>
<td>(n = 40)</td>
<td>(n = 52)</td>
</tr>
<tr>
<td>Patient age, years</td>
<td>52.12 (37–69)</td>
<td>47.73 (31–65)</td>
</tr>
<tr>
<td>Male sex, % of patients</td>
<td>57.50</td>
<td>61.54</td>
</tr>
<tr>
<td>Donor age, years</td>
<td>45.00 (13–77)</td>
<td>40.34 (11–74)</td>
</tr>
<tr>
<td>Child-Turcotte-Pugh score</td>
<td>8.79 (5–13)</td>
<td>8.67 (5–13)</td>
</tr>
<tr>
<td>CMV-positive donor/CMV-negative recipient status, % of patients</td>
<td>22.50</td>
<td>9.62</td>
</tr>
<tr>
<td>Allograft rejection, % of patients</td>
<td>50.00</td>
<td>36.54</td>
</tr>
<tr>
<td>Daily steroid dose, mg/day</td>
<td>57.65 (16–191)</td>
<td>50.52 (16–201)</td>
</tr>
<tr>
<td>Cyclosporine use, % of patients</td>
<td>46.15</td>
<td>30.61</td>
</tr>
<tr>
<td>FK506 use, % of patients</td>
<td>64.10</td>
<td>77.55</td>
</tr>
<tr>
<td>Mycophenolate mofetil use, % of patients</td>
<td>10.53</td>
<td>16.33</td>
</tr>
</tbody>
</table>

NOTE. Data are mean (range), unless otherwise indicated. CMV, cytomegalovirus; HHV-6, human herpesvirus type 6; MELD, Model for End-Stage Liver Disease.

a Factors associated with CMV disease: CMV-positive donor/CMV-negative recipient status (P = .0188) and allograft rejection (P = .0102) were strongly associated with progression to CMV disease; a trend for CMV disease was also observed among older patients (P = .1974) and among those who received higher doses of steroids (P = .1226).
HHV-6, human herpesvirus type 6; RR, risk ratio.

failure and mortality ( ). CMV, cytomegalovirus; HCV, hepatitis C virus; addition, the HCV genotype ( ) and the HCV load before and at weeks 

P

NOTE. Other covariates that were evaluated but not found to be significantly associated with primary end points were patient sex (P = .6238); cold ischemia time (P = .8909); pretransplantation disease severity, as assessed by the Model for End-Stage Liver Disease (P = .4108) and Child-Turcotte-Pugh score (P = .5765); United Network of Organ Sharing status (P = .5623); serum bilirubin level (P = .9720); serum albumin level (P = .4745); prothrombin time (P = .4514); serum creatinine level (P = .2625); pretransplantation use of alcohol (P = .7865); and presence of hepatocellular carcinoma (P = .7865). In addition, the HCV genotype (P = .4344) and the HCV load before and at weeks 16 and 52 after transplantation were not significantly associated with allograft failure and mortality (P = NS). CMV, cytomegalovirus; HCV, hepatitis C virus; HbV6, human herpesvirus type 6; RR, risk ratio.

a The significant predictors of CMV infection, such as patient age, CMV-positive donor/CMV-negative recipient serostatus, and acute cellular rejection, were not significantly associated with allograft failure and mortality (P = NS).

b Only 3 patients received OKT3 treatment.

c CMV replication during the first 6 weeks after liver transplantation.

d The association between HHV6 reactivation and the primary end point was analyzed with geometric HHV6 levels as the variable. No significant association was demonstrated when the incidence of HHV6 was used as the variable. No significant association was demonstrated when the incidence of HHV6 was used as the variable.

The finding generated from this study, the largest to date of HCV-infected liver transplant recipients, should help clinicians design strategies for the prevention of CMV infection in this rapidly expanding subset of persons who have undergone LT. Present practice recommends the use of antiviral agents for patients at risk for CMV disease but not for patients who may have asymptomatic CMV replication. Effective CMV prophylaxis has decreased the incidence of CMV disease [42–45] and the impact of its indirect effects [18, 46]. Thus, the use of universal prophylaxis to predisposed HCV-infected liver transplant recipients, or the aggressive implementation of CMV surveillance by use of highly sensitive assays [32] to guide anti-CMV therapy, may positively influence the outcome of HCV-infected patients who have undergone LT.

In a smaller study of HCV-infected liver transplant recipients that used a PCR assay to guide prevention of CMV infection [20], short-term viremia was not associated with fibrosis. Although the investigators concluded that CMV did not influence fibrosis [20], the observations in our study suggest that the aggressive prevention of CMV infection in their patients may have positively influenced their patients’ outcomes. The uncontrolled antiviral prophylaxis administered to our patients did not allow us to reliably assess any beneficial effect from CMV prevention. However, our observations should pave the

age, and use of MMF, CMV infection remained strongly and independently associated with post-LT HCV-induced allograft failure and mortality. Moreover, we observed that even subclinical CMV reactivation that did not evolve into clinical disease influenced HCV outcome, an observation that could also apply to immunocompetent patients in whom subclinical CMV replication can be occasionally observed [33, 40, 41]. These observations have enormous applicability in the management of post-LT HCV infection, particularly because the prevention and treatment of CMV is currently attainable, whereas the prevention and treatment of post-LT HCV recurrence has yet to be defined.

The impact of subclinical CMV reactivation on post-LT HCV infection is both surprising and novel. In the field of organ transplantation, a long-lasting and ongoing debate has focused on the relevance and impact of asymptomatic CMV reactivation. This study provides a strong argument in favor of its relevance—at least in HCV-infected patients. Furthermore, our observation that mortality was observed exclusively among patients with CMV replication during the first 6 weeks after LT, regardless of whether the condition evolved to clinical disease, has substantial clinical relevance. The detection of CMV reactivation could serve as valuable prognostic marker of outcome. More importantly, it argues for early and aggressive prevention of not only CMV disease, but also of subclinical CMV reactivation.

Characteristic RR (95% CI) P

Patient age 0.966 (0.922–1.012) .1361

Year of transplantation 1.443 (1.108–1.897) .0027

Donor age 1.047 (1.022–1.073) .0001

Acute cellular rejection 1.299 (0.599–2.819) .5099

OKT3 use 4.624 (1.053–20.300) .0926

Mycophenolate mofetil use 2.686 (1.118–6.453) .0304

Tacrolimus use 1.239 (0.469–3.269) .6265

Average daily steroid dose 0.994 (0.983–1.005) .2168

CMV-positive donor/CMV-negative recipient status 1.525 (0.573–4.059) .4187

CMV infection 2.510 (1.113–5.661) .0224

CMV disease 2.634 (1.215–5.713) .0160

Early CMV replication 1.002 (1.001–1.004) .0003

HHV6 reactivation 0.996 (0.989–1.003) .254

HCV RNA level 1.078 (0.999–1.014) .1119

16 Weeks after transplantation 1.121 (0.997–1.128) .0162

52 Weeks after transplantation 1.12 (0.997–1.128) .0162

NOTE. Other covariates that were evaluated but not found to be significantly associated with primary end points were patient sex (P = .6238); cold ischemia time (P = .8909); pretransplantation disease severity, as assessed by the Model for End-Stage Liver Disease (P = .4108) and Child-Turcotte-Pugh score (P = .5765); United Network of Organ Sharing status (P = .5623); serum bilirubin level (P = .9720); serum albumin level (P = .4745); prothrombin time (P = .4514); serum creatinine level (P = .2625); pretransplantation use of alcohol (P = .7865); and presence of hepatocellular carcinoma (P = .7865). In addition, the HCV genotype (P = .4344) and the HCV load before and at weeks 16 and 52 after transplantation were not significantly associated with allograft failure and mortality (P = NS). CMV, cytomegalovirus; HCV, hepatitis C virus; HbV6, human herpesvirus type 6; RR, risk ratio.

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Figure 1. Kaplan-Meier estimation of the probabilities of surviving and retaining the liver without fibrosis among hepatitis C virus–infected liver transplant recipients with or without cytomegalovirus (CMV) infection.

way for clinical trials to determine whether aggressive CMV suppression improves the clinical outcome of HCV-infected liver transplant recipients.

Likewise, we infer that, because subclinical CMV replication affected outcome, CMV may potentially influence HCV even in immunocompetent hosts. Although clinically significant CMV reactivation is uncommon among immunocompetent individuals, CMV has been detected among patients with myocardial infarction, sepsis, and other illnesses that require admission to intensive care units [33, 40, 41]. Such intervening circumstances could predispose critically ill HCV-infected patients to develop an accelerated course of HCV infection. Similarly, conditions that lead to natural immunosuppression, such as age, could favor some degree of CMV reactivation that could accelerate HCV pathogenesis.

The mechanism by which CMV influences HCV is unclear, but this study should prompt its investigation. A common feature among the mechanisms proposed to account for an accelerated course of HCV infection after LT is a state of immunosuppression [10, 11, 39]. In the absence of objective tests that measure the degree of immunosuppression, the reactivation of latent infections may serve as indirect reflection of the level of immune dysfunction. Thus, the higher incidence of allograft failure and mortality among our CMV-infected patients may imply an association of these end points with a more intense immunosuppression. Indeed, CMV infection may just be a consequence of immune dysfunction and not directly causal to the observed outcomes.

Of interest, CMV has immunomodulating properties. Thus, one alternative (or additional) mechanism whereby CMV influences HCV may be through enhanced immunosuppression [22, 23]. CMV-enhanced immunosuppression could accelerate HCV pathogenesis and partially account for the allograft failure and mortality, the observed trends (albeit nonsignificant) in

| Secondary end point | Time after transplantation, weeks | CMV infection | | CMV disease | |
|---------------------|---------------------------------|---------------|-----------------|-----------------|
|                     |                                 | CMV-positive patients (n = 40) | CMV-negative patients (n = 52) | P | CMV-positive patients (n = 23) | CMV-negative patients (n = 69) | P |
| HAI score           | 16                              | 3.94 ± 2.80 | 2.79 ± 2.40 | .06 | 4.17 ± 3.07 | 3.00 ± 2.42 | .10 |
|                     | 52                              | 2.41 ± 1.91 | 2.93 ± 2.46 | .35 | 2.73 ± 1.83 | 2.73 ± 2.38 | .99 |
| Fibrosis stage      | 16                              | 0.87 ± 1.13 | 0.43 ± 0.74 | .04 | 1.00 ± 1.19 | 0.50 ± 0.83 | .05 |
|                     | 52                              | 1.00 ± 1.24 | 1.04 ± 1.24 | .88 | 1.20 ± 1.47 | 0.98 ± 1.17 | .54 |
| HCV RNA level       | 16                              | 43.14 ± 45.05 | 38.22 ± 51.04 | .64 | 55.71 ± 50.47 | 35.52 ± 47.03 | .10 |
|                     | 52                              | 26.48 ± 27.95 | 19.47 ± 22.15 | .22 | 23.43 ± 28.82 | 21.97 ± 23.69 | .83 |

**NOTE.** HAI, modified hepatitis activity index.
HCV levels and degree of hepatitis, and the severity of fibrosis (at 16 weeks after LT) among patients with CMV disease. However, there are findings that suggest a more direct HCV-CMV interaction. With the intense immunosuppression that reactivated CMV, one would expect a consequent HHV-7 replication, a finding that was not observed. Some caution is needed in interpreting this finding, because, although plasma is acceptable as a sample for CMV detection [47], this may not be the case for HHV-7. Moreover, the lack of significant impact by HHV-6 (an immunomodulating virus) suggests that overall immunosuppression is not the only factor that accounts for the increased allograft failure and mortality in CMV-infected liver transplant recipients. Indeed, the lack of influence by HHV-6 [26, 28] on HCV implies that the degree of CMV-induced immunosuppression is more intense and/or that CMV may somehow inhibit HCV-specific immunity. Virus-virus interactions have been demonstrated to modify the pathogenesis of human viral infections. The association between CMV and HCV may be analogous to the proposed interaction between HIV and HCV [48].

In summary, our study demonstrated that there is a significant and independent association between CMV infection and allograft failure and mortality after LT for patients with HCV-induced cirrhosis. Our observations suggest that a direct CMV and HCV interaction exists that is beyond the “overall immunosuppression” theory. Studies to define the nature of HCV-CMV interaction, to evaluate the role of CMV in HCV-infected immunocompetent patients, and to assess whether aggressive prevention of clinical and subclinical CMV reactivation positively influences outcome of HCV-infected liver transplant recipients are warranted.

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References

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