Retrospective Study

Two strategies for prevention of cytomegalovirus infections after liver transplantation

Philipp Simon, Max Sasse, Sven Laudi, David Petroff, Michael Bartels, Udo X Kaisers, Sven Bercker

Philipp Simon, Max Sasse, Sven Laudi, Udo X Kaisers, Sven Bercker, Department of Anesthesia and Intensive Care Medicine, Medical Faculty, University of Leipzig, 04103 Leipzig, Germany

David Petroff, Clinical Trial Centre Leipzig, University of Leipzig, 04103 Leipzig, Germany

Michael Bartels, Department of Visceral, Transplantation, Vascular and Thoracic Surgery, Medical Faculty, University of Leipzig, 04103 Leipzig, Germany

Author contributions: Simon P and Bercker S designed research; Simon P and Sasse M performed research; Simon P and Bercker S contributed new reagents or analytic tools; Simon P, Sasse M and Petroff D analyzed data; Simon P, Petroff D, Bercker S, Laudi S, Bartels M and Kaisers UX wrote the paper.

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Correspondence to: Philipp Simon, MD, Department of Anesthesia and Intensive Care Medicine, Medical Faculty, University of Leipzig, Liebigstraße 20, 04103 Leipzig, Germany. philipp.simon@medizin.uni-leipzig.de
Telephone: +49-341-971700
Fax: +49-341-9717709

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Abstract

AIM: To analyze differences in patients’ clinical course, we compared two regimes of either preemptive therapy or prophylaxis after liver transplantation.

METHODS: This retrospective study was reviewed and approved by the institutional review board of the University of Leipzig. Cytomegalovirus (CMV) prophylaxis with valganciclovir hydrochloride for liver transplant recipients was replaced by a preemptive strategy in October 2009. We retrospectively compared liver transplant recipients 2 years before and after October 2009. During the first period, all patients received valganciclovir daily. During the second period all patients included in the analysis were treated following a preemptive strategy. Outcomes included one year survival and therapeutic intervention due to CMV viremia or infection.

RESULTS: Between 2007 and 2010 n = 226 patients underwent liver transplantation in our center. n = 55 patients were D/R high risk recipients and were excluded from further analysis. A further 43 patients had to be excluded since CMV prophylaxis/preemptive strategy was not followed although there was no clinical reason for the deviation. Of the remaining 128 patients whose data were analyzed, 60 received
CONCLUSION: These data suggest that CMV prophylaxis is superior to a preemptive strategy in patients undergoing liver transplantation.

Key words: Transplantation; Liver; Cytomegalovirus; Preemptive; Prophylaxis; Valganciclovir; Therapy

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Core tip: This retrospective study compares a preemptive therapy to prophylaxis for cytomegalovirus (CMV) infection in 128 patients after liver transplantation (LTx). CMV infections are frequent and increase morbidity and mortality that preventive strategies are routine procedures. The one-year mortality did not differ significantly between the preemptive (n = 68) and prophylaxis (n = 60) groups, though it was 10% (95%CI: 8%-28%, P = 0.31) higher for the former. Preemptive patients had a significantly higher rate of intervention with ganciclovir (23.5% vs 4.9%, P = 0.003). Our data suggest that CMV prophylaxis is superior to a preemptive strategy after LTx.

INTRODUCTION

Patients who undergo immunosuppressive therapy after solid organ transplantation are at higher risk for opportunistic bacterial, fungal, and viral infections. Infections with cytomegalovirus (CMV) are frequent and have been shown to increase morbidity and mortality in particular shortly after transplantation[1]. Estimates for the incidence of CMV infections after liver transplantation (LTx) range from 22% to 29%[1-3]. Therefore, strategies for preventing CMV infections are a routine procedure after solid organ transplantation[4]. Prophylaxis with antiviral substances leads to a reduction in the incidence and the severity of CMV infections. However, appropriate substances for prophylaxis have major side effects including myelodepression. Therefore, preemptive therapy has been proposed as an alternative regimen[1,5-7]. Preemptive therapy aims at suppressing viral replication after detection of CMV viremia, but prior to the onset of clinical symptoms. Antiviral therapy is then initiated in order to prevent clinically relevant infections[8-13]. However, to date, there is no strong clinical evidence indicating superiority of one regimen in liver transplant recipients over the other. To accumulate more evidence on the clinical course in patients after liver transplantation, we used retrospective data to compare preemptive therapy to prophylaxis during the liver transplantation program of the university hospital of Leipzig.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the university of Leipzig (No. 122-12-16042012). Prophylaxis with valganciclovir hydrochloride had been the standard treatment for liver transplant recipients in our center irrespective of their CMV serological status. Since patients presented with serious side effects including pancytopenia, prophylaxis was replaced by a preemptive strategy in October 2009. To assess differences in safety and efficacy of the two regimens, we retrospectively compared all liver transplant recipients two years before and after October 2009 during hospital stay after liver transplantation. Data on mortality was collected up to one year after transplantation. All patients treated according to the prophylaxis regimen received 450mg valganciclovir twice daily. If necessary doses were adapted to renal function. For patients treated after October 2009, only high-risk seronegative recipients, who received an organ from a seropositive donor (D+/R-), received prophylaxis and therefore all D+/R- patients in both groups were excluded from analysis. For both regimens, CMV polymerase chain reaction (PCR) was performed twice weekly. When PCR was positive, all patients in both groups were treated with ganciclovir for at least 14 d, whether or not there were clinical symptoms.

The data collected included baseline data, antibody patterns against CMV for donor and recipients (D/R), viremia during the intensive care unit (ICU) stay and occurrence of CMV infections. Furthermore, occurrence of sepsis, thrombocytopenia [platelet count < 50 giga particles (GPT)/L], leukocytopenia (white blood cells < 4 GPT/L) and anemia (hematocrit < 30%) starting 72 h after ICU admission was documented. LabMELD (Model of end stage liver disease) score was calculated for each patient on the day of transplantation. All MELD points were calculated retrospectively using validated laboratory data. Mortality data were collected during initial hospital stay and at day 28, day 90 and 1 year after transplantation. All patients received the same
standard immunosuppression with mycophenolate mofetil, steroids (tapered within 8 wk) and tacrolimus (days 1-14 FK506 level 10 ng/mL, days 15-28 8 ng/mL and continuing with 5 ng/mL). In the event of severe infection or side effects, immunosuppressive therapy was chosen by the physicians on an individual basis.

**Statistical analysis**

Data were collected in an Excel 2010 spreadsheet (Microsoft Corp., Redmond, United States). Statistical analysis was performed using SPSS Statistics 20.0 (SPSS GmbH Software, Munich, Germany) and R version 3.1.0. (R Foundation for Statistical Computing, Vienna, Austria). Survival analyses were performed using a log-rank test with the R package “survival”. Categorical data are expressed as absolute or relative frequencies and the χ² or Fisher’s exact test was used for inferential statistics depending on the number of expected counts. The confidence interval for differences in proportions makes use of a Wilson confidence interval. Continuous data or categorical ones with fewer than six levels are expressed as mean and standard deviation and a t-test was used for comparing groups. If categorical data has five or fewer levels, then median and interquartile range are presented and differences between groups are compared using the Wilcoxon-Mann-Whitney U test. A P value of less 0.05 was considered to be statistically significant.

**RESULTS**

Between 2007 and 2010 n = 226 patients underwent liver transplantation in our center. n = 55 patients were D/R high risk recipients and were excluded from further analysis. A further 43 patients had to be excluded since CMV prophylaxis/preemptive strategy was not followed although there was no clinical reason for the deviation. These 43 patients do not differ markedly from the remainder with respect to sex, age, or labMELD. Of the remaining 128 patients whose data were analyzed, 60 received prophylaxis and 68 were treated following a preemptive strategy.

Mean age of all analyzed patients was 54 ± 10 years, 90 patients were male and 38 were female (Table 1). The mean labMELD score before transplantation was 18.5 ± 9.4. At day 1 after transplantation patients had a mean APACHE II (Acute Physiology And Chronic Health Evaluation II) score of 14.2 ± 6.7 and a SOFA (simplified organ failure assessment) of 9.1 ± 4.0.

Mortality did not differ significantly between the groups (Figure 1). At one year, the mortality was 18/60 (30%, 95%CI: 20%-43%) for the prophylaxis strategy and 27/67 (40%, 95%CI: 29%-52%) for the preemptive strategy, where one censored case accounts for the denominator of 67 instead of 68 patients. However, this difference did not reach significance (P = 0.31).

There was a nonhomogeneous distribution of donors and recipients serologic CMV patterns in our series, which was not significant. We found 22% D/R in the preemptive group compared with 10% in the prophylaxis group (Table 1).

There were no significant differences in blood count abnormalities or the incidence of sepsis and infections other than CMV (Table 2). In total 19 patients (15%) received ganciclovir due to CMV viremia and/or infections. The therapy started 29 ± 20 d after transplantation on average and lasted for a mean of 18 ± 12 d. Patients who were treated according to the preemptive algorithm had a significantly higher rate of therapeutic intervention with ganciclovir [n = 16 (24%) vs n = 3 (5%), P = 0.005]. From these 19 patients 16 patients (84.0%) had clinical symptoms allegeable by CMV in context of the viremia [prophylaxis n = 2 (12.5%), preemptive therapy n = 14 (87.5%)].

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**Table 1** Patient demographics n (%)

<table>
<thead>
<tr>
<th></th>
<th>All (n = 128)</th>
<th>Prophylaxis (n = 60)</th>
<th>Preemptive therapy (n = 68)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54 ± 10</td>
<td>52 ± 12</td>
<td>56 ± 8.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>90 (70)</td>
<td>42 (70)</td>
<td>48 (71)</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>38 (30)</td>
<td>18 (30)</td>
<td>20 (29)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 ± 16</td>
<td>81 ± 13</td>
<td>79 ± 19</td>
<td>0.52</td>
</tr>
<tr>
<td>SOFA</td>
<td>9.1 ± 4.0</td>
<td>8.8 ± 3.8</td>
<td>9.4 ± 4.3</td>
<td>0.34</td>
</tr>
<tr>
<td>APACHE II</td>
<td>14.2 ± 6.7</td>
<td>13.3 ± 5.5</td>
<td>15.0 ± 7.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Lab. MELD at</td>
<td>18.5 ± 9.4</td>
<td>18.8 ± 8.8</td>
<td>18.2 ± 9.9</td>
<td>0.73</td>
</tr>
<tr>
<td>Transplantation CMV-status D/R</td>
<td>19 (17)</td>
<td>5 (10)</td>
<td>14 (22)</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>+/-</td>
<td>+/−</td>
<td>−/+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>33 (29)</td>
<td>16 (33)</td>
<td>17 (27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 (54)</td>
<td>28 (57)</td>
<td>32 (51)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/−</td>
<td>Excluded</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or n (%). Complete CMV-status was unavailable for 16 patients, but was known not to be +/−. D/R: Donor/receptor; CMV: Cytomegalovirus; Lab.MELD: Model of end stage liver disease.
There is a broad variety of possible causes. However, 
movement, the incidence of graft loss and opportunistic 
viral[24], bacterial or fungal infections[25]. Otherwise, 
prophylaxis increases the risk of drug-resistance and the 
incidence of late-onset CMV disease[25].

The incidence of CMV infection varies depending 
upon donor and/or recipient serological status[19,27,28]. 
Hodson et al[25] suggested in a systematic review of 
randomized trials, that CMV infections are more 
frequently in sero-negative patients and current 
guidelines suggest antiviral prophylaxis at least in 
D+/R patients[29,30]. In the presented study, these 
patients have been excluded from analysis. There is 
an imbalance of sero-negative patients between the 
two groups in our study (Table 1) and following the 
above argument, one might have supposed that the 
prophylaxis group was at higher risk of infection. It 
turns out that none of the 19 sero-negative patients in 
the study had CMV viremia/infection, however, so that 
this could not have contributed to our findings.

The presented retrospective study of consecutive 
treatment groups has limitations. Due to the retro-
spective character and lack of randomization, a 
variety of factors such as slight changes in therapeutic 
regimens over-time may have influenced results. On 
the other hand, we demonstrated that groups did not 
differ concerning demographic baseline data, severity 
of liver failure or severity of disease at admission, and 
therefore suggest that our results strongly support the 
hypothesis that the higher incidence of CMV 
viremia was mainly influenced by the introduction of 
a preemptive strategy. Attributing clinical symptoms 
such as diarrhea or elevation of liver enzymes in the 
early course after LTX to CMV remains uncertain as 
there are a broad variety of possible causes. However, 
we suggest that our results support the hypothesis 
that prophylaxis is more effective in preventing CMV 
viremia and infection even in patients with low or mid 
risk for CMV infection. In conclusion, we demonstrated 
a significantly lower rate of CMV viremia/infection with 
prophylaxis when compared to a preemptive strategy. 
Our data indicate that prophylaxis might be superior 
to a preemptive strategy. To confirm this hypothesis, 
randomized prospective trials in liver transplant 
recipients are needed.

For adult liver transplant recipients, data from 
randomized studies are not available. In clinical practice 
there is a broad variety of strategies concerning the 
selection of substances, the timing and the duration of 
either prophylaxis or preemptive strategies. However, 
most centers tend to use prophylaxis at least in high-
risk patients[16].

All told, there is no strong evidence from randomized 
studies indicating which of the two strategies is 
superior after liver transplantation. Accordingly, several 
authors consider both treatment options to be similarly 
effective[8,11,12,20-22].

Positive effects of a preemptive strategy can be the 
reduction of side effects and costs. When compared to 
no preventive strategy at all, preemptive therapy leads 
to less graft rejection and may improve CMV specific 
cell-mediated immunity and lead to a decreased risk of 
late CMV infections[11,13,23]. On the other hand, the use 
of prophylactic strategies has been shown to reduce 
mortality, the incidence of graft loss and opportunistic 

Table 2 Infection/blood count abnormalities (n (%))

<table>
<thead>
<tr>
<th></th>
<th>All (n = 128)</th>
<th>Prophylaxis (n = 60)</th>
<th>Preemptive therapy (n = 68)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re - LTx</td>
<td>17 (13)</td>
<td>10 (17)</td>
<td>7 (10)</td>
<td>0.31</td>
</tr>
<tr>
<td>Infection</td>
<td>86 (71)</td>
<td>40 (69)</td>
<td>46 (72)</td>
<td>0.84</td>
</tr>
<tr>
<td>Sepsis</td>
<td>63 (52)</td>
<td>30 (52)</td>
<td>33 (52)</td>
<td>1.00</td>
</tr>
<tr>
<td>Thrombocytopenia (PLT &lt; 50 Gpt/L; &gt; 72 h post-LTx)</td>
<td>69 (57)</td>
<td>32 (53)</td>
<td>37 (56)</td>
<td>0.86</td>
</tr>
<tr>
<td>Leukocytopenia (WBC &lt; 4 Gpt/L; &gt; 72 h post-LTx)</td>
<td>38 (31)</td>
<td>15 (26)</td>
<td>23 (36)</td>
<td>0.25</td>
</tr>
<tr>
<td>Anaemia (Hct &lt; 30%; &gt; 72 h post-LTx)</td>
<td>114 (93)</td>
<td>54 (93)</td>
<td>60 (94)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

GPT: Giga particles; LTx: Liver transplantation; PLT: Platelet count; WBC: White blood cells; Hct: Haematocrit.

DISCUSSION

We retrospectively compared the effects of a 
preemptive and a prophylactic strategy to prevent 
CMV infections during the early phase after liver 
transplantation. We could demonstrate that a preemptive 
strategy was associated with significantly more 
episodes of CMV viremia/infections in patients with 
mid/low risk without evidence for more side effects of 
the antiviral substances.

Recommendations for prevention of CMV infections 
in solid organ transplantation are heterogeneous 
and rather difficult to interpret. There are a few 
prospective randomized studies comparing both 
regimens after kidney transplantation. Kliem et 
al[15] demonstrated that prophylaxis reduced the 
incidence of CMV infections by 65% and the authors 
suggest that prophylaxis might improve long-term 
graft survival and recommend limiting preemptive 
strategies to low-risk patients. In a series of 296 
kidney transplant patients, there was a reduction of 
CMV infections by 28 percentage points in the group 
who received prophylactic therapy (38.7% vs 11%, 
P < 0.0001)[16]. On the other hand, Reischig 
et al[17] and Khoury et al[18] found a similar incidence of CMV 
infections in both groups (6% vs 9%, P = 0.567) and 
therefore suggested a comparable efficacy of both 
strategies. Gerna et al[19] performed a controlled, 
randomized, open-label study in 21 children after liver 
transplantation and did not report any CMV disease, 
irrespective of the procedure. A recent Cochrane 
analysis concluded that data is not yet sufficient to 
recommend one strategy over the other prophylaxis or 
preemptive strategies[14].

For adult liver transplant recipients, data from 
randomized studies are not available. In clinical practice 
there is a broad variety of strategies concerning the 
selection of substances, the timing and the duration of 
either prophylaxis or preemptive strategies. However,
COMMENTS

Background

Patients after solid organ transplantation who undergo immunosuppressive therapy are at higher risk for infections with cytomegalovirus. They are frequent and have been shown to increase morbidity and mortality, particularly during the early stages after liver transplantation. Therefore, strategies for preventing cytomegalovirus (CMV) infections are a routine procedure after liver transplantation. Prophylaxis with antiviral substances leads to a reduction in the incidence and the severity of CMV infections. Preemptive therapy aims at suppression of viral replication after detection of CMV viremia and prior to the onset of clinical symptoms. The authors compared preemptive therapy to prophylaxis during the liver transplantation program of the university hospital of Leipzig to analyze differences in the clinical course in patients after liver transplantation.

Research frontiers

There is no strong evidence from randomized studies demonstrating which of the strategies is superior after liver transplantation. Accordingly, several authors consider both treatment options to be similarly effective. The authors demonstrated a significantly lower rate of CMV viremia/infection using prophylaxis when compared to a preemptive strategy. The data indicate that prophylaxis might be superior to a preemptive strategy.

Innovations and breakthroughs

Current study found a lower incidence of CMV viremia/infection with prophylaxis compared to a preemptive strategy without significant differences in blood count abnormalities or the incidence of infections and differences in mortality at any time. These data indicate that prophylaxis might be superior to a preemptive strategy.

Applications

The data indicate that prophylaxis might be superior to a preemptive strategy. To confirm this hypothesis randomized prospective trials in liver transplant recipients are needed.

Peer-review

The topic has a great interest given the lack of studies in this field in liver transplant recipients. Nevertheless the higher rate of seronegative patients in the pre-emptive group could explain the higher rate of infections in this group. It would be interesting to include some data regarding duration of treatment in both groups and regarding the specific period of time after transplant in which the CMV infection occurred (early infection vs late infection).

REFERENCES


