TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

INVITED COMMENTARY

The best way to prevent cytomegalovirus infection after liver transplantation: the debate goes on

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Conflicts of interest
None.

Received: 1 April 2013
Accepted: 4 April 2013

doi:10.1111/tri.12108

Cytomegalovirus (CMV) infection is an opportunistic infection frequently found in liver transplant recipients, especially in CMV-seronegative recipients of grafts from CMV-seropositive donors (D+/R−). In these high-risk patients, CMV infection can become clinically apparent with a mononucleosis-like syndrome, hepatitis, gastrointestinal ulceration and pneumonia [1]. In the past, when specific therapy and rapid diagnostic tools were lacking, CMV disease, which can be classified into infection with organ involvement (tissue invasive CMV disease) and without organ involvement (CMV syndrome), was associated with high mortality. However, this has changed dramatically with the introduction of specific virostatics and improved diagnostics. The availability of (val)ganciclovir (VGC) and real-time RT-PCR to quantify CMV DNA enabled the clinician to interfere in a preclinical phase of disease development.

These so-called prevention strategies can be divided in prophylaxis and preemptive therapy with antiviral medication. The recommended agents and dose for prophylaxis are VGC 900 mg or ganciclovir 5 mg/kg once daily for at least 3 months after transplantation, whereas in preemptive therapy, patients are closely monitored and given VGC 900 mg or ganciclovir 5 mg/kg twice daily whenever CMV viremia is detected [2]. A recent update of a Cochrane review first published in 2005 stated that both strategies were effective in reducing the risk of CMV disease. However, the efficacy of preemptive therapy compared with prophylaxis to prevent CMV disease remains unclear because of significant heterogeneity between studies. Additional head to head studies are required to determine the risks and benefits of either strategy to prevent CMV disease in solid organ transplant recipients [3].

A recent international survey of cytomegalovirus management practices showed that prophylaxis is the most commonly used preventive strategy, but significant variation exists in the way it is implemented. Specifically, duration of prophylaxis is extremely variable [4]. A study comparing 100 vs. 200 days of VGC prophylaxis showed a significantly lower incidence of CMV disease in the longer treated patient group [5]. This finding suggests that prophylaxis should be longer than the first 100 days after transplantation. An argument in favour of the prophylactic strategy is a recent French publication showing that preemptive therapy is associated with a higher virostatic drug

resistance [6]. However, this intriguing finding needs to be confirmed in other studies.

In the current edition of *Transplant International*, Onor *et al.* [7] evaluated the clinical outcome of prophylactic versus preemptive CMV strategy in an all-inclusive cohort of CMV donor and recipient serologic status of liver transplant recipients. They performed a retrospective study in two consecutive liver transplant cohorts with different CMV regimens: prophylactic and pre-emptive therapy with VGC. The main reasons for the authors to switch from a prophylactic regimen to a preemptive strategy were the high incidence of leukopenia in the prophylactic group and a publication by Kalil *et al.* [8] showing that VGV prophylaxis was associated with a significant increased risk of CMV-tissue invasive disease.

This study in 109 patients shows (as can be expected) that the incidence and time to onset of CMV viremia were significantly lower in the prophylaxis group during the treatment period. A higher incidence of CMV viremia was observed in the 3 months after discontinuing prophylactic treatment. Still, the cumulative 6-month incidence of CMV viremia was significantly lower in the prophylactic group. In contrast, no differences in the incidence of CMV tissue invasive disease, leukopenia, opportunistic infection rates and mortality were observed between both groups. In their final conclusion, the authors do not make a statement which regimen is to be preferred.

As pointed out by the authors, this study has several limitations, such as the retrospective nature, lack of randomization and small sample size, especially in the high-risk patient group (D+/R−) of 22 patients (prophylactic group $n = 15$ and preemptive group $n = 7$). Including D−/R− patients is in our view not logical. The average CMV viral load per week after transplant in the prophylactic and preemptive cohort shows high viral load in both the groups. To allow prompt intervention before CMV replication is allowed to accelerate and to avoid the risk of developing CMV disease and CMV resistance regularly monitoring for emerging CMV infection should have been implemented too. Theoretically, each liver transplant recipient should have had 18 CMV PCR results within the first 6 months after liver transplantation. In the study, the mean CMV PCR results reported was 66% complete in the prophylactic group and 64% complete in the preemptive cohort. This incomplete monitoring could have influenced outcome. Moreover, no information is given about the mean duration of therapy in case of CMV viremia and whether there is a difference between both groups.

Still, the head to head comparison and close CMV surveillance protocol are strong points in this study.

What we can learn from this study is that both prophylactic and preemptive therapy with VGC seems to be equally effective in the prevention of CMV tissue invasive disease after liver transplantation. This is in contrast with a recent study in renal transplant recipients showing a significant lower incidence of CMV disease in the prophylactic group [9]. Therefore, there is still a need for more randomized controlled trials in liver transplant recipients. Importantly, in new studies the issue of virostatic resistance should be closely monitored too.

An alternative prevention strategy that could be taken into consideration is a hybrid approach in which prophylaxis is started and the patient is simultaneously, monitored for CMV DNAemia on a weekly basis. In case of CMV DNAemia, the dose of VGC should be increased.

In conclusion, the study by Onor *et al.* shows no advantage for either prophylaxis or preemptive therapy to prevent CMV infection and disease after liver transplantation. This study certainly does not end the debate, which is the best way to prevent CMV infection and disease.

Funding

None.

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