

Interactions between Cytomegalovirus and Other Viruses (HHV6, HHV7, HCV and EBV) in Transplantation – a Review

Julio C. Medina¹, Graciela Pérez-Sartori¹ and José M. Aguado²

¹Cátedra de Enfermedades Infecciosas, Universidad de la República, Uruguay; ²Unit of Infectious Diseases, University Hospital 12 de Octubre, Madrid, Spain

Abstract

The real role of human herpesvirus 6 and human herpesvirus 7 in solid-organ transplant recipients remains obscure. Whether these viruses are mainly pathogens or co-pathogens that interact with cytomegalovirus is still a matter of discussion. In this review we analyze the current evidence with respect to the potential role of the interaction of human herpesviruses 6 and 7 with cytomegalovirus in causing disease in solid-organ transplant recipients. The current evidence suggests that there is a temporal relationship between the detection of human herpesviruses 6 and 7 and the appearance of cytomegalovirus infection and also with cytomegalovirus disease. There also seems to be an association between human herpesviruses 6 and 7 with cytomegalovirus and graft rejection.

We also give an overview of the interaction of other viruses such as hepatitis C virus and Epstein-Barr virus with cytomegalovirus. The impact of cytomegalovirus infection post-liver transplantation in hepatitis C virus-infected individuals has led to contradictory findings. Cytomegalovirus infection and disease could have a negative impact on liver allograft, causing greater recurrence of hepatitis C and organ rejection. An early detection of the cytomegalovirus viremia and an early treatment (preemptive therapy) may prevent these deleterious effects.

Many factors, including cytomegalovirus infection, have been associated to posttransplant lymphoproliferative disorders. There is incipient in vitro evidence and some clinical data that suggests that in some cases there may be an association between cytomegalovirus and Epstein-Barr virus. (Trends in Transplant. 2007;1:129-36)

Corresponding author: Jose M. Aguado, jaguadog@medynet.com

Key words

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Correspondence to:

Jose M. Aguado
Unit of Infectious Diseases
University Hospital 12 de Octubre
Av. de Andalucía Km. 5,400
28041 Madrid, Spain
E-mail: jaguadog@medynet.com

Interaction of cytomegalovirus and human herpesviruses 6 and 7

Human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7) are β -herpesviruses that can be pathogenic in immunocompromised patients like transplant recipients. Pretransplant seropositivity of recipients for HHV-6 and HHV-7 could be as high as 92 and 94%, respectively¹. Reactivation from latency and increase of viral replication occurs during periods of immune dysfunction.

These viruses may have indirect immunomodulatory effects, which may be due to cytokine dysregulation. *In vitro* studies show that HHV-6 results in downregulation of interleukin-2 mRNA and protein synthesis. Moreover, HHV-6 infection is a potent inducer of tumor necrosis factor- α , a cytokine involved in cytomegalovirus (CMV) reactivation².

Human herpesvirus 6 reactivates in approximately 50% of the seropositive recipients and this occurs most frequently in the first four weeks, but there are reports of reactivation even months or years after transplantation. Reactivation depends on the type of immunosuppression; for example, the use of sirolimus or daclizumab is a risk factor for HHV-6 reactivation³. Several diseases associated to HHV-6 have been documented. Fever, rash, myelosuppression, and encephalitis are the most frequently reported symptoms, and pneumonitis, hepatitis, sinusitis, or gastrointestinal disease are less frequently documented. Both viruses have been implicated in the development of graft rejection and graft-versus-host disease, and HHV-6 infection is considered by some authors as a risk factor for CMV and fungal disease⁴⁻⁶.

Human herpesvirus 7 is similar to HHV-6. Like HHV-6, HHV-7 infection is also widespread in the population and can cause febrile illness in childhood including *exanthema subitum*. The virus appears to have a restricted cell tropism, using CD4 lymphocytes as a cellular receptor to infect T-cells⁷. Reactivation of disease or infection is the most common mechanism of infection.

Because of the high prevalence of HHV-6 and HHV-7, primary infection is rare and occurs in susceptible HHV-6 and HHV-7 seronegative transplant recipients. Acute allograft rejection and use of high doses of steroids have been associated to HHV-6 reactivation. Factors promoting HHV-7 reactivation are less well known⁸.

While the role of CMV in transplant patients is quite clear, the role of HHV-6 and HHV-7 in solid-organ transplant recipients remains controversial. Furthermore, their association with CMV is still obscure. The major impact of HHV-6 and HHV-7 seems to be related to the indirect effects more than direct ones. The HHV-6 and/or HHV-7 induced immunosuppression may predispose to exacerbate CMV disease and other bacterial or fungal opportunistic infections⁸.

During the last decade many authors have investigated the potential of the infection/disease of both viruses as well as the correlation between them and CMV (Table 1). Oña, et al.⁹ evaluated prospectively the relationship between HHV-6 and HHV-7 reactivation after cardiac transplantation and CMV disease. They followed-up 42 heart transplant recipients for at least three months. The HHV-6 preceded CMV infection in 16/26 (61.5%) and HHV-7 in 15/26 (57.7%) of the cases, and HHV-6 preceded the development of CMV disease in 6/8 patients and HHV-7 in 5/8 patients. The authors did not find any symptomatic patient who was only positive to HHV-6 or HHV-7 but negative to CMV. Moreover, in the patients positive to HHV-6 or HHV-7 before seropositivity to CMV, the symptoms started when the CMV was detected. This finding differs from other authors who identified HHV-6 and HHV-7 as the only cause of fever, myelosuppression, hepatitis, encephalitis, and pneumonitis in solid organ recipients¹⁰⁻¹³.

Oña, et al.⁹ documented that the three herpesviruses appear in sequence: first HHV-6, second HHV-7, and finally CMV. This occurs both with infection and with disease. Recently, Härmä, et al.¹⁴ studied 64 liver transplant recipients and found that both HHV-6 and HHV-7 antigenemia usually appeared in as-

Table 1. Studies of HHV-6 and HHV-7 infection and association with CMV following solid-organ transplantation

Authors	Transplant type/number	Virus HHV-6 HHV-7	Diagnosis	Infections (%)	Multivariate analysis	Association with CMV (infection and/or disease)
DesJardin, et al. ¹⁷	Liver/139	HHV-6	serology	87 (62.6)	Yes	Yes
Lautenschlager, et al. ¹⁸	Liver/75	HHV-6	serology	21 (28)	No	Yes
Chapenko, et al. ¹⁹	Kidney /49	HHV-7	nPCR	31 (63.3)	No	Yes
Humar, et al. ²⁰	Liver/88	HHV-6	PCR	48 (54.4)	Yes	Yes
Härmä, et al. ¹⁴	Liver/64	HHV-6 HHV-7	antigenemia	16 (25) 15 (23.4)	No	Yes
Kidd, et al. ¹	Kidney/52	HHV-6 HHV-7	PCR	12 (23) 24 (46)	No	Yes (only HHV-7)
Tong, et al. ¹⁶	Kidney/37	HHV-6 HHV-7	PCR	7 (19) 13 (35)	Yes	Yes (only HHV-7)
Osman, et al. ¹⁵	Kidney/56	HHV-6 HHV-7	PCR	20 (36) 22 (39)	No	Yes (only HHV-7)
Oña, et al. ⁹	Heart/42	HHV-6 HHV-7	PCR	16 (61.5) 15 (57.7)	No	Yes
Griffiths, et al. ¹⁰	Liver/60	HHV-6 HHV-7	PCR	19 (32) 29 (48)	Yes	No
Pascher, et al. ³⁷	Intestinal/11	HHV-6 HHV-7	PCR	?	No	No
Lehto, et al. ²²	Lung or heart-lung/22	HHV-6 HHV-7	antigenemia	20 (91) 11 (50)	No	Yes
Jacobs, et al. ²³	Lung or heart-lung/30	HHV-6	PCR	20 (66)	No	No
DesJardin, et al. ²¹	Kidney/53	HHV-6	serology	35 (66)	No	Yes
Mendez, et al. ²⁴	Liver/33	HHV-6 HHV-7	PCR	11 (33) 14 (42)	No	Yes
Lautenschlager, et al. ²⁵	Liver/8	HHV-6	serology and biopsy	8 (100)	No	Yes

HHV: human herpesvirus; CMV: cytomegalovirus; nPCR: nested polymerase chain reaction.

sociation with CMV disease. The HHV-6 antigenemia preceded CMV, but HHV-7 appeared together with CMV or only a few days earlier.

Kidd, et al.¹ evaluated in a prospective study the natural history of HHV-6, HHV-7, and CMV infection after renal transplantation in 52 patients. Polymerase chain reaction (PCR) was used to detect active but not latent infection, and to quantify the viral load of the three viruses. Examining the time to the first PCR positivity, HHV-7 was detected earlier than CMV ($p = 0.05$). Clinicopathologic analyses identified HHV-7 as being associated to more episodes of rejection ($p = 0.02$). There was more CMV disease in those patients with CMV and HHV-7 coinfection than in the ones with only CMV infection. The authors concluded that HHV-7

might potentially exacerbate graft rejection. No clear pathologic role was found for HHV-6. This finding is consistent with the results from the study by Osman, et al.¹⁵, which showed an increased relative risk of CMV disease for patients with concurrent HHV-7 and CMV infection. This study monitored 56 renal transplant recipients. Twenty-eight developed CMV infection; eight of them developed CMV disease. The risk of progression to CMV disease was increased in patients with concurrent DNAemia to HHV-7 (RR: 3.5; 95% CI: 1.1-11.6), suggesting that HHV-7 may be interacting with CMV to precipitate disease or predispose to CMV infection.

Tong, et al.¹⁶ prospectively evaluated 37 renal transplant recipients and identified, using a logistic regression model, that the HHV-7

DNA detection in peripheral blood was an independent risk factor for CMV disease. Moreover, the patients with detectable HHV-7 DNA had a higher peak of CMV plasma viral load ($p = 0.01$). The association of HHV-7 and CMV disease found in this study was independent of other potentially confounding factors such as increased immunosuppression or graft rejection. The authors believe that it is possible that HHV-7 may favor CMV disease, either by direct interaction with CMV or by immunomodulatory effects on the host immune system, and it is possible that HHV-7 could also transactivate CMV, leading to increased systemic viral load and thereby CMV disease. In agreement with Kidd, et al. they did not find a clear pathologic role of HHV-6¹.

DesJardin, et al.¹⁷ and Lautenschlager, et al.¹⁸ analyzed the relationship between HHV-6 and CMV using serological tests for diagnosis. Both groups found an association between these two β -herpesviruses, although, using a multivariate analysis, this association only persisted for severe CMV disease¹⁷. Other investigators also identified a relationship between CMV disease and HHV-6 and HHV-7 infection using PCR technique^{19,20}.

The findings of Griffiths, et al.¹⁰ contrasted with that of the previous authors. They followed-up 60 liver transplant recipients for HHV-6, HHV-7, and CMV infection by PCR, with viral loads determined by quantitative competitive PCR. Both HHV-6 and CMV were independently associated with biopsy-proven graft rejection. Nevertheless, the multivariate analysis did not show an association between the development of CMV disease and HHV-6 or HHV-7 infection.

DesJardin, et al.²¹ retrospectively evaluated the association between HHV-6 and CMV in 53 renal transplant recipients, of which 66% had a reactivation of the infection by HHV-6. The authors documented that HHV-6 reactivation was associated with primary CMV infection ($p = 0.001$) and CMV syndrome ($p = 0.003$) and that there was a non-significant tendency to serious CMV disease ($p = 0.085$). They

concluded that HHV-6 reactivation in kidney transplant recipients at risk for primary CMV infection is associated with CMV infection and CMV-related disease. This was a retrospective study without a multivariate analysis; nevertheless we believe that because of the important statistic significance, it is reasonable to think that an association between HHV-6 and CMV exists.

Lehto, et al.²² monitored 22 lung and heart-lung recipients for HHV-6, HHV-7, and CMV by antigenemia during a 12-month postoperative period. The HHV-6, HHV-7, and CMV antigenemia was detected in 20 (91%), 11 (50%), and 12 (55%) of the recipients, with a median of detection of 16, 31, and 165 days after transplantation, respectively. Five patients had CMV disease (four pneumonia, one enteritis). Detection of HHV-6 or HHV-7 occurred concomitantly in 9/13 (69%) and 5/13 (38%) patients with CMV infections without CMV disease, whereas 4/5 (80%) of the CMV disease cases were associated with HHV-6 and HHV-7 antigenemia.

Jacobs, et al.²³ evaluated prospectively 30 lung and heart-lung transplant recipients. The authors analyzed the infectious complications, comparing the periods with HHV-6 infections versus the period without HHV-6 infection. During the period with HHV-6, three CMV infections were documented, while only one CMV infection was detected in the period without HHV-6 ($p = 0.837$). We should underline the small number of patients included in this study.

Méndez, et al.²⁴ prospectively investigated 33 liver transplant recipients to analyze the possible association between CMV, HHV-6, and HHV-7. Quantitative PCR was done. They detected an association between HHV-6 and HHV-7 with the concomitant occurrence of CMV disease that suggests a significant interaction among the three members of the β -herpesvirus family. They also documented that high levels of HHV-6 or HHV-7 selectively occur in CMV D⁺/R⁻ patients and suggests a unique interaction between CMV with HHV-6 and HHV-7. These findings led the authors to question if

the viral etiology of the clinical syndrome defined as CMV disease is due only to this single virus.

Finally, Lautenschlager, et al.²⁵ documented that an interaction between CMV with HHV-6 and HHV-7 was related to graft rejection. These authors retrospectively studied eight liver transplant recipients. The diagnosis was based on serology and demonstration of HHV-6 specific antigens in liver biopsy specimens with the use of monoclonal antibodies and immunoperoxidase staining. The HHV-6 early antigens were detected in the six available liver biopsy specimens. Histologic examination of biopsy specimens demonstrated acute rejection in five of the eight patients. In five patients CMV infection was associated with HHV-6 infection; in four cases CMV antigens were also detected in the biopsy specimens. The authors concluded that HHV-6 may infect the liver allograft and cause graft dysfunction and may possibly be associated with rejection and/or CMV infection.

In summary, we have seen that the majority of the information with respect to the interaction between CMV with HHV-6 and HHV-7 has been collected in renal or liver transplantation. There are few studies that analyze this point in heart, lung, or intestinal transplantation. The number of patients in the majority of the series is not high and the methods used for diagnosis are not homogenous. Many studies did not perform a multivariate analysis and many are retrospective. Despite these limitations, some evidence appears to exist to support an association between HHV-6 and HHV-7 with CMV. We consider that the evidence for this interaction seems to be clearer for HHV-7 with CMV than HHV-6 with CMV, since in many studies that evaluated both viruses with molecular techniques the associations were seen only with HHV-7. The studies previously discussed showed a temporal relationship between the detection of HHV-6 and HHV-7 and the appearance of CMV infection and disease. A group of investigators also documented the association between HHV-6²⁵ or HHV-7¹ with CMV and graft rejection. There is a need of prospective, multicentric studies,

with a bigger number of patients, using adequate methods to diagnose active infection and clear definitions of interaction to clarify this dilemma. There are many questions to solve: i) is it reasonable to give prophylaxis or even preemptive therapy with antivirals for those solid organ recipients who have high viral load of HHV-6 or HHV-7 to minimize CMV disease and decrease the morbidity/mortality; ii) are HHV-6 and HHV-7 mainly pathogens or co-pathogens with CMV; iii) is the immunomodulator property the most important factor to cause disease.

Interaction of CMV and hepatitis C virus

Recurrence of hepatitis C virus (HCV) infection after liver transplantation is nearly universal and may lead to increased graft loss and mortality. The RNA of HCV may be detected as soon as 48 hours posttransplantation.

The recurrence of hepatitis C progresses to cirrhosis in a high percentage of liver transplant recipients. The impact of CMV infection post-liver transplantation in HCV-infected individuals has led to contradictory findings.

Many studies have evaluated the role of coinfection by CMV in the prognosis of HCV infection following solid-organ transplantation (Table 2). Rosen, et al.²⁶ evaluated the impact of the CMV infection in the histopathologic recurrence of hepatitis C after liver transplantation. Eight patients that developed CMV viremia in the posttransplant period (group 1) were compared with 35 patients that did not develop CMV viremia (group 2). The mean total Knodell score of the allograft biopsy was significantly greater in group 1 ($p = 0.016$), with most of the difference due to periportal/bridging necrosis ($p = 0.009$) and lobular activity ($p = 0.01$) scores. Half of the CMV-viremic patients developed allograft cirrhosis as compared with 11% of the CMV-negative patients ($p = 0.027$). The cirrhosis-free survival by Kaplan-Meier estimates was significantly diminished in the CMV-viremic patients. The authors concluded that after liver

Table 2. Studies of hepatitis C virus following solid-organ transplantation and association with CMV

Authors	Transplant type/number	Diagnosis	Multivariate analysis	Association with CMV (infection and/or disease)
Rosen, et al. ²⁶	Liver/43	PCR	No	Yes
Chopra, et al. ²⁷	Liver/58	PCR	No	Yes
Burak, et al. ²⁸	Liver/93	PCR	Yes	Yes
Humar, et al. ²⁹	Liver/66	PCR	No	Yes
Teixeira, et al. ³⁰	Liver/39	PCR	No	No
Nebbia, et al. ³¹	Liver/69	PCR	No	No

CMV: cytomegalovirus; PCR: nested polymerase chain reaction.

transplant for chronic hepatitis C, patients who develop CMV viremia have a significantly greater risk of severe hepatitis C recurrence.

Chopra, et al.²⁷ evaluated 58 liver transplant recipients in order to identify the factors associated to the progression to fibrosis in recurrent HCV infection. Thirty-one recipients were HCV genotype 1a (53%). Patients with CMV infection post-orthotopic liver transplantation (n = 4) had a higher fibrosis progression rate compared with those without CMV (n = 54) (mean fibrosis-free survival 29.0 vs. 53.0 months; p = 0.0004, log-rank test). The authors concluded that patients with HCV genotype 1a and those developing CMV post-orthotopic liver transplantation have a higher rate of hepatic fibrosis progression after orthotopic liver transplantation for HCV-related chronic liver disease.

Coincidentally, Burak, et al.²⁸ studied the impact of CMV infection on patient and graft outcomes in 93 consecutive HCV-infected liver transplant recipients. Graft failure was significantly more common in CMV-positive compared with CMV-negative patients (52 vs. 19.1%; p = 0.002). The CMV infections examined in a time-dependent manner remained as a strong predictor of graft failure (RR: 3.73; 95% CI: 1.65-8.45). The authors concluded that CMV infection is an independent risk factor for graft failure in these patients.

Humar, et al.²⁹ prospectively evaluated if CMV or HHV-6 could be associated to hepatitis C recurrence in 66 liver transplant recipients. The recurrence of hepatitis C by biopsy was

demonstrated in 41/66 (62.1%) of cases. The authors did not find an association between CMV infection or disease and hepatitis C recurrence; nevertheless, the mean fibrosis score at last follow-up was 1.67 versus 0.56 in patients with CMV disease versus those without CMV disease (p = 0.016) and 1.03 versus 0.50 in patients with CMV infection versus those without CMV infection (p = 0.063). The authors concluded that CMV infection and viral load were not associated with an increase in the overall rates of hepatitis C recurrence or HCV viral load after liver transplantation, but may be associated with more severe forms of recurrence. The limitations of this study are that they did not perform HCV genotyping and there was not a liver biopsy protocol.

Teixeira, et al.³⁰ did not find a relation between CMV viremia and recurrence of hepatitis C in liver transplant recipients. The authors performed a one-year follow-up of 39 liver transplant recipients for HCV-related cirrhosis. Differently to the previous authors, they gave preemptive treatment with ganciclovir when CMV PCR was detected. This early intervention on CMV, that allowed only a transitory viremia, could be the reason why the authors did not document a bigger recurrence of hepatitis C in the group with CMV viremia. There was no difference either in the incidence or in the grade of acute rejection episodes.

Recently, Nebbia, et al.³¹ investigated a cohort of 69 HCV-infected liver transplant recipients and 188 HCV-negative liver transplant recipients and monitored them for CMV infec-

tion. The authors gave preemptive therapy when CMV viremia was detected by PCR. The maximum HCV viral load within 150 days post-liver transplant was not significantly higher in patients with simultaneous human CMV replication. They did not either document a difference between the incidence and grade of acute rejection. In agreement with Teixeira, et al. the authors concluded that a short CMV viremia does not correlate to more hepatitis C recurrence.

In summary, the data of different studies are not conclusive on the impact of CMV in liver transplantation for HCV-related cirrhosis. These studies were not multicentric, few patients were included, the majority was retrospective, and a multivariate analysis of other risk factors implicated was not performed. However, with the current evidence it seems that CMV infection and disease could have a negative impact on the liver allograft, generating more hepatitis C recurrence and organ rejection. An early detection of CMV viremia and an early intervention with preemptive therapy may avoid these deleterious effects.

There are still some unsolved questions: i) what is the real impact of CMV over HCV in liver transplant recipients; ii) is there a benefit in reducing the immunosuppression of these patients when CMV viremia is detected; iii) does CMV preemptive therapy really prevent an increase in the hepatitis C recurrence and allograft rejection.

Interaction of CMV with Epstein-Barr virus

Epstein-Barr virus (EBV) is a tumorigenic herpesvirus that affects more than 90% of the world population. The virus has the potential to cause changes when it interacts with the immune system of the host. The most important aspect of EBV infection is its pathogenic role in developing posttransplant lymphoproliferative disorders (PTLD). From a clinical point of view, PTLD consists of a polymorphic hyperplasia of B-cells, or even a monoclonal proliferation of B-cells with extensive nodal or extranodal

infiltration³². The PTLD results from an uncontrolled lymphoproliferation of EBV-infected B-cells in transplant patients³³. Many factors have been associated to PTLD; active CMV infection is one of them^{34,35}. The interaction between EBV and CMV is complex and difficult to understand. In part this is due to the existence of multiple strains of EBV that coexists in the human being at the same time. Infection with mixed virus subtype populations may be disadvantageous compared to single virus subtype infections³⁶.

Pascher, et al.³⁷ evaluated 11 intestinal transplant recipients and documented with PCR technique that four patients had six episodes of EBV viremia. Two developed EBV enteritis concurrent with CMV enteritis during acute rejection. The invasion of the intestinal tissue by EBV and CMV occurred only during or immediately after therapy with steroids or OKT3.

While PTLD is a disease with multifactorial pathogenesis, it is clear that the principal factor in the pathogenesis of the PTLD is the immunosuppression and the EBV infection. Nevertheless, CMV infection has been also related as a risk factor for developing PTLD^{38,39}. Moreover, some studies showed that patients with an active CMV infection develop a reactivation of EBV^{40,41}.

Arcenas, et al.⁴² studied the effect *in vitro* of superinfection with CMV in cells infected by EBV. The EBV-infected cells were susceptible to the superinfection by CMV. The authors concluded that the results from the *in vitro* superinfections support the *in vivo* studies, suggesting that CMV infection is related to an EBV reactivation and that CMV may be important as a cofactor in EBV pathogenesis in the immunocompromised patient. In summary, there is incipient *in vitro* evidence and clinical data that support that in some cases, an interaction between CMV and EBV could exist.

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