Human Herpesviruses 6 and 7 in Solid Organ Transplant Recipients

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The impact of cytomegalovirus, a member of the β-herpesvirus subgroup of the Herpesviridae, on patients who have undergone transplantation cannot be overstated. However, in the last 15 years, 2 additional members of the human β-herpesvirus family have been discovered: human herpesviruses 6 and 7 (HHV-6 and HHV-7). The impact of HHV-6 and HHV-7 is assessed, as is the well-being of transplant recipients. Also discussed is whether the data on the pathological consequences of infection warrant routine screening for these viruses in solid organ transplant recipients.

Human herpesvirus (HHV)–6 was first isolated in 1986 from the peripheral blood of patients with lymphoproliferative disorders and AIDS [1]; HHV-7 was isolated in 1990 [2]. The complete genomic sequence of HHV-6 (variants A and B) and HHV-7 are now available [3–5]. The viruses show more similarity to each other than they do to their closest evolutionary relative, cytomegalovirus (CMV). As expected, many of the core genes of the herpesviruses are conserved within the genome of HHV-6 and HHV-7, although the viruses also possess novel genes that are likely to be important to the survival of the virus in the host. These genes include the homolog of the adenovirus associated rep protein (U94) in HHV-6 but not HHV-7, chemokine, and 2 chemokine receptors. HHV-6 is highly prevalent in the human population (>95% seropositive) and infection, most likely transmitted by means of saliva, usually occurs during the first 2 years of life.

Primary HHV-6 infection has been associated with febrile illness, including exanthem subitum, and the virus uses CD46 as a cellular receptor [6, 7]. Infection with HHV-7 is also widespread in the population, with primary infection occurring early in life, probably through salivary transmission. HHV-7 has also been associated with febrile illness in children and is another etiologic agent of exanthem subitum [8]. The virus uses CD4 as a cellular receptor to infect T cells [9].

IMPACT OF HHV-6 AFTER TRANSPLANTATION

Many studies, which have used both cell culture and more sensitive PCR methodologies, have shown that HHV-6 infection during the period after transplantation is a common occurrence; the B variant is predominately detected. HHV-6 has been associated with a range of clinical diseases in bone marrow transplant (BMT) recipients, including encephalitis, pneumonitis, early marrow graft failure, and bone marrow suppression. In solid organ transplant recipients, HHV-6 has been associated with bone marrow suppression and interstitial pneumonitis after liver transplantation [10]. Recently, Dockrell et al. [11] reported that HHV-6 seronegativity before transplantation was associated with an increased risk of fungal infection during the first 90 days after transplantation, whereas DesJardin et al. [12] showed that HHV-6 reactivation was associated with CMV infection in patients at risk of primary CMV infection. However, other studies have not been able to identify specific disease associations with HHV-6 infection in patients who have undergone liver transplantation or renal transplantation [13, 14].

To provide a critical assessment of the clinical impact of HHV-6 in the posttransplant period, high-quality prospective studies are required that use sensitive detection methods that are not confounded by detection of latent infection. A number of studies of both BMT recipients and solid organ transplant recipients are available, although the current literature is biased in favor of BMT studies (table 1). In a study from our center...
of 60 consecutive liver transplant recipients, we have shown that the detection of HHV-6 (but not of HHV-7) by means of PCR was independently associated with biopsy-proven graft rejection, suggesting that HHV-6 may be a previously unrecognized pathogen in this group [15]. In these analyses, CMV was also associated with biopsy-proven graft rejection that remained independent of the HHV-6 association in multivariate statistical analysis.

Obviously, HHV-6 could either be participating in the rejection process per se or potentially exacerbating the inflammatory response characteristic of rejection. Of interest, HHV-6 infection in the liver has been shown to increase the expression of adhesion molecules and the number of human leukocyte antigen class II–positive T cells [16, 22]. Because HHV-6 infection is common after transplantation, it is conceivable that viral interactions may occur to exacerbate existing pathological processes. In this context, studies have shown that HHV-6 reactivation (documented by a 4-fold rise in antibody titer) was associated with an increase risk of CMV disease after primary CMV infection in renal transplant recipients [12].

In addition, in liver transplant recipients, HHV-6 seroconversion was associated with an increase of incidence of CMV disease in CMV-positive recipients of transplants from CMV-positive donors [23]. Historically, this group of patients is usually at intermediate risk of CMV disease because the host immune system is already primed against the pathogen. There are also data showing that in both liver and renal transplant recipients, concomitant infection with both HHV-6 and CMV is associated with more severe clinical CMV disease and an extended hospital stay [15, 23]. In a series of 33 liver transplant patients investigated by use of semiquantitative PCR methods for HHV-6 and HHV-7, CMV disease was associated with high HHV-6 and HHV-7 loads [21].

An alternative method for diagnosing HHV-6 infection after liver transplantation has been through the application of an HHV-6 antigenemia assay similar to the assay used to detect CMV infection [20]. In a study of 622 blood specimens from 51 consecutive liver transplant recipients, HHV-6 infection was diagnosed in ~22% of patients during the first year after transplantation. Consistent with results from our group [15], significant graft dysfunction consistent with organ rejection was associated with the detection of HHV-6 antigenemia in 8 of the 11 patients, and, importantly, HHV-6 viral antigens could also be detected in the liver biopsy specimens of 3 of these patients.

**IMPACT OF HHV-7 AFTER TRANSPLANTATION**

A few of the studies summarized in the previous section have also investigated HHV-7 infection in the same patient group. In addition, other studies have investigated HHV-7 as a pathogen in its own right. A report by Osman et al. [16] in 1996 provided a clue that HHV-7 infection was associated with pathological consequences after renal transplantation when these authors showed that the presence of active HHV-7 infection was associated with a greater risk of developing CMV disease. This study investigated 56 renal transplant recipients for ~3 months after transplantation. Twenty-eight patients had CMV DNAemia detected by means of PCR, and 8 developed CMV disease. The risk of progression to CMV disease was increased in patients with concurrent HHV-7 DNAemia (RR, 3.5; 95% CI, 1.1–11.6).

Consistent with a potential role of HHV-7 in predisposing the patient to CMV disease was the detection of increasing antibody titers to HHV-7 in patients with CMV disease. The possibility of HHV-7 affecting the replication of other β-herpesviruses is supported by reports showing that HHV-7 infection can reactivate latent HHV-6 in children with a history of exanthem subitum. A subsequent study by the same group investigated 37 renal transplant recipients for the presence of HHV-6 and HHV-7 DNA and serologic responses to these viruses for 12 weeks after renal transplantation [19]. In this study,
plasma CMV load and the occurrence of CMV disease was related to the serologic response to HHV-6 and HHV-7, although only the presence of HHV-7 DNA in peripheral blood leukocytes and donor/recipient CMV serostatus were significantly associated with CMV disease in logistic regression analysis. Consistent with data showing that high CMV load increases the probability of CMV disease, patients with detectable HHV-7 DNA had significantly higher peak plasma CMV loads.

In our center, a prospective study of β-herpesviruses in patients who had undergone renal transplantation was performed by use of qualitative and quantitative PCR methodologies in 52 patients [18]. A total of 596 blood samples were obtained from these patients and subjected to PCR analysis. CMV was the most commonly detected virus after transplantation (30 patients [58%]), followed by HHV-7 (24 [46%]) and HHV-6 (12 [23%]). Of interest, HHV-7 infection was detected earlier than was CMV infection ($P = .05$). Clinical pathological analysis revealed that in those patients who were exhibiting rejection episodes, HHV-7 detection was associated with more episodes of cellular rejection. In contrast to the situation in liver transplant recipients, no association was found between HHV-6 infection and rejection. In addition—and consistent with the studies summarized above—a significant increase in the occurrence of CMV disease in patients with both CMV and HHV-7 coinfection was seen, compared with those only exhibiting active CMV infection after transplantation. The conclusions of these prospective studies implicate HHV-7 as an important pathogen that exacerbates the pathological effects CMV infection, whereas at present, HHV-6 appears to have few pathological consequences in the renal transplant recipient.

**ANTIVIRAL CHEMOTHERAPY FOR HHV-6 AND HHV-7**

To date, there have been no controlled trials of antiviral therapy against either HHV-6 or HHV-7 infection. However, a number of case reports attest to the ability of existing antiviral agents used for CMV to suppress HHV-6 replication in vivo. Clinical response of HHV-6 encephalitis or other CNS disease to therapy with ganciclovir, foscarnet, or both drugs in combination has been reported, and ganciclovir-foscarnet has been used to suppress HHV-6 replication in a BMT recipient who experienced secondary graft failure [24]. My group has shown that the U69 protein (a homolog of the UL97 phosphotransferase of CMV) is able to phosphorylate ganciclovir with comparable efficiency to the CMV (UL97) gene product [25]. HHV-7 encodes a gene homologous to HHV-6 U69, although no functional studies on this gene product have been reported.

Some studies have reported that HHV-7 shows a similar degree of susceptibility to ganciclovir as HHV-6 [26], whereas other studies have not shown such an effect [27]; only 1 study reported that orally or iv administered ganciclovir given to renal transplant recipients had no effect on HHV-7 replication [28]. In vitro, acyclovir has relatively low activity against HHV-6 and HHV-7. Nevertheless, in BMT recipients who were receiving high-dose acyclovir (compared with untreated patients), there were fewer HHV-6 PCR-positive blood samples in patients who were receiving high-dose acyclovir [29]. These results imply that in vivo, high-dose acyclovir may provide some inhibitory effects against HHV-6 replication and that these results should be compared with the dichotomy between the in vitro sensitivity of clinical CMV strains (relatively poor) versus the in vivo ability to reduce CMV replication and CMV disease (reasonable when sufficiently high acyclovir levels can be achieved). Indeed, the result of valacyclovir prophylaxis in renal transplant recipients showing a significant decrease in organ rejection in those receiving drug versus placebo could be accounted for by the inhibitory effect of this drug on HHV-6 and HHV-7 replication in addition to its effects on CMV replication [30].

**CAN WE JUSTIFY MONITORING FOR HHV-6 AND HHV-7 AFTER ORGAN TRANSPLANTATION?**

The impact of β-herpesviruses after solid organ transplantation can be ranked CMV > HHV-6 ≈ HHV-7, with the relative importance of HHV-6 and HHV-7 being dependent on the transplant group under consideration. Whereas a number of in-house and commercial rapid diagnostic assays are available for CMV, at present, there are no commercial assays for HHV-6 or HHV-7 detection that have been evaluated clinically. Therefore, any center wishing to perform real-time diagnostic procedures for HHV-6 and HHV-7 will require the use of in-house methodologies, such as PCR or the recently described antigenemia assay for HHV-6.

In our center, a multiplex PCR for HHV-6 and HHV-7 is used to perform routine analysis on BMT recipients and renal and liver recipients during the posttransplantation period. In my opinion, the primary objective of any posttransplantation virological surveillance should be to ensure that the diagnosis of CMV infection is being performed in a timely fashion because this will impact most on the well-being of the patient under consideration. However, if budget support can be obtained, incorporating HHV-6 and HHV-7 PCR into the routine diagnostic laboratory is not impossible. Access to the results in real time allows the consideration of bone marrow suppressive disease after bone marrow transplantation and also the possibility of intervention against HHV-6 graft dysfunction or the exacerbation of CMV disease after renal transplantation.

Nevertheless, I think it is difficult to recommend aggressive antiviral chemotherapy on the basis of HHV-6 or HHV-7 PCR positivity in the blood without further evidence of clinicopath-
ological symptoms (e.g., acute suppression of bone marrow engraftment). To fully quantify the full impact of the new β-herpesviruses after solid organ transplantation, further long-term prospective studies are needed, together with data from trials of antiherpesvirus agents with anti-HHV-6 and anti-HHV-7 activity.

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References