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EDITORIAL

Human herpesvirus 6 infections after liver transplantation

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Abstract

Human herpesvirus 6 (HHV-6) infections occur in > 95% of humans. Primary infection, which occurs in early childhood as an asymptomatic illness or manifested clinically as roseola infantum, leads to a state of subclinical viral persistence and latency. Reactivation of latent HHV-6 is common after liver transplantation, possibly induced and facilitated by allograft rejection and immunosuppressive therapy. Since the vast majority of humans harbor the virus in a latent state, HHV-6 infections after liver transplantation are believed to be mostly due to endogenous reactivation or superinfection (reactivation in the transplanted organ). In a minority of cases, however, primary HHV-6 infection may occur when an HHV-6 negative individual receives a liver allograft from an HHV-6 positive donor. The vast majority of documented HHV-6 infections after liver transplantation are asymptomatic. In a minority of cases, HHV-6 has been implicated as a cause of febrile illness with rash and myelosuppression, hepatitis, pneumonitis, and encephalitis after liver transplantation. In addition, HHV-6 has been associated with a variety of indirect effects such as allograft rejection, and increased predisposition and severity of other infections including cytomegalovirus (CMV), hepatitis C virus, and opportunistic fungi. Because of the uncommon nature of the clinical illnesses directly attributed to HHV-6, there is currently no recommended HHV-6-specific approach to prevention. However, ganciclovir and valganciclovir, which are primarily intended for the prevention of CMV disease, are also active against HHV-6 and may prevent its reactivation after transplantation. The treatment of established HHV-6 disease is usually with intravenous ganciclovir, cidofovir, or foscarnet, complemented by reduction in the degree of immunosuppression. This article reviews the current advances in the pathogenesis, clinical diagnosis, and therapeutic modalities against HHV6 in the setting of liver transplantation.

Key words: Immunocompromised; Antivirals; Human herpesvirus 6; Liver transplantation; Opportunistic infections

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INTRODUCTION

Human herpesvirus 6 (HHV-6), a member of the β-Herpesviridae subfamily of human herpesviruses, is a ubiquitous virus that was first isolated from peripheral blood leukocytes in 1986[1]. The virus was not associated with any clinical illness until 2 years later, when HHV-6 was isolated from the peripheral blood of patients with roseola infantum (also known as exanthem subitum or sixth disease), which is a common febrile illness in children[2]. Since then, there have been large-scale epidemiologic studies that have established the natural history of HHV-6 infections in humans. Primary infection with HHV-6 occurs most commonly during the first 2 years of life, with a peak incidence between 6 and 12 mo after birth. By 2 years, more than 90% of individuals have been infected, as evidenced by a positive HHV-6 antibody. Primary HHV-6 infections may present as an asymptomatic illness or as a febrile syndrome accompanied later on by a maculopapular rash (exanthem subitum). In addition, primary HHV-6 infection has been associated with otitis, gastrointestinal symptoms, respiratory distress, and seizures[3,4].

There are two variants of HHV-6, variant A and variant B (HHV-6A and HHV-6B, respectively). These variants share certain biological properties and have a high level of sequence homology, differing from one another only by up to 8% at the nucleotide level[5,6]. However, the two HHV-6 variants differ epidemiologically and clinically. HHV-6B is implicated in the majority of primary HHV-6 infections during the first 2 years of life. HHV-6B replicates in the salivary glands[7] and hence, the mechanism of transmission between humans is thought to be via salivary secretions. In contrast, HHV-6A seems to be more neurotropic and has been implicated in neurologic diseases[8,9]. HHV-6A is also more frequently detected among patients with acquired immunodeficiency syndrome[10]. The age of acquisition of HHV-6A remains undetermined and, unlike HHV-6B, it does not seem to replicate in salivary glands and thus, the mode of transmission is not known.

PATHOPHYSIOLOGY

HHV-6 infects mainly CD4+ T lymphocytes, and to a lesser extent, CD8+ T lymphocytes and natural killer cells[11-13]. HHV-6 binds to the CD46 receptor[14] that is located on what is called a "lipid raft," which then carries the virus inside the cell. The HHV-6 envelope fuses to the cell membrane, and the viral nucleocapsid is transported into the nucleoplasm where the viral DNA genome is released[15]. The virus then replicates, assembles, and exits the infected cell to infect other cells. The first proteins synthesized during viral replication are the immediate-early (IE) proteins[16]. It was recently reported that two proteins, IE1 and IE2, distinguish the variants, HHV-6A and HHV-6B, respectively (L. Flamand, abstract 3-2, 6th International Conference on HHV6 & 7, 2008). However, the exact mechanism of HHV-6 replication and assembly is not clear, although viral assembly occurs inside multivesicular bodies which are subsequently transported toward the cell surface to facilitate virus exit from the cell.

One of the mechanisms postulated to explain the ability of HHV-6 to escape the immune system and establish latency is its property of immunomodulation. HHV-6 infection results in altered cytokine responses resulting in the selective suppression of interferon-γ[17], interleukin-2[18] and up-regulation of tumor necrosis factor-α production[19]. In addition, HHV6 down-regulates the expression of its CD46 receptor[12,14], which functions as a regulator of complement activation[20] and an important link between the innate and adaptive arms of the immune system. Finally, HHV-6 has been demonstrated to enhance apoptosis *in vitro*[21,22].

LATENCY AND CHROMOSOMALLY-INTEGRATED HHV-6

After primary infection, HHV-6 establishes a state of subclinical persistence or latency. This is a property that it shares with the other members of the human herpes virus family. During latency, the HHV-6 genome is harbored as separate circular DNA inside various cells, such as lymphocytes and probably monocytes. HHV-6 DNA sequences have been detected in peripheral blood mononuclear cells of as many as 90% of one study population[23].

In rare cases, instead of existing as a separate circular DNA, HHV-6 integrates into a human chromosome [termed chromosomally-integrated HHV-6 (CIHHV-6)]. Both HHV-6A and HHV-6B have been found to have this ability to become integrated into the chromosome. The incidence of CIHHV-6 is not exactly known, although a recent study of blood donors from the United Kingdom estimated an incidence between 0.2%-1%[24]. It is suggested that CIHHV-6 may also be vertically transmitted (mother to child transmission)[25], since it was found in germ cell lines, however, this has not been confirmed by other investigators[26]. Individuals with CIHHV-6 have a characteristic persistently high levels of HHV-6 DNA in the blood, sera, and hair follicles, without causing clinical illness[27]. Individuals with CIHHV-6 persistently have high levels of HHV-6 DNA in the blood, usually millions of genomic copies, while patients with acute HHV-6 infection or reactivation only have viral copies in the tens of thousands, even in the setting of immune compromise. A reliable method which can be used to distinguish CIHHV-6 is a quantitative PCR of a hair follicle sample, which often is negative in non-CIHHV-6 infections. The high level of DNA found in the blood and other body fluids in CIHHV-6 is due to cellular proliferation and cellular lysis and not as a result of viral replication. The clinical significance of CIHHV-6 is not clear. While many believe this is not related to significant clinical problems, there are few reports suggesting that CIHHV-6 may be associated with an increased risk of lymphoproliferative disease[28,29].

MECHANISMS OF HHV-6 INFECTION AFTER TRANSPLANTATION

Because the vast majority of humans harbor latent HHV-6, infection with this virus after transplantation is believed to result from viral reactivation. Viral reactivation may also occur in the transplanted allograft to cause HHV-6 superinfection in a previously-infected individual. In a minority of cases, primary HHV-6 infection may occur in a transplant recipient through the allograft or blood products, or through natural transmission (e.g. exposure to oropharyngeal secretions). Primary HHV-6 infection is likely more common in the pediatric transplant population, especially in children less than 2 years of age, who have not been exposed to infection. In this very young group of patients, there is a higher likelihood of receiving an allograft or blood products from a previously infected donor.

INCIDENCE OF AND RISK FACTORS FOR HHV-6 INFECTION AFTER LIVER TRANSPLANTATION

The incidence of HHV-6 infection after liver

transplantation has been reported to range between 14% and 82%[30-32]. HHV-6 infections typically occur during the first 2-8 wk after liver transplantation when the level of immunosuppression is most intense. However, HHV-6 infections as early as 10 d and as late as 5 years after liver transplantation have been reported[33]. Since the vast majority of patients have developed HHV-6 infections during early life and harbor the latent virus, the vast majority of HHV-6 infections after transplantation are believed to be due to endogenous reactivation. Factors that have been associated with HHV-6 reactivation after liver transplantation are acute allograft rejection and receipt of high doses of corticosteroids[33,34]. The presence of HHV-6 infection in cases of acute liver failure has also been reported as a risk factor for the development of allograft hepatitis after liver transplantation[35].

CLINICAL SYNDROMES ASSOCIATED WITH HHV-6 INFECTION AFTER LIVER TRANSPLANTATION

A myriad of clinical syndromes have been associated with HHV-6 infection after liver transplantation. These have been classified as either direct or indirect effects of HHV-6. The direct clinical manifestations due to HHV-6 include a febrile illness with or without rash, myelosuppression, hepatitis, pneumonitis and neurological diseases[33,36-38]. The indirect effects attributed to HHV-6 include an exacerbation of cytomegalovirus (CMV) disease, an increased severity of hepatitis C virus (HCV) recurrence, an increased risk of other opportunistic infections, allograft dysfunction, and acute cellular rejection (Table 1)[33,36,39-45].

Table 1 Clinical syndromes attributed to HHV-6 after liver transplantation

HHV-6 direct effects	Ref.	HHV-6 indirect effects	Ref.
Fever and rash	[36]	Increased incidence and severity of cytomegalovirus disease	[31,40,41]
Hepatitis	[33,36,49]	Earlier and more severe recurrence of hepatitis C virus	[42]
Myelosuppression	[37]	Higher incidence of fungal infections	[44]
Pneumonitis	[37]	Higher incidence of opportunistic Infection	[36]
Neurologic illness	[38,44,51]	Higher incidence of allograft rejection	[33,36,45,53]

HHV-6: Human herpesvirus 6.

Direct HHV-6 effects

Fever and rash: The most frequently reported clinical presentation of HHV-6 infection after liver transplantation is a febrile illness that can be associated with a rash[34,36,46]. In a study of 200 liver transplant recipients, two patients (1%) presented with a febrile illness and HHV-6 was implicated as the causative agent, after excluding all other pathogens or etiologies of the fever[36]. In many cases, this febrile illness may clinically mimic, and thus be misdiagnosed as, CMV syndrome[47]. Thus, it has been suggested that the syndrome of febrile illness with myelosuppression and rash after transplantation be termed as β-herpesvirus syndrome while the specific viral etiology is being investigated[48] Co-infections with HHV-6 and CMV have been demonstrated in these cases[47]. However, a recent large study of solid organ transplant recipients demonstrated that HHV-6 was not significantly associated with any clinical symptoms during CMV disease[41].

Hepatitis: HHV-6 has been implicated as a cause of hepatitis after liver transplantation. In a review of 121 patients who developed hepatitis after liver transplantation, 8 (6.7%) cases were thought to be secondary to HHV-6 infection[33], as documented by serology and immunoperoxidase staining of liver biopsy specimens. Clinically, HHV-6 infection was associated with elevated liver enzymes, allograft dysfunction, acute rejection, and lymphocytic infiltration. These clinical findings were also observed in another report of one patient who had lymphocytic infiltration and elevated aminotransferases during HHV-6 infection[36]. In another report, an HHV-6B infected transplant recipient developed syncytial giant cell hepatitis as a result of donor-transmitted HHV6-A infection[49]. Serologic, molecular, and immunohistochemical methods were used to identify HHV-6A superinfection as the etiologic agent in this patient with a latent HHV-6B infection[49]. Finally, another study showed that nine of 18 patients who had pre-transplant HHV-6 infection developed HHV-6 hepatitis after liver transplantation[50].

Myelosuppression and pneumonitis: Bone marrow suppression is another clinical presentation attributed to HHV-6 infection. In a report of four liver transplant recipients, HHV-6 associated myelosuppression occurred at a median of 50 d (range 17-90 d) after liver transplantation. While all the cell lineages were affected, leukopenia was the most common presentation. One of the four patients in this report also had concomitant interstitial HHV-6 pneumonitis, as documented by a positive HHV-6 immunostaining of the lung biopsy[37].

Neurological illness: Encephalitis due to HHV-6 infection has been reported in two liver transplant recipients[38,51]. In another report, central nervous system complications such as mental status changes of unidentified etiology were more likely to occur in liver transplant recipients who had HHV-6 infection[44]. However, another report found no significant association between HHV-6 infection and neurological illnesses[36]. These contradictory results may be due to the differences in neurotropism between HHV6 variants, with HHV-6A as the neurotropic variant. These differences in clinical manifestations should be considered in the analysis of the clinical impact of HHV-6 after liver transplantation.

Indirect HHV-6 Effects

Impact on CMV disease: HHV-6 is postulated to have immunomodulating properties that enhance the reactivation of CMV. Alternatively, the presence of HHV-6 may serve as a marker of an over-immunosuppressed state and hence the predisposition to develop other infections such as CMV. In one study, liver transplant recipients with documented primary HHV-6 seroconversion had a higher incidence of symptomatic CMV disease compared to those who did not have HHV-6 seroconversion[39]. This finding was again demonstrated in a prospective study wherein liver transplant recipients who developed CMV disease had detectable HHV-6 DNA in the blood[31]. Recently, a retrospective study showed that 16 of 19 liver transplant recipients who developed symptomatic CMV infection had concomitant HHV-6 antigenemia, including 12 patients who developed HHV-6 infection prior to CMV antigenemia[40]. However, this association between HHV-6 and CMV was not observed in a large cohort of solid organ transplant recipients who received oral ganciclovir and valganciclovir prophylaxis, wherein the incidence of CMV disease was not significantly different between those who develop and those who did not develop HHV-6 DNAemia[41].

Impact on HCV disease: A prospective study reported that HCV-positive patients who developed HHV-6 viremia after liver transplantation had an earlier recurrence and a higher fibrosis score upon hepatitis C recurrence when compared to patients without HHV6 viremia[42]. In another analysis of 60 liver transplant recipients with chronic hepatitis C, HHV-6 infection did not influence the incidence of hepatitis C recurrence, but was associated with more severe hepatitis and a higher fibrosis score[43]. In contrast, a study of 93 hepatitis C infected liver transplant recipients showed no association between HHV-6 and the incidence and severity of hepatitis C recurrence after transplantation[52].

Impact on fungal and other opportunistic infections: Because of its immunomodulating properties, HHV-6 has been postulated to influence the occurrence of other opportunistic infections after liver transplantation. In one study of 200 liver transplant recipients, the impact of HHV-6 infection on opportunistic infections, including CMV, Epstein Barr virus-related post-transplant lymphoproliferative disease, varicella zoster virus, invasive fungal infections, and mycobacterial disease, was demonstrated. In a multivariate analysis, HHV-6 was found to be a significant risk factor for the occurrence of these opportunistic infections[36]. In another study, HHV-6 was independently associated with invasive fungal infections in a cohort of 80 liver transplant recipients[44]. Similarly, in a study of 247 patients, the incidence of invasive fungal infection was 2-fold higher in patients with HHV-6 seroconversion compared to those without HHV-6 seroconversion[36]. It was further demonstrated that HHV-6 infection was an independent predictor of invasive fungal infections during the first 90 d after liver transplantation[36]. Whether this is due to the immunomodulating properties of the virus, or whether this is due to an over-immunosuppressed state (with HHV-6 reactivation as a marker of over-immunosuppression) remains to be defined.

Impact on allograft rejection and function: The association between HHV-6 and allograft dysfunction and rejection has been demonstrated in a few studies[33,36]. Local HHV-6 infection in the allograft was associated with increased expression of adhesion molecules on vascular endothelial cells and infiltrating leukocytes, and this could lead to local inflammation and graft damage leading to dysfunction and possible rejection[53]. In an analysis of liver transplant recipients who developed allograft rejection, HHV-6 infection and peak HHV-6 load were the only factors significantly associated with rejection beyond 30 d after liver transplantation[36]. Another study further supported the independent association between HHV-6 and biopsy-proven acute allograft rejection after liver transplantation[45]. However, these associations remain debatable since treatment for allograft rejection may also lead to HHV-6 reactivation. Hence, the association between HHV-6 and allograft rejection may be bidirectional.

DIAGNOSIS OF HHV-6 INFECTION

Distinguishing HHV-6 reactivation (i.e. active replication) from latency can be challenging because of the highly prevalent nature of latent HHV-6 infection in humans. Over 95% of adults have been exposed to the virus and express antibodies against HHV-6. The various assays used to diagnose active HHV-6 infection are summarized in Table 2.

Real time polymerase chain reaction (PCR)

Molecular assays are the most commonly used laboratory methods to detect HHV-6 reactivation and replication after transplantation. Both quantitative and qualitative methods have been developed to detect HHV-6 DNA in blood and clinical samples[54-57]. In addition to blood samples, HHV-6 detection by PCR can be performed on biopsy and tissue specimens[58]. These assays can differentiate between the variants HHV-6A and HHV-6B as a result of base-differences[54]. PCR testing has some limitations, mainly due to the inability of most assays to distinguish latent from replicating virus. To address this, it is suggested that serum samples are used, since the virus is cell-associated and the detection of free viral particles in cell-free serum would be more indicative of active HHV-6 infection[54]. This is not the case for whole blood specimens where latent HHV-6 may be present and amplified from leukocytes. The use of quantitative PCR assays may be helpful in distinguishing replicating from latent HHV-6, with the premise that high HHV-6 levels or increasing viral levels over time would indicate true HHV-6 replication[55]. In this context, it is emphasized that one may rarely detect the presence of CIHHV-6, as discussed above, so that high levels (often

Table 2 Tests for the laboratory diagnosis of HHV-6 infection

Test	Detects active infection	Distinguish HHV-6 variants A and B	Commercially available
Serology (IFA and ELISA)	No	No	Yes
Real time PCR			
Qualitative	No	Yes	Yes[1]
Quantitative	Yes	Yes	Yes[1]
Culture	Yes	Yes	Yes[2]
Real time reverse transcriptase PCR	Yes	Yes	No[3]
Antigen testing	Yes	Yes	No
Antibody avidity testing	Yes	No	No
Immunohistochemical technique	Yes	Yes	No
PCR *in situ*	Yes	Yes	No

IFA: Immunofluorescence assay; ELISA: Enzyme-linked immunosorbent assay; PCR: Polymerase chain reaction; [1]Available at reference and commercial laboratories; [2]Requires viral stimulation by chemicals; [3]Very specialized research laboratories.

in the million copies) in CIHHV-6 infected individuals do not necessarily reflect active viral replication. The detection of HHV-6 RNA by real time reverse transcriptase PCR assay, on the other hand, would indicate the presence of actively replicating virus[57].

Serology

Serologic assays by immunofluorescence assay (IFA) or enzyme-linked immunosorbent assay (ELISA) are commercially available to detect antibodies against HHV-6 in plasma and serum samples. However, these assays cannot differentiate between HHV-6A and HHV-6B variants. IFA seems to be more useful as titers can be followed over time to demonstrate a rise or fall in antibody levels. In contrast, ELISA cannot be used to compare the index value over time. Both IgM and IgG can be measured. HHV-6 IgM increases during the first few weeks after infection and will be detected for several months thereafter. However, the clinical utility of serology testing after transplantation is often questionable since the results are not uncommonly false-negative due to the inability of immunosuppressed patients to develop antibodies. Nonetheless, the presence of HHV-6 IgM antibodies confirms a primary infection. HHV-6 IgG antibodies are detected initially several weeks after primary infection, and they remain elevated during latent infection. In transplant recipients, elevated IgG level has been used to suggest HHV-6 reactivation, although this is of questionable significance. An antibody avidity test may differentiate recent and past infection[59]. Some patients, particularly those receiving potent immunosuppressive therapy, may not be able to generate antibodies, and hence, using HHV-6 serology alone may miss an acute infection or reactivation.

Culture

Culture is not widely available for the detection of HHV-6 for various reasons. It is time consuming, expensive, and the virus is difficult to grow unless it is activated by chemicals. Moreover, growth of the virus does not necessarily distinguish latency from active growth *in vivo*[37,60,61].

Table 3 Antiviral molecules and their activity against HHV-6

Antiviral drug	*In vitro* activity	*In vivo* activity[1]	Mechanism of antiviral resistance
Acyclovir[73,81]	No	No	
Ganciclovir[66-68,70-72]	Yes	Yes	Mutation in U38 DNA polymerase Mutation in U69 phosphotransferase
Foscarnet[65,82-85]	Yes	Yes[2]	Mutation in U38 DNA polymerase
Cidofovir[76,86,95]	Yes	Yes	Mutation in U38 DNA polymerase
Maribavir[87,88]	No	Not available	
Cyclopropavir[89]	Yes	Not available	
CMV 423[91]	Yes[3]	Not available	
HDP-CDV[90]	Yes[3]	Not available	
3 Deaza-HPMPA[92]	Yes	Not available	

CMV 423: A New anti-CMV (Cytomegalovirus) molecule (2-chloro 3-pyridine 3-yl 5,6,7,8-tetrahydroindolizine 1-carboxamide); HDP-CDV: Hexadecyloxopropyl-cidofovir; 3 Deaza-HPMPA: (S)-9-[5-Hydroxy-2-(phosphonomethoxy) propyl]-3 deazaadenosine. [1]Based on very limited studies and case reports; [2]Combination of foscarnet with ganciclovir or cidofovir has been reported and can be efficacious; [3]Activity *in vitro* demonstrated against HHV6-A.

Antigen testing

HHV6 antigenemia can be detected in whole blood samples or tissue specimens using specific monoclonal antibodies. It often indicates the presence of an active infection, and may distinguish variant HHV-6A from HHV-6B. However, this technique is labor-intensive, semi-quantitative, and it is not widely available for clinical use[55,62].

PREVENTION AND TREATMENT OF HHV-6 INFECTIONS

There have been no randomized clinical trials conducted on antiviral drugs for the prevention and treatment of HHV-6 disease in humans. As a result, there is currently no antiviral drug that is FDA-approved for clinical use in HHV-6 infection. Nonetheless, ganciclovir, cidofovir and foscarnet have been used in the clinical setting for the treatment of HHV-6 associated diseases, although the potential efficacy of these drugs have been based mainly on *in vitro* experimental data and on anecdotal case reports (Table 3).

Acyclic nucleoside analogues (Ganciclovir)

Ganciclovir is the most commonly used drug for the management of HHV-6 infections. However, this use is not supported by randomized controlled clinical trials. Ganciclovir inhibits viral DNA polymerase, which functions during viral replication. For it to exert its antiviral properties, ganciclovir must undergo tri-

phosphorylation into the active metabolite, ganciclovir-triphosphate. The initial phosphorylation requires the enzyme phosphotransferase, which is expressed by HHV-6[63]. *In vitro* studies demonstrated the activity of ganciclovir against HHV-6[64,65]. Clinically, ganciclovir has been shown to be effective in HHV-6 infected bone marrow transplant recipients[66-70]. Likewise, case reports suggest that ganciclovir is effective for the treatment of HHV-6 infections after liver transplantation[66-68,70-72]. Ganciclovir prophylaxis has been shown to be effective in preventing HHV-6 reactivation in stem cell transplant recipients[73-75]. However, some cases of fulminant HHV-6 infections may not respond to ganciclovir[68,69]. The inconsistencies in these reports could be due to the differential susceptibilities to ganciclovir between variants HHV-6A and HHV-6B. Studies have demonstrated that HHV-6B is less susceptible to ganciclovir when compared to HHV-6A[76,77]. In the clinical setting, this differential susceptibility could partly explain the occurrence of HHV-6B (but not HHV-6A) infections in a large cohort of solid organ transplant recipients who received anti-CMV prophylaxis with ganciclovir or valganciclovir[41]. In addition, HHV-6 isolates that are resistant to ganciclovir have been described. This is due to mutations in the U38 DNA polymerase or the U69 phosphotransferase genes[78-80]. Unlike ganciclovir, acyclovir appears to be ineffective against HHV-6 clinically and *in vitro*[81]. Acyclovir prophylaxis was not effective in preventing HHV-6 reactivation in stem cell transplant recipients[73-75].

Foscarnet (phosphonoformic acid)

Foscarnet is a pyrophosphate analogue which inhibits viral replication by targeting viral DNA polymerase. Foscarnet has been shown to be active against HHV-6 *in vivo* and *in vitro*[65,82,83]. The combination of foscarnet with ganciclovir or cidofovir was also shown to be efficacious based on a case report[84]. *In vitro* studies showed that mutation in the DNA polymerase would render HHV-6 resistant to foscarnet[85].

Cidofovir

Cidofovir is an acyclic nucleoside phosphonate analogue that has been shown to have excellent activity against HHV-6 *in vitro*[76]. There have been clinical reports where cidofovir was used successfully to treat HHV-6 infections. However, cidofovir is considered a second line treatment because of its nephrotoxicity. A mutation in the U38 gene encoding DNA polymerase was found to be responsible for a mutant HHV-6 that is highly resistant to cidofovir[86].

Investigational agents

Although several agents being developed for the treatment of viral pathogens do not specifically target HHV-6, some have been tested for their activity against this pathogen. Maribavir, a benzimidazole derivative that is being developed for the management of CMV infection, was demonstrated to be inactive against HHV-6 *in vitro*[87,88]. Recently, the clinical development of maribavir for the prevention of primary CMV disease after liver transplantation has been terminated since it was not demonstrated to be superior to placebo in stem cell transplant recipients. On the other hand, cyclopropavir, a recently developed guanine nucleoside analogue, has been shown to have activity against HHV-6 *in vitro*[89]. Hexadecyloxopropyl-cidofovir, a prodrug of cidofovir, has also been shown to be three times more potent than cidofovir against DNA viruses, including HHV6-A[90]. CMV 423, a new anti-CMV molecule (2-chloro 3-pyridine 3-yl 5,6,7,8-tetrahydroindolizine 1-carboxamide) that inhibits tyrosine kinases, likewise has been shown to have good activity against HHV-6A[91]. 3 Deaza-HPMPA[(S)-9-(5-Hydroxy-2-(phosphonomethoxy) propyl)-3 deazaadenosine] has been shown to be 6-fold more active than cidofovir *in vitro* against HHV-6A and HHV-6B[92]. Finally, arysulfone derivatives[93] and artesunate[94] seem to have some activity against HHV-6. However, the clinical development of these investigational drugs is at an early stage and it is not clear on whether they will eventually reach the bedside.

CONCLUSION

Subclinical HHV-6 infections in immunocompromised transplant recipients are common, while clinical HHV-6 disease is uncommon. Indeed, some have even suggested that detection of HHV-6 infection after liver transplantation may just serve as a virologic marker of an over-immunosuppressed status. Nonetheless, some of the reported HHV-6 associated diseases have led to serious complications and even mortality. The immunomodulatory effect of HHV-6, particularly its interaction with other viruses, and its effect on allograft survival in liver transplant recipients are very intriguing and need to be further elucidated. Hence, a better understanding of the pathobiology of HHV-6 in liver transplant recipients is needed. This goal, however, is hampered by the challenges in clinical diagnosis due to the lack of standardized diagnostic methodologies. Although currently-available antivirals have been used to treat severe cases of HHV-6 infections, well-controlled clinical studies that support the use are lacking. Novel anti-herpetic agents under development have been shown to exhibit activity against HHV-6 *in vitro*, but data on their efficacy in the clinical setting is lacking and need to be assessed in future clinical studies.

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