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TOPIC HIGHLIGHT

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Cytomegalovirus infection in liver transplant recipients: Updates on clinical management

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Abstract

Cytomegalovirus (CMV) infection is a common complication after liver transplantation, and it is associated with multiple direct and indirect effects. Management of CMV infection and disease has evolved over the years, and clinical guidelines have been recently updated. Universal antiviral prophylaxis and a pre-emptive treatment strategy are options for prevention. A currently-recruiting randomized clinical trial is comparing the efficacy and safety of the two prevention strategies in the highest risk D+R- liver recipients. Drug-resistant CMV infection remains uncommon but is now increasing in incidence. This highlights the currently limited therapeutic options, and the need for novel drug discoveries. Immunotherapy and antiviral drugs with novel mechanisms of action are being investigated, including letermovir (AIC246) and brincidofovir (CMX001). This article reviews the current state of CMV management after liver transplantation, including the updated practice guidelines, and summarizes the data on investigational drugs and vaccines in clinical development.

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Key words: Cytomegalovirus; Liver transplantation; Valganciclovir; Prophylaxis; Treatment; Resistance; Investigational; Letermovir; Brincidofovir

Core tip: In this article, the authors review the current literature of cytomegalovirus (CMV) infection after liver transplantation, including the approaches to diagnosis, prevention and treatment. The review highlights the pros and cons of the prophylaxis *vs* pre-emptive prevention strategies, especially in the highest risk D+/R- population. Treatment of CMV infection in liver transplant patients is discussed in addition to management of CMV resistance, with detailed discussion of recently updated clinical CMV management guidelines. Finally, the future management of CMV in liver transplant recipients relies on new drug discoveries, and the authors describe multiple investigational drugs and vaccines in clinical trials.

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INTRODUCTION

Cytomegalovirus (CMV) is a ubiquitous double-stranded DNA virus also known as human herpesvirus 5 (HHV-5). CMV seroprevalence has been reported to be around 60% in the United States[1-4]; higher prevalence has been noted in developing countries[2] and among high risk

patients, including patients infected with human immunodeficiency virus (HIV)[5]. Variable rates of prevalence have been reported among ethnic groups in the United States, with greater prevalence in the non-Hispanic blacks and Mexican-Americans[1]. CMV is an important cause of clinical disease in neonates and immunocompromised patients, and it appears to also be associated with poor outcome in critically ill immunocompetent patients[6]. All members of the Herpesviridae family establish latency in infected cells, with the life-long potential for reactivation and production of infective viral particles[7,8]. Primary CMV infection in immunocompetent hosts is usually asymptomatic or a nonspecific viral illness followed by latency; however immunocompromised hosts are at higher risk for developing serious primary infection or reactivation. CMV remains latent primarily in lymphoid organs and myeloid cells[8]. It can be transmitted by exposure to body fluids including saliva, semen, blood and breast milk[2], and can also be transmitted *via* transplantation of solid organs including heart, kidney, lungs and liver[7]. CMV can be a significant problem for transplantation, as it can increase the predisposition to develop serious infections, and increases the risk of allograft rejection and mortality[9]. In this article, we highlight the impact of CMV on liver transplantation and reviews recent advances in the prevention, diagnosis, and treatment of CMV in liver transplant recipients.

CLINICAL IMPACT OF CMV

CMV disease vs infection

CMV remains as one of the most important infectious complications after liver transplantation[3,10]. Multiple risk factors are associated with its occurrence, but most notable among them are the donor/recipient CMV serostatus and the severity of pharmacologic immunosuppression[1]. CMV infection represents the presence of the virus, as indicated by the detection of viral proteins or nucleic acids in body fluids or tissue samples, regardless of clinical symptoms[11]; the presence of any clinical symptoms in patients with CMV infection is termed CMV disease. CMV disease in immunocompromised patients may affect one or multiple organs, but may also have atypical presentations, requiring close monitoring and high index of suspicion in transplant patients[12].

Direct effects

The direct effects of CMV after liver transplantation can be categorized as CMV syndrome or tissue invasive disease (Table 1). CMV syndrome is the term for the clinical illness characterized by fever, constitutional symptoms, and myelosuppression in the presence of CMV infection[7,8,11]; this accounts for the majority of CMV disease cases in liver transplant recipients. In addition, CMV can invade end-organs and cause tissue-invasive disease. The most common organ affected is the gastrointestinal tract, causing esophagitis, gastritis, enteritis, or colitis[7]. There is the predisposition for the transplanted allograft to develop CMV infection in solid organ transplant (SOT) recipients, likely secondary to an abnormal allograft immune response[13]. It is therefore not uncommon for liver transplant recipients to develop CMV hepatitis[14]. Allograft invasion by CMV is likely the result of viral reactivation in the transplanted liver allograft that contains donor-transmitted virus[2,9].

Table 1 Direct and indirect clinical effects of cytomegalovirus in transplant recipients

Direct clinical effects	Indirect clinical effects
CMV syndrome	Acute allograft rejection
Fever > 38 ℃ for 2/4 d	Chronic allograft rejection
Malaise	Allograft failure
Myelosuppression	Vanishing duct syndrome/ductopenia
Tissue-invasive CMV disease[1]	Allograft hepatitis and fibrosis
Gastrointestinal disease	
(entire gastrointestinal tract	Vascular thrombosis
can be affected)	Opportunistic and other infections
Hepatitis	Fungal (Aspergillus, Pneumocystis)
Pneumonitis	Bacterial (Nocardia)
Retinitis	Viral (HHV-6, HHV-7, EBV)
CNS disease	Hepatitis C virus recurrence
Carditis	EBV associated PTLD
Mortality	Mortality

[1]Can affect any organ, listed are most common organs affected. PTLD: Post-transplant lymphoproliferative disorder; HHV: Human herpes virus; EBV: Epstein-Barr virus; CMV: Cytomegalovirus.

Indirect effects

Indirect effects of CMV include inflammatory cytokine-mediated acute and/or chronic graft rejection, decreased graft survival, and increased patient mortality[8,15,16]. CMV can also have an immunomodulatory effect in liver recipients, further enhancing the immunosuppression and predisposition to opportunistic infections with bacteria, fungi or other viruses, including EBV-related post-transplant lymphoproliferative disorder and accelerated HCV recurrence[8,13,15]. CMV disease has been found to be an independent risk factor in the development of invasive fungal infections in liver transplant recipients[10].

RISK FACTORS

The most important clinical predictor for the development of CMV infection and disease after liver transplantation is the CMV serostatus of the donor and the recipient[13,17-19]. Accordingly, prior to transplantation, donors and recipients are screened for CMV IgG antibodies to accurately stratify patients into risk groups for CMV disease[13]. The risk for serious CMV disease is highest for primary infections in CMV seronegative recipients receiving CMV seropositive allografts (CMV D+/R- mismatch)[13,19]. One study reported an almost universal CMV infection among D+/R- liver transplant recipients[20]. In contrast, double negative donor-recipient combinations (CMV D-/R-) have the lowest risk for CMV disease after liver transplantation[21]. Only about 1%-2% of this CMV

D-/R- transplant population will develop CMV disease during the first year after liver transplantation, either as a result of natural transmission or through blood transfusion. In order to preserve this low CMV risk, these patients must receive leukoreduced and/or CMV antibody negative blood products[13,20].

The intensity of the immunosuppressive regimen used in the post-transplant period plays an important role in determining the patient's overall immune status[20,22]. Patients given antilymphocyte antibodies (such as thymoglobulin, alemtuzumab, among others) are significantly increased risk of CMV infection and disease compared to their counterparts not receiving this therapy, whether these agents are used as induction or anti-rejection therapy[13]. After these therapies are administered, there is a systemic release of tumor-necrosis factor-alpha, which is a potent transactivator of latent CMV[23]. The incidence rates of CMV infection and disease in liver transplant recipients are higher during treatment for allograft rejection, likely due to the accelerated inflammatory state[13,21], especially among those who did not receive CMV prophylaxis[23].

Certain co-infections also increase the risk for developing CMV infection and disease, especially HHV6 and HHV7[13,20,24]. There are also reports correlating CMV disease risk with lower model for end stage liver disease scores, lower total bilirubin, and higher operating time, but these findings have been inconsistent among different studies[25].

Deficiencies in innate and cell-mediated adaptive immunity have been associated with CMV disease after liver transplantation. Specifically, functional polymorphisms in Toll-like receptors, which are important receptors that recognizes CMV, has been associated with increased risk of CMV disease after liver transplantation[26]. Homozygosity for Toll-like receptor 2 R753Q single nucleotide polymorphism is a marker for tissue-invasive CMV disease after liver transplantation, independent of other traditional risk factors[27]. Likewise, liver transplant recipients who are deficient in CMV-specific T cells, as indicated by undetectable or low levels of interferon-gamma during stimulation with CMV antigens, are at significantly higher risk of CMV disease.

DIAGNOSIS

Several methods are used for the diagnosis of CMV infection after transplantation. Among them, the most commonly used technique is nucleic acid testing (NAT), which is often performed using polymerase chain reaction (PCR). Using this approach, CMV viral load has been used for various indications, including (1) rapid diagnosis of CMV infection; (2) prognostication of the severity of infection; (3) monitoring for antiviral efficacy; and (4) assessing the risk of relapse[20,28]. Real-time NAT are faster technologies with rapid turn-around time that will confirm the suspicion of CMV disease within hours of testing[28]. Its quantitative ability allows for assessing the severity of infection (higher viral load is associated with higher likelihood of severe disease). Serial monitoring will also allow for assessment of viral load rise (associated with disease progression) or decline (associated with antiviral response). Indeed, the rate of change of viral load over time is as important as the absolute viral load values in CMV disease assessment and prognostication[13,20,28]. CMV NAT is often performed on blood samples, and there is ongoing debate as to which compartment of the blood is ideal for CMV NAT. Whole blood samples often allow for the detection of viremia earlier and for longer periods than plasma samples[29]; whether this is better for diagnostic purposes is still debated. The only FDA approved CMV NAT assay in the US detects the virus on plasma samples[28]. It is important to point out that a negative CMV NAT in blood samples does not completely rule out the presence of compartmentalized and localized tissue-invasive CMV cases (such as some cases of reactivation CMV gastrointestinal disease, and CMV retinitis)[13].

Until recently, CMV NAT assays are not directly comparable. Differences in assay design, platform, target, calibrators, and samples (among others) have limited direct comparison and portability of viral load results from one assay to another. Accordingly, there were no widely accepted viral load thresholds that can be used for CMV disease management[30,31]. To address this, a World Health Organization (WHO) International Standard was developed to which assays can be calibrated for viral load reporting[32,33]. Using an assay that has been calibrated to this WHO standard, one study had suggested a viral load of 3983 IU/mL (2600 copies/mL), with a 99.6% negative predictive value (89.9% sensitivity and 88.9% specificity) as an appropriate cut-off for initiating treatment in CMV-seropositive SOT recipients[31]. Another study reported that suppression of the viral load to < 137 IU is associated with faster clinical CMV disease resolution. Whether this will also result in lower rate of CMV disease relapse, and what viral load threshold can be used for various indication are now being investigated in the clinical setting.

The gold standard for diagnosis of tissue invasive CMV disease remains the demonstration of CMV pathology in a biopsy specimen from the involved organ. CMV can be demonstrated in the biopsy specimen using histology (such as demonstration of CMV inclusion bodies), immunohistochemical identification of CMV antigens, in-situ DNA hybridization or (less preferred) CMV culture[28]. Serology to demonstrate CMV IgG in the blood of transplant recipients is not recommended for the diagnosis of acute CMV infection after transplantation. Liver transplant recipients may have delayed and impaired ability to mount antibody production, thereby making serology not as reliable in diagnosis of acute infection after transplantation.

Detection of CMV pp65 using fluorescent methods on infected peripheral blood leukocytes is another method for the rapid diagnosis and surveillance of CMV infec-

Table 2 Comparison of antiviral prophylaxis and pre-emptive strategies for cytomegalovirus prevention in liver transplant patients

Prevention characteristics	Prophylaxis strategy	Pre-emptive strategy
CMV disease	Very effective at preventing CMV infection and disease	Effective to prevent CMV disease; does not prevent CMV infection
Late-onset CMV disease	Higher risk of late and very-late onset CMV disease	Reduces incidence of late onset CMV disease
Ideal treatment population	CMV D+R- are highest risk patients	CMV R+ patients
Logistics of strategy	Logistically more feasible, but still requires frequent monitoring of adverse effects	Requires weekly viral load testing; standardized viral load thresholds still being investigated
Cost	Higher drug costs; lower laboratory/monitoring costs	Higher laboratory/monitoring costs; lower drug costs
Safety/adverse effects	More frequent adverse effects such as myelosuppression due to longer treatment periods	Shorter treatment periods; fewer toxicities
Indirect CMV effects	Better evidence showing reduction of graft rejection, improved graft survival, opportunistic infections	Limited evidence overall, but may not reduce indirect effects
Effect on mortality	Reduces mortality from CMV disease	Limited evidence regarding mortality reduction
CMV resistance	More common compared to pre-emptive strategy	Some evidence regarding effect on resistance but overall uncommon

CMV: Cytomegalovirus.

tion in transplant recipients. Its utility has been declining with the rise in molecular methods such as CMV NAT. In some studies, the CMV pp65 had comparable sensitivity to CMV PCR, and higher sensitivity compared to culture-based methods[13]. However, the pp65 antigenemia assay has lower rates of detection in the lower viral load ranges[30,34]. Additionally, although the specificity of the antigenemia assay and CMV NAT are comparable, the CMV NAT have a higher negative and positive predictive value and much higher sensitivity than the pp65 assay in SOT recipients[30]. Moreover, the pp65 antigenemia assay is time sensitive: samples must be obtained and tested in 8 h. There is also significant biological variation, and its accuracy decreases in leukopenic patients with absolute neutrophil counts less than 1000/mm^3 (since pp65 antigen is detected on leukocyte populations)[28,34].

PREVENTION

In the absence of any prevention strategy, CMV infection (36%-100%) and disease (11%-72%) can be expected to occur within the first 3-4 mo after liver transplantation[2,14,35]. This may be subclinical or may present clinically as CMV syndrome or end organ disease[14]. In a large cohort of liver transplant patients, there was an independent association between CMV infection or disease within the first year of liver transplantation and the composite outcome of allograft loss or mortality (RR = 3.04, 95%CI: 1.56-5.92, $P = 0.001$)[36].

Prevention of CMV infection and disease in liver transplant recipients is therefore a priority in post-transplant management. This can be accomplished either with antiviral prophylaxis or pre-emptive therapy, and the strategies vary according to institution. Universal prophylaxis provides antiviral therapy to all patients at risk for CMV infection after liver transplantation, while the preemptive strategy involves frequent viral load monitoring and treatment at the early stages of CMV infection before symptomatic disease develops[13]. In a retrospective analysis of two liver transplant cohorts receiving prophylaxis or preemptive therapy, CMV viremia expectedly occurred within the first 3 mo after liver transplantation in the preemptive strategy group, while this occurred during months 3-6 among patients who received 3 mo of antiviral prophylaxis[37]. Each of the two approaches has advantages and disadvantages as shown in Table 2 but the prophylaxis strategy has been preferred among the majority of transplant programs in the United States, partly due to better long-term outcome and for logistic reasons[38]. The major disadvantage of antiviral prophylaxis is the occurrence of late-onset CMV disease. To reduce this complication, some institutions have adopted a hybrid approach whereby patients who receive antiviral prophylaxis initially are subjected to a preemptive strategy during the high-risk period after antiviral prophylaxis[20].

Antiviral prophylaxis

CMV prophylaxis is usually given to all patients at-risk during the initial 3-6 mo after liver transplantation. Additionally, antiviral prophylaxis is given to patients receiving lymphocyte-depleting therapy for acute allograft rejection[20]. The recommendations for CMV prophylaxis vary depending on the serostatus of the donor and recipient. CMV D+/R- liver recipients are recommended to receive 3-6 mo of CMV prophylaxis, while 3 mo of prophylaxis may be sufficient for the CMV-seropositive liver recipients. Most commonly, CMV prophylaxis is with the use of valganciclovir (dose 900 mg daily, adjusted based on renal function). Alternative agents are oral ganciclovir (3 g per day) or intravenous ganciclovir (5-mg/kg daily)[13]. Because of the higher rates of tissue-invasive CMV disease in liver transplant recipients who received valganciclovir compared to oral ganciclovir prophylaxis, the US FDA did not approve the use of valganciclovir for CMV prophylaxis in liver transplant recipients. Notwithstanding this statement, multiple experts recommend the use of valganciclovir for prevention of CMV in liver transplant patients, and it is subsequently the preferred therapy in a large majority (> 70%) of transplant centers in the United States[38]. A more recent study confirmed the increased incidence of late-onset CMV disease in liver recipients[39]. However, valganciclovir has superior bioavailability compared to oral ganciclovir (50%-60% compared to 6%-9%)[13,40]. A number of more recent retrospective

studies found no significant difference in incidence of CMV disease in liver transplant patients treated with oral ganciclovir *vs* valganciclovir[41,42].

Due to the major adverse effect of leukopenia and the high cost of the drug, low-dose valganciclovir dosing has been proposed. In a recent review, there remains a high risk of CMV disease in liver transplant patients, despite the use of valganciclovir prophylaxis at a dose of 900-mg daily[43]. In a large meta-analysis, the efficacy of valganciclovir 450-mg was equivalent to valganciclovir 900-mg dosing, and the low-dose program was associated with lower incidence of leukopenia and fewer instances of CMV disease or graft rejection[44]. It is possible that the low dose valganciclovir would allow for a low level exposure of the immune system to CMV antigens, thereby allowing for T cells to mount an immune response[44]; this however remains speculative. In an earlier retrospective study of liver transplant recipients, the efficacy of valganciclovir at 450-mg dosing was similar to oral ganciclovir[40].

One of the major drawbacks to antiviral prophylaxis is the occurrence of late-onset CMV disease, which is the term for CMV disease cases that occur soon after the completion of universal prophylaxis. Among liver transplant recipients who receive 3 mo of antiviral prophylaxis, late-onset CMV disease would typically occur at about 3-6 mo after transplantation[14,45]. The incidence of late-onset CMV disease has been reported to vary between 17%-37% depending on the length of valganciclovir prophylaxis[45-47]. Late-onset CMV disease is almost exclusively a condition that occurs in CMV D+/R- SOT recipients who received antiviral prophylaxis, and rarely is observed in CMV-seropositive transplant recipients. To address the issue of late-onset CMV disease, many have suggested longer periods of CMV prophylaxis[45,46]. In a study of kidney transplant recipients (The IMPACT study), antiviral prophylaxis for 200 d was associated with lower incidence of CMV disease compared to 100 d of prophylaxis, and that the number needed to treat to avoid one additional CMV disease diagnosis up to 12 mo post-transplant was 5[45,46]. Fewer patients in the 200 d group developed CMV disease at 6, 9, 12 and 24 mo (7.1%, 14.2%, 16.1% and 21.3% respectively) compared to the 100 d group at 6, 9, 12 and 24 mo (31.3%, 35%, 36.8% and 38.7% respectively); P value < 0.0001 in all cases[45,46]. Additionally, longer prophylaxis was associated with fewer opportunistic infections than standard prophylaxis (12.9% compared with 27%, $P = 0.001$)[45,46]. While this was conducted in kidney transplant recipients, many centers have extrapolated the findings to high risk CMV D+/R- liver transplant recipients.

Preemptive therapy

Preemptive therapy is the approach wherein antiviral therapy is provided to liver transplant recipients with low-level asymptomatic CMV infection. The mainstay of preemptive therapy is close laboratory monitoring of the at-risk patients and the initiation of early antiviral treatment when a viral load threshold is reached, so that the infection does not progress to CMV disease[13,14]. Typically, the preemptive approach involves weekly CMV monitoring with the use of pp65 antigenemia assay or CMV NAT by PCR, for at least 12 wk after liver transplantation[13,14]. Once the virus is detected, antiviral treatment can be initiated either with oral valganciclovir (900 mg twice daily) or IV ganciclovir (5 mg/kg every 12 h). Antiviral treatment is continued until the virus is no longer detected in the blood[13,14]. Many transplant centers are not comfortable with using this approach in the highest risk CMV D+/R- group because the rapid viral replication dynamics in this high-risk patient may lead to the inability to detect CMV soon enough for the initiation of effective antiviral treatment. Many studies however have demonstrated the efficacy of preemptive therapy in moderate-risk groups such as CMV R+ liver transplant recipients[13,14]. In a study of liver transplant population (a third were D+/R-), the use of preemptive therapy guided by CMV NAT by PCR was associated with CMV disease rates < 1% at one year and < 2% overall, and the inclusion of CMV D+/R- in this study suggests that it is also feasible even in high-risk patient groups[48].

The preemptive strategy is advantageous in terms of reducing cost and drug toxicity if used in recipients who are at lower risk for developing CMV disease. Given the advantages of the preemptive approach in cost-effectiveness and adverse effect reduction, more studies need to be designed to test this approach in the highest risk D+/R- patients for whom the prophylaxis strategy is currently recommended. One ongoing phase 4 randomized, controlled study is performing direct head to head comparisons of the prophylaxis and preemptive strategies in D+/R- liver transplant patients[49], and hopefully the results of this and subsequent trials should help to answer this question (ClinicalTrials.gov Identifier: NCT01552369).

TREATMENT

The standard of care for the treatment of CMV disease is IV ganciclovir, at 5 mg/kg twice daily, or valganciclovir, at 900-mg orally twice daily[13]. IV ganciclovir administration requires intravenous access, the potential need for inpatient hospitalization, and may be complicated by catheter-related bacterial or fungal infections. Oral valganciclovir has excellent bioavailability that provides systemic ganciclovir levels comparable to IV ganciclovir, but it relies on efficient absorption through the gastrointestinal tract. Both valganciclovir and intravenous ganciclovir have been demonstrated to be efficacious for the treatment of mild to moderate CMV disease and asymptomatic CMV infection in SOT recipients. In the VICTOR study, the safety and non-inferiority of oral valganciclovir at 900 mg twice daily was demonstrated in comparison to IV ganciclovir for the treatment of CMV disease in SOT patients, 7% of whom were liver transplant recipients[50]. Oral valganciclovir administration resulted in almost

identical mean times to clinical resolution of disease as IV ganciclovir, with no differences in the incidence of graft rejection or adverse effects at the end of the 21-d treatment period[50]. One year follow up of these patients revealed no difference in long-term treatment outcomes in patients treated with oral valganciclovir compared to IV ganciclovir. Guidelines therefore recommend the use of oral valganciclovir for treatment of mild-to-moderate CMV disease, but not in life-threatening CMV disease cases, those with very high viral load, those patients with poor oral absorption, and those with questionable compliance with medications. In such cases, IV ganciclovir would be more appropriate[51]. Oral ganciclovir, acyclovir or valacyclovir should not be used for treatment of CMV disease[51]. IV foscarnet and cidofovir should not be used as first-line drugs for the treatment of CMV disease due to their toxicity profiles, but are considered alternative agents for treatment of ganciclovir-resistant CMV.

The duration of treatment of CMV disease should be guided by viral load monitoring. Previous studies have demonstrated that the greatest predictor of clinical relapse was the persistence of CMV viremia at the end of treatment[52]. Indeed, suppression of CMV viral load to less than 137 IU/mL was associated with resolution of clinical disease. Thus, it is recommended that transplant recipients with CMV disease should undergo weekly viral load monitoring, which will guide the duration of treatment. Guidelines currently recommend antiviral treatment until two weekly negative CMV PCR's are demonstrated. Patients treated with valganciclovir and intravenous ganciclovir should also be monitored closely for adverse effects, which include leukopenia[51].

In addition to antiviral drugs, SOT recipients with CMV disease should be assessed for the intensity of immunosuppression. In theory, CMV is an opportunistic pathogen and its onset is often correlated with a more severe intensity of immune dysfunction. Accordingly, one should consider reducing the dose of immunosuppressive therapy in patients with CMV disease, especially if the illness is severe. This should however be done cautiously since drastic and precipitous reduction in immunosuppression may precipitate allograft rejection.

Antiviral resistance

Ganciclovir resistant CMV is still uncommon in the general SOT population, although it has been described to occur in up to 7% of high-risk SOT recipients who previously received prolonged ganciclovir prophylaxis[53]. Prolonged use of ganciclovir predisposes to the development of CMV resistance[51]. It should be suspected if viral loads do not decline despite effective antiviral therapy for at least 2-3 wk, if clinical symptoms recur, or if viral load is not suppressed to undetectable levels despite prolonged effective therapy[51,54].

To become an active drug, ganciclovir must be phosphorylated to ganciclovir triphosphate *via* three enzymatic steps; the initial phosphorylation is catalyzed by *UL97*-encoded viral kinase[54]. The ganciclovir triphosphate subsequently incorporates competitively into the DNA *via* the *UL54* DNA polymerase and stops viral replication[54]. Cidofovir and foscarnet do not require the initial *UL97*-catalyzed phosphorylation, but they also act on *UL54* DNA polymerase to terminate viral replication. The primary mechanism for CMV resistance to ganciclovir is due to mutations of the *UL97* phosphotransferase gene which is responsible for the initial ganciclovir monophosphorylation step[55]. Less commonly, mutations in *UL54* may occur, and this may result in cross-resistance among ganciclovir, foscarnet and cidofovir.

The CMV D+/R- transplant recipients are at highest risk of drug resistance with an incidence of 5%-10%; rates of resistance vary depending on the organ transplanted, with greater incidence in lung and pancreas recipients[54,55]. While traditionally considered to be at a lower risk, transplant patients on preemptive therapy have also been demonstrated to be at risk of ganciclovir-resistant CMV disease, especially if preemptive therapy is prolonged or when oral preemptive therapy is started when the viral load is initially high[54,55]. Earlier studies described an increased incidence of resistance in patients treated with oral ganciclovir compared to valganciclovir, attributed to better viral suppression in the valganciclovir group[39,56]. More recently however, SOT recipients treated with either IV ganciclovir or oral valganciclovir have been found to have similar risk of developing ganciclovir resistance[55]. Genotypic drug assays have been developed to identify ganciclovir resistance mutations to *UL97* and *UL54* and can provide relatively rapid confirmation in cases of suspected ganciclovir resistance[51,54].

In life-threatening cases where antiviral resistance is suspected, an empiric switch in treatment, often to foscarnet, is recommended. If low-level resistance is confirmed, increasing the dose of IV ganciclovir (or switching from oral valganciclovir to IV ganciclovir) is recommended as first-line of treatment with close monitoring for myelosuppressive and nephrotoxic adverse effects[51]. In cases of high-level resistance, foscarnet is the recommended antiviral therapy[51]; since many ganciclovir resistance mutations also confer cidofovir resistance, the latter is a poor alternative[54]. Foscarnet (second line) and cidofovir (third line) are associated with significant nephrotoxicity however, and can be challenging to administer in patients with reduced renal function or electrolyte imbalances. Ganciclovir-foscarnet combination therapy has been proposed as an option for treatment of resistant CMV, but this has variable response and is no longer strongly recommended since it was associated with more toxicity without proven clinical benefits[57].

There are some data to support the use of adjunctive treatments like intravenous immunoglobulin or CMV immunoglobulin (CMV Ig), a switch to mammalian target of rapamycin inhibitors (sirolimus, everolimus), or use of leflunomide[51]. The incidence of CMV disease has been lower than expected in transplant recipients on sirolimus-containing immunosuppressive regimens[58]. Another recent study revealed that while CMV-Ig and CMV neutral-

izing antibodies may be able to reduce viral spread during initial infection, during subsequent reactivation, they are unable to stop cell-to-cell viral spread[59]. Additionally, CMV-Ig has been shown to reduce CMV related mortality in SOT patients[60].

Several drugs in clinical development have been used for prevention and treatment of CMV disease, including those caused by drug-resistant CMV. Maribavir, a benzimidazole inhibitor of the *UL97* kinase, has been shown to be a potential drug for the treatment of drug-resistant CMV. However, the clinical trials in HSCT and liver transplant recipients were disappointing and the drug was not effective for CMV infection and disease prevention. In a randomized controlled trial comparing maribavir to oral ganciclovir as prophylaxis in liver transplant patients, there were significantly fewer patients with CMV infection or disease at 3 or 6 mo when treated with ganciclovir compared to maribavir[61]. Some have speculated that the dose of maribavir chosen (100-mg twice daily) contributed to the inability to prove noninferiority, as previous phase Ⅱ trials demonstrated adequate antiviral activity at higher doses (400-mg twice daily), but higher doses were associated with significant dysgeusia[62]. Maribavir may still remain an option for treatment of multi-drug resistant CMV due to differences in resistance mechanisms[63]. New clinical trials (ClinicalTrials.gov Identifier: NCT01611974) are actively recruiting SOT and HSCT patients to investigate maribavir as a treatment for resistant or refractory CMV[64].

Another investigational agent is letermovir (AIC246) which inhibits the enzyme UL56 terminase and shows promise in early studies with antiviral efficacy against drug resistant strains and minimal cross-resistance[51,65-67]. Additionally, cyclopropavir is another novel compound that has been shown to be effective against CMV by inhibition of the *UL97* kinase[68,69]. Resistance usually involves mutations of *UL97* kinase that are different from those seen in ganciclovir resistance, therefore cyclopropavir can potentially still retain activity against ganciclovir resistant strains[68]. CMX001 (Brincidofovir) is another investigational therapy with activity against multiple DNA viruses[70]. It is a well-tolerated oral lipid-conjugate derivative prodrug of cidofovir which delivers antiviral directly to target cells before being cleaved, and with no evidence of nephrotoxicity or myelosuppression and increased potency compared to cidofovir[63,71]. Multiple clinical trials using CMX001 are ongoing, including one which preliminarily reported that CMV viremia was reduced with CMX001 use in HSCT patients with refractory CMV disease[72]. Additionally, results of the phase Ⅱ randomized, controlled, dose-escalated clinical trial presented at the 2012 BMT Tandem meetings revealed a reduction in new or progressive CMV infection in HSCT patients using higher doses of CMX001 for CMV prophylaxis[73]. The phase Ⅲ study (ClinicalTrials.gov Identifier: NCT01769170) is now recruiting participants to continue to study the safety and efficacy of CMX001 for CMV prevention in HSCT patients[74]. Resistance patterns in CMX001 would theoretically be similar to cidofovir, however a *de novo* CMX001 resistant strain (D542E, a novel *UL54* mutation) has been generated after prolonged selection pressure *in vitro*[75]. Clinical trials of these compounds in the liver transplant population are yet to be performed.

Other drugs approved for other indications have been used off-label and anecdotally for treatment of resistant CMV. Leflunomide is an anti-inflammatory drug approved for rheumatoid arthritis that also causes inhibition of CMV viral kinases and pyrimidine synthesis[54]; however more investigations need to be conducted to identify its role in the treatment of multi-drug resistant CMV. Similarly, artesunate is an antimalarial with activity against drug resistant CMV, with proposed activity against viral kinase signaling pathways; experience with artesunate in this capacity has only been anecdotal[54].

Due to the virus' ability to evade host defenses, primary infection with CMV has not been shown to confer immunity from subsequent infections[76]. Notwithstanding this, there are efforts to develop CMV vaccine for prevention and therapy. These however remain in clinical development, and none has been subjected to phase Ⅲ clinical trials.

CONCLUSION

Despite decades of studies dedicated to the discovery of new treatment and prevention options, CMV remains the single most devastating viral infection causing morbidity and mortality in liver transplant patients[20]. It is known that contributions from both the innate and adaptive immune system are necessary for a complete immune response to CMV, but the virus has a unique ability to evade both arms, causing latency and reactivation. Multiple antiviral therapies are approved for treatment and prophylaxis of CMV infection in transplant patients, but ganciclovir (and valganciclovir) is the most commonly used antiviral drug. High-risk D+/R- liver transplant patients require a more aggressive form of prevention, which in many centers have translated to longer duration of antiviral prophylaxis. Preemptive therapy may also work, if coordinated properly. Multiple viral mutations in *UL97* and less commonly *UL54* gene contribute to CMV resistance, and the challenge in these times is to produce a reliable alternative treatment option in cases of multi drug resistant CMV. Several drugs and compounds are currently being developed in clinical trials, including a potentially effective vaccine to reduce the impact of CMV on transplantation outcomes[77].

REFERENCES

1 **Staras SA**, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. *Clin Infect Dis* 2006; **43**: 1143-1151 [PMID: 17029132 DOI: 10.1086/508173]

2 **Beam E**, Razonable RR. Cytomegalovirus in solid organ transplantation: epidemiology, prevention, and treatment. *Curr Infect Dis Rep* 2012; **14**: 633-641 [PMID: 22992839 DOI: 10.1007/s11908-012-0292-2]

3 **Razonable RR**. Cytomegalovirus infection after liver transplantation: current concepts and challenges. *World J Gastroenterol* 2008; **14**: 4849-4860 [PMID: 18756591]

4 **Zhang LJ**, Hanff P, Rutherford C, Churchill WH, Crumpacker CS. Detection of human cytomegalovirus DNA, RNA, and antibody in normal donor blood. *J Infect Dis* 1995; **171**: 1002-1006 [PMID: 7706776]

5 **Wohl DA**, Kendall MA, Andersen J, Crumpacker C, Spector SA, Feinberg J, Alston-Smith B, Owens S, Chafey S, Marco M, Maxwell S, Lurain N, Jabs D, Benson C, Keiser P, Jacobson MA. Low rate of CMV end-organ disease in HIV-infected patients despite low CD4+ cell counts and CMV viremia: results of ACTG protocol A5030. *HIV Clin Trials* 2009; **10**: 143-152 [PMID: 19632953 DOI: 10.1310/hct1003-143]

6 **Limaye AP**, Boeckh M. CMV in critically ill patients: pathogen or bystander? *Rev Med Virol* 2010; **20**: 372-379 [PMID: 20931610 DOI: 10.1002/rmv.664]

7 **Croen KD**. Latency of the human herpesviruses. *Annu Rev Med* 1991; **42**: 61-67 [PMID: 1852149 DOI: 10.1146/annurev.me.42.020191.000425]

8 **Stratta RJ**, Pietrangeli C, Baillie GM. Defining the risks for cytomegalovirus infection and disease after solid organ transplantation. *Pharmacotherapy* 2010; **30**: 144-157 [PMID: 20099989 DOI: 10.1592/phco.30.2.144]

9 **Razonable RR**. Epidemiology of cytomegalovirus disease in solid organ and hematopoietic stem cell transplant recipients. *Am J Health Syst Pharm* 2005; **62**: S7-13 [PMID: 15821266]

10 **George MJ**, Snydman DR, Werner BG, Griffith J, Falagas ME, Dougherty NN, Rubin RH. The independent role of cytomegalovirus as a risk factor for invasive fungal disease in orthotopic liver transplant recipients. Boston Center for Liver Transplantation CMVIG-Study Group. Cytogam, MedImmune, Inc. Gaithersburg, Maryland. *Am J Med* 1997; **103**: 106-113 [PMID: 9274893]

11 **Ljungman P**, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clin Infect Dis* 2002; **34**: 1094-1097 [PMID: 11914998 DOI: 10.1086/339329]

12 **Bansal N**, Arora A, Kumaran V, Mehta N, Varma V, Sharma P, Tyagi P, Sachdeva M, Kumar A. Atypical Presentation of Cytomegalovirus Infection in a Liver Transplant Patient. *J Clin Exp Hepatol* 2011; **1**: 207-209 [DOI: 10.1016/S0973-6883(11)60236-3]

13 **Humar A**, Snydman D. Cytomegalovirus in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S78-S86 [PMID: 20070700 DOI: 10.1111/j.1600-6143.2009.02897.x]

14 **Lautenschlager I**, Loginov R, Mäkisalo H, Höckerstedt K. Prospective study on CMV-reactivations under preemptive strategy in CMV-seropositive adult liver transplant recipients. *J Clin Virol* 2013; **57**: 50-53 [PMID: 23403239 DOI: 10.1016/j.jcv.2013.01.013]

15 **Arthurs SK**, Eid AJ, Pedersen RA, Dierkhising RA, Kremers WK, Patel R, Razonable RR. Delayed-onset primary cytomegalovirus disease after liver transplantation. *Liver Transpl* 2007; **13**: 1703-1709 [PMID: 18044717 DOI: 10.1002/lt.21280]

16 **Linares L**, Sanclemente G, Cervera C, Hoyo I, Cofán F, Ricart MJ, Pérez-Villa F, Navasa M, Marcos MA, Antón A, Pumarola T, Moreno A. Influence of cytomegalovirus disease in outcome of solid organ transplant patients. *Transplant Proc* 2011; **43**: 2145-2148 [PMID: 21839217 DOI: 10.1016/j.transproceed.2011.05.007]

17 **Montejo M**, Montejo E, Gastaca M, Valdivieso A, Fernandez JR, Testillano M, Gonzalez J, Bustamante J, Ruiz P, Suarez MJ, Ventoso A, Rubio MC, de Urbina JO. Prophylactic therapy with valgancyclovir in high-risk (cytomegalovirus D+/R-) liver transplant recipients: a single-center experience. *Transplant Proc* 2009; **41**: 2189-2191 [PMID: 19715869 DOI: 10.1016/j.transproceed.2009.06.005]

18 **Razonable RR**. Management strategies for cytomegalovirus infection and disease in solid organ transplant recipients. *Infect Dis Clin North Am* 2013; **27**: 317-342 [PMID: 23714343 DOI: 10.1016/j.idc.2013.02.005]

19 **Harvala H**, Stewart C, Muller K, Burns S, Marson L, MacGilchrist A, Johannessen I. High risk of cytomegalovirus infection following solid organ transplantation despite prophylactic therapy. *J Med Virol* 2013; **85**: 893-898 [PMID: 23508914 DOI: 10.1002/jmv.23539]

20 **Atabani SF**, Smith C, Atkinson C, Aldridge RW, Rodriguez-Perálvarez M, Rolando N, Harber M, Jones G, O'Riordan A, Burroughs AK, Thorburn D, O'Beirne J, Milne RS, Emery VC, Griffiths PD. Cytomegalovirus replication kinetics in solid organ transplant recipients managed by preemptive therapy. *Am J Transplant* 2012; **12**: 2457-2464 [PMID: 22594993 DOI: 10.1111/j.1600-6143.2012.04087.x]

21 **Razonable RR**, Humar A. Cytomegalovirus in solid organ transplantation. *Am J Transplant* 2013; **13** Suppl 4: 93-106 [PMID: 23465003 DOI: 10.1111/ajt.12103]

22 **Manuel O**, Kralidis G, Mueller NJ, Hirsch HH, Garzoni C, van Delden C, Berger C, Boggian K, Cusini A, Koller MT, Weisser M, Pascual M, Meylan PR. Impact of antiviral preventive strategies on the incidence and outcomes of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2013; **13**: 2402-2410 [PMID: 23914796 DOI: 10.1111/ajt.12388]

23 **Issa NC**, Fishman JA. Infectious complications of antilymphocyte therapies in solid organ transplantation. *Clin Infect Dis* 2009; **48**: 772-786 [PMID: 19207081 DOI: 10.1086/597089]

24 **Sampaio AM**, Guardia AC, Milan A, Sasaki AN, Andrade PD, Bonon SH, Stucchi RS, Botelho Costa SC, Boin IF. Co-infection and clinical impact of human herpesvirus 5 and 6 in liver transplantation. *Transplant Proc* 2012; **44**: 2455-2458 [PMID: 23026619 DOI: 10.1016/j.transproceed.2012.07.034]

25 **Katsolis JG**, Bosch W, Heckman MG, Diehl NN, Shalev JA, Pungpapong S, Gonwa TA, Hellinger WC. Evaluation of risk factors for cytomegalovirus infection and disease occurring within 1 year of liver transplantation in high-risk patients. *Transpl Infect Dis* 2013; **15**: 171-180 [PMID: 23331429 DOI: 10.1111/tid.12050]

26 **Brown RA**, Gralewski JH, Razonable RR. The R753Q polymorphism abrogates toll-like receptor 2 signaling in response to human cytomegalovirus. *Clin Infect Dis* 2009; **49**: e96-e99 [PMID: 19814623 DOI: 10.1086/644501]

27 **Kang SH**, Abdel-Massih RC, Brown RA, Dierkhising RA, Kremers WK, Razonable RR. Homozygosity for the toll-like receptor 2 R753Q single-nucleotide polymorphism is a risk factor for cytomegalovirus disease after liver transplantation. *J Infect Dis* 2012; **205**: 639-646 [PMID: 22219347 DOI: 10.1093/infdis/jir819]

28 **Kotton CN**, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L, Humar A. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 2013; **96**: 333-360 [PMID: 23896556 DOI: 10.1097/TP.0b013e31829df29d]

29 **Lisboa LF**, Asberg A, Kumar D, Pang X, Hartmann A, Preiksaitis JK, Pescovitz MD, Rollag H, Jardine AG, Humar A. The clinical utility of whole blood versus plasma cytomegalovirus viral load assays for monitoring therapeutic response. *Transplantation* 2011; **91**: 231-236 [PMID: 21048530 DOI: 10.1097/TP.0b013e3181ff8719]

30 **Marchetti S**, Santangelo R, Manzara S, D'onghia S, Fadda G, Cattani P. Comparison of real-time PCR and pp65 antigen assays for monitoring the development of Cytomegalovirus disease in recipients of solid organ and bone marrow transplants. *New Microbiol* 2011; **34**: 157-164 [PMID: 21617827]

31 **Martín-Gandul C**, Pérez-Romero P, Sánchez M, Bernal G, Suárez G, Sobrino M, Merino L, Cisneros JM, Cordero E. Determination, validation and standardization of a CMV DNA cut-off value in plasma for preemptive treatment of CMV infection in solid organ transplant recipients at lower risk for CMV infection. *J Clin Virol* 2013; **56**: 13-18 [PMID: 23131346 DOI: 10.1016/j.jcv.2012.09.017]

32 **Hirsch HH**, Lautenschlager I, Pinsky BA, Cardeñoso L, Aslam S, Cobb B, Vilchez RA, Valsamakis A. An internation-

al multicenter performance analysis of cytomegalovirus load tests. *Clin Infect Dis* 2013; **56**: 367-373 [PMID: 23097587 DOI: 10.1093/cid/cis900]
33 **Fryer J**, Heath AB, Anderson R, Minor PD; the Collaborative Study Group. Collaborative study to evaluate the proposed 1st [first] WHO international standard for human cytomegalovirus (HCMV) for nucleic acid amplification (NAT)-based assays. Geneva: World Health Organization, 2010: 40
34 **Hardie DR**, Korsman SN, Hsiao NY. Cytomegalovirus load in whole blood is more reliable for predicting and assessing CMV disease than pp65 antigenaemia. *J Virol Methods* 2013; **193**: 166-168 [PMID: 23792685 DOI: 10.1016/j.jviromet.2013.06.019]
35 **Bodro M**, Sabé N, Lladó L, Baliellas C, Niubó J, Castellote J, Fabregat J, Rafecas A, Carratalà J. Prophylaxis versus preemptive therapy for cytomegalovirus disease in high-risk liver transplant recipients. *Liver Transpl* 2012; **18**: 1093-1099 [PMID: 22532316 DOI: 10.1002/lt.23460]
36 **Bosch W**, Heckman MG, Diehl NN, Shalev JA, Pungpapong S, Hellinger WC. Association of cytomegalovirus infection and disease with death and graft loss after liver transplant in high-risk recipients. *Am J Transplant* 2011; **11**: 2181-2189 [PMID: 21827609 DOI: 10.1111/j.1600-6143.2011.03618.x]
37 **Onor IO**, Todd SB, Meredith E, Perez SD, Mehta AK, Marshall Lyon G, Knechtle SJ, Hanish SI. Evaluation of clinical outcomes of prophylactic versus preemptive cytomegalovirus strategy in liver transplant recipients. *Transpl Int* 2013; **26**: 592-600 [PMID: 23590709 DOI: 10.1111/tri.12101]
38 **Levitsky J**, Singh N, Wagener MM, Stosor V, Abecassis M, Ison MG. A survey of CMV prevention strategies after liver transplantation. *Am J Transplant* 2008; **8**: 158-161 [PMID: 17973961 DOI: 10.1111/j.1600-6143.2007.02026.x]
39 **Paya C**, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B, Freeman R, Heaton N, Pescovitz MD. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; **4**: 611-620 [PMID: 15023154 DOI: 10.1111/j.1600-6143.2004.00382.x]
40 **Park JM**, Lake KD, Arenas JD, Fontana RJ. Efficacy and safety of low-dose valganciclovir in the prevention of cytomegalovirus disease in adult liver transplant recipients. *Liver Transpl* 2006; **12**: 112-116 [PMID: 16382458 DOI: 10.1002/lt.20562]
41 **Brady RL**, Green K, Frei C, Maxwell P. Oral ganciclovir versus valganciclovir for cytomegalovirus prophylaxis in high-risk liver transplant recipients. *Transpl Infect Dis* 2009; **11**: 106-111 [PMID: 19054381 DOI: 10.1111/j.1399-3062.2008.00356.x]
42 **Fayek SA**, Mantipisitkul W, Rasetto F, Munivenkatappa R, Barth RN, Philosophe B. Valganciclovir is an effective prophylaxis for cytomegalovirus disease in liver transplant recipients. *HPB* (Oxford) 2010; **12**: 657-663 [PMID: 21083790 DOI: 10.1111/j.1477-2574.2010.00226.x]
43 **Kalil AC**, Mindru C, Botha JF, Grant WJ, Mercer DF, Olivera MA, McCartan MA, McCashland TM, Langnas AN, Florescu DF. Risk of cytomegalovirus disease in high-risk liver transplant recipients on valganciclovir prophylaxis: a systematic review and meta-analysis. *Liver Transpl* 2012; **18**: 1440-1447 [PMID: 22887929 DOI: 10.1002/lt.23530]
44 **Kalil AC**, Mindru C, Florescu DF. Effectiveness of valganciclovir 900 mg versus 450 mg for cytomegalovirus prophylaxis in transplantation: direct and indirect treatment comparison meta-analysis. *Clin Infect Dis* 2011; **52**: 313-321 [PMID: 21189424 DOI: 10.1093/cid/ciq143]
45 **Humar A**, Lebranchu Y, Vincenti F, Blumberg EA, Punch JD, Limaye AP, Abramowicz D, Jardine AG, Voulgari AT, Ives J, Hauser IA, Peeters P. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Am J Transplant* 2010; **10**: 1228-1237 [PMID: 20353469 DOI: 10.1111/j.1600-6143.2010.03074.x]
46 **Humar A**, Limaye AP, Blumberg EA, Hauser IA, Vincenti F, Jardine AG, Abramowicz D, Ives JA, Farhan M, Peeters P. Extended valganciclovir prophylaxis in D+/R- kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: two-year results of the IMPACT study. *Transplantation* 2010; **90**: 1427-1431 [PMID: 21197713]
47 **Sun HY**, Wagener MM, Singh N. Prevention of posttransplant cytomegalovirus disease and related outcomes with valganciclovir: a systematic review. *Am J Transplant* 2008; **8**: 2111-2118 [PMID: 18828771 DOI: 10.1111/j.1600-6143.2008.02369.x]
48 **Sun HY**, Cacciarelli TV, Wagener MM, Singh N. Preemptive therapy for cytomegalovirus based on real-time measurement of viral load in liver transplant recipients. *Transpl Immunol* 2010; **23**: 166-169 [PMID: 20609386 DOI: 10.1016/j.trim.2010.06.013]
49 **University of Pittsburgh**. Prophylaxis Versus Preemptive Therapy for the Prevention of CMV in Liver Transplant Recipients ('CAPSIL' Study). In: ClinicalTrialsgov [Internet]. Bethesda (MD): National Library of Medicine (US), 2000-2013. Available from: URL: http://clinicaltrials.gov/ct2/show/record/NCT01552369 NLM Identifier: NCT01552369
50 **Asberg A**, Humar A, Rollag H, Jardine AG, Mouas H, Pescovitz MD, Sgarabotto D, Tuncer M, Noronha IL, Hartmann A. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2007; **7**: 2106-2113 [PMID: 17640310 DOI: 10.1111/j.1600-6143.2007.01910.x]
51 **Kotton CN**, Kumar D, Caliendo AM, Asberg A, Chou S, Snydman DR, Allen U, Humar A. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation* 2010; **89**: 779-795 [PMID: 20224515 DOI: 10.1097/TP.0b013e3181cee42f]
52 **Asberg A**, Humar A, Jardine AG, Rollag H, Pescovitz MD, Mouas H, Bignamini A, Töz H, Dittmer I, Montejo M, Hartmann A. Long-term outcomes of CMV disease treatment with valganciclovir versus IV ganciclovir in solid organ transplant recipients. *Am J Transplant* 2009; **9**: 1205-1213 [PMID: 19422345 DOI: 10.1111/j.1600-6143.2009.02617.x]
53 **Limaye AP**, Corey L, Koelle DM, Davis CL, Boeckh M. Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. *Lancet* 2000; **356**: 645-649 [PMID: 10968438 DOI: 10.1016/S0140-6736(00)02607-6]
54 **Lurain NS**, Chou S. Antiviral drug resistance of human cytomegalovirus. *Clin Microbiol Rev* 2010; **23**: 689-712 [PMID: 20930070 DOI: 10.1128/CMR.00009-10]
55 **Owers DS**, Webster AC, Strippoli GF, Kable K, Hodson EM. Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst Rev* 2013; **2**: CD005133 [PMID: 23450558]
56 **Boivin G**, Goyette N, Gilbert C, Roberts N, Macey K, Paya C, Pescovitz MD, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B, Freeman R, Heaton N, Covington E. Absence of cytomegalovirus-resistance mutations after valganciclovir prophylaxis, in a prospective multicenter study of solid-organ transplant recipients. *J Infect Dis* 2004; **189**: 1615-1618 [PMID: 15116297 DOI: 10.1086/382753]
57 **Avery RK**. Management of late, recurrent, and resistant cytomegalovirus in transplant patients. *Trans Reviews* 2007; **21**: 65-76 [DOI: 10.1016/j.trre.2007.02.001]
58 **Marty FM**, Bryar J, Browne SK, Schwarzberg T, Ho VT, Bassett IV, Koreth J, Alyea EP, Soiffer RJ, Cutler CS, Antin JH, Baden LR. Sirolimus-based graft-versus-host disease prophylaxis protects against cytomegalovirus reactivation after allogeneic hematopoietic stem cell transplantation: a cohort analysis. *Blood* 2007; **110**: 490-500 [PMID: 17392502 DOI: 10.1182/blood-2007-01-069294]
59 **Jacob CL**, Lamorte L, Sepulveda E, Lorenz IC, Gauthier A, Franti M. Neutralizing antibodies are unable to inhibit direct viral cell-to-cell spread of human cytomegalovirus. *Virology* 2013; **444**: 140-147 [PMID: 23849792 DOI: 10.1016/j.virol.2013.06.002]
60 **Razonable RR**. Immune-based therapies for cytomegalovirus

infection. *Immunotherapy* 2010; **2**: 117-130 [PMID: 20635892 DOI: 10.2217/imt.09.82]
61 **Winston DJ**, Saliba F, Blumberg E, Abouljoud M, Garcia-Diaz JB, Goss JA, Clough L, Avery R, Limaye AP, Ericzon BG, Navasa M, Troisi RI, Chen H, Villano SA, Uknis ME. Efficacy and safety of maribavir dosed at 100 mg orally twice daily for the prevention of cytomegalovirus disease in liver transplant recipients: a randomized, double-blind, multicenter controlled trial. *Am J Transplant* 2012; **12**: 3021-3030 [PMID: 22947426 DOI: 10.1111/j.1600-6143.2012.04231.x]
62 **Marty FM**, Boeckh M. Maribavir and human cytomegalovirus-what happened in the clinical trials and why might the drug have failed? *Curr Opin Virol* 2011; **1**: 555-562 [PMID: 22440913 DOI: 10.1016/j.coviro.2011.10.011]
63 **Eid AJ**, Razonable RR. New developments in the management of cytomegalovirus infection after solid organ transplantation. *Drugs* 2010; **70**: 965-981 [PMID: 20481654 DOI: 10.2165/10898540-000000000-00000]
64 **Viro Pharma**. Maribavir for Treatment of Resistant or Refractory CMV Infections in Transplant Recipients. In: ClinicalTrialsgov [Internet]. Bethesda (MD): National Library of Medicine (US), 2000-2013. Available from: URL: http://clinicaltrials.gov/ct2/show/study/NCT01611974?term=maribavir&rank=1 NLM Identifier: NCT01611974
65 **Goldner T**, Hewlett G, Ettischer N, Ruebsamen-Schaeff H, Zimmermann H, Lischka P. The novel anticytomegalovirus compound AIC246 (Letermovir) inhibits human cytomegalovirus replication through a specific antiviral mechanism that involves the viral terminase. *J Virol* 2011; **85**: 10884-10893 [PMID: 21752907 DOI: 10.1128/jvi.05265-11]
66 **Marschall M**, Stamminger T, Urban A, Wildum S, Ruebsamen-Schaeff H, Zimmermann H, Lischka P. In vitro evaluation of the activities of the novel anticytomegalovirus compound AIC246 (letermovir) against herpesviruses and other human pathogenic viruses. *Antimicrob Agents Chemother* 2012; **56**: 1135-1137 [PMID: 22106211 DOI: 10.1128/aac.05908-11]
67 **Lischka P**, Hewlett G, Wunberg T, Baumeister J, Paulsen D, Goldner T, Ruebsamen-Schaeff H, Zimmermann H. In vitro and in vivo activities of the novel anticytomegalovirus compound AIC246. *Antimicrob Agents Chemother* 2010; **54**: 1290-1297 [PMID: 20047911 DOI: 10.1128/aac.01596-09]
68 **James SH**, Hartline CB, Harden EA, Driebe EM, Schupp JM, Engelthaler DM, Keim PS, Bowlin TL, Kern ER, Prichard MN. Cyclopropavir inhibits the normal function of the human cytomegalovirus UL97 kinase. *Antimicrob Agents Chemother* 2011; **55**: 4682-4691 [PMID: 21788463 DOI: 10.1128/aac.00571-11]
69 **Price NB**, Prichard MN. Progress in the development of new therapies for herpesvirus infections. *Curr Opin Virol* 2011; **1**: 548-554 [PMID: 22162744 DOI: 10.1016/j.coviro.2011.10.015]
70 **Florescu DF**, Pergam SA, Neely MN, Qiu F, Johnston C, Way S, Sande J, Lewinsohn DA, Guzman-Cottrill JA, Graham ML, Papanicolaou G, Kurtzberg J, Rigdon J, Painter W, Mommeja-Marin H, Lanier R, Anderson M, van der Horst C. Safety and efficacy of CMX001 as salvage therapy for severe adenovirus infections in immunocompromised patients. *Biol Blood Marrow Transplant* 2012; **18**: 731-738 [PMID: 21963623 DOI: 10.1016/j.bbmt.2011.09.007]
71 **Painter W**, Robertson A, Trost LC, Godkin S, Lampert B, Painter G. First pharmacokinetic and safety study in humans of the novel lipid antiviral conjugate CMX001, a broad-spectrum oral drug active against double-stranded DNA viruses. *Antimicrob Agents Chemother* 2012; **56**: 2726-2734 [PMID: 22391537 DOI: 10.1128/aac.05983-11]
72 **Papanicolau G**, Kurtzberg J, Westervelt P, Gea-Banacloche J, Warlick E, Lanier R, Anderson M, Painter W. Experience With CMX001, a Novel Antiviral Drug, for Cytomegalovirus infections in Stem Cell Transplant Patients. *Biol Blood Marrow Transplant* 2011; **17**: S273-S274
73 **Marty FM**, Winston D, Rowley SD, Boeckh M, Vance E, Papanicolaou G, Robertson A, Godkin S, Painter W. CMX001 for Prevention and Control of CMV Infection in CMV-Seropositive Allogeneic Stem-Cell Transplant Recipients: A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Trial of Safety, Tolerability and Antiviral Activity. *Biol Blood Marrow Transplant* 2012; **18**: S203-S204
74 **Chimerix**. A Study of the Safety and Efficacy for the Prevention of Cytomegalovirus (CMV) Infection in CMV-seropositive (R) Hematopoietic Stem Cell Transplant Recipients. Identifier: NCT01769170. In: ClinicalTrialsgov [Internet]. Bethesda (MD): National Library of Medicine (US), 2000-2013. Available from: URL: http://clinicaltrials.gov/ct2/show/study/NCT01769170?term=cmx001&rank=6 NLM
75 **James SH**, Price NB, Hartline CB, Lanier ER, Prichard MN. Selection and recombinant phenotyping of a novel CMX001 and cidofovir resistance mutation in human cytomegalovirus. *Antimicrob Agents Chemother* 2013; **57**: 3321-3325 [PMID: 23650158 DOI: 10.1128/aac.00062-13]
76 **Griffiths P**, Plotkin S, Mocarski E, Pass R, Schleiss M, Krause P, Bialek S. Desirability and feasibility of a vaccine against cytomegalovirus. *Vaccine* 2013; **31** Suppl 2: B197-B203 [PMID: 23598482 DOI: 10.1016/j.vaccine.2012.10.074]
77 **Dasari V**, Smith C, Khanna R. Recent advances in designing an effective vaccine to prevent cytomegalovirus-associated clinical diseases. *Expert Rev Vaccines* 2013; **12**: 661-676 [PMID: 23750795 DOI: 10.1586/erv.13.46]

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