Benefits of CMV Prophylaxis in Solid Organ Transplantation

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Abstract

Cytomegalovirus infection continues to be one of the leading causes of morbidity in transplant patients. Cytomegalovirus disease causes both direct and indirect effects, with special consideration being given to the latter in recent years. The indirect effects of cytomegalovirus disease include the viral syndrome and the symptoms resulting from direct invasion of the tissues by the virus. The indirect effects are due to the immunomodulation caused by the virus, resulting in an increased incidence of acute rejection, cardiovascular disease, and opportunistic infections. The two main strategies for preventing cytomegalovirus disease are universal prophylaxis and preemptive therapy, with ganciclovir and valganciclovir being the drugs that have shown the most efficacy. Numerous studies have been conducted to evaluate the efficacy of these two strategies. Prophylaxis appears to have shown greater efficacy than preemptive therapy for preventing the indirect effects of cytomegalovirus disease, while both strategies appear to be similar in terms of preventing direct effects. In recent years, late cytomegalovirus disease and the occurrence of ganciclovir-resistant cytomegalovirus strains have taken on special interest. Many issues are still unresolved, such as the most appropriate duration of prophylaxis or which strategy is most appropriate depending on the patient's risk of acquiring the disease. **(Trends in Transplant 2007;1:76-87)**

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Key words

Cytomegalovirus. Prophylaxis. Preemptive therapy. Indirect effects.

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Introduction

Cytomegalovirus (CMV) infection continues to be one of the leading causes of morbidity and mortality in solid organ transplantation[1,2], and can cause both direct and indirect effects in transplant patients. The direct effects, or CMV disease, are related to the presence of high rates of viral replication, and are caused by direct tissue damage. The indirect effects are independent of the level of viral replication. They result from the interaction of CMV with the host immune system and have acquired great importance in recent years[3,4]. These effects appear to be related to the presence of low levels of viral replication for prolonged periods. The indirect effects reported include an increased risk of acute and chronic rejection, mortality, and opportunistic infections (Fig. 1)[5]. Part of the indirect effects are mediated by CMV-induced immunosuppression, which leads to a dysfunction in lymphocytes and monocytes, altering their ability to produce cytokines and inverting the CD4/CD8 ratio[6]. Other indirect effects such as graft rejection may be mediated by CMV-induced mRNA synthesis in infected cells. This activation leads to an increased production of immunoglobulin receptors, intracellular adhesion molecules, and glycoproteins similar to major histocompatibility complex (MHC) class I antigens[4].

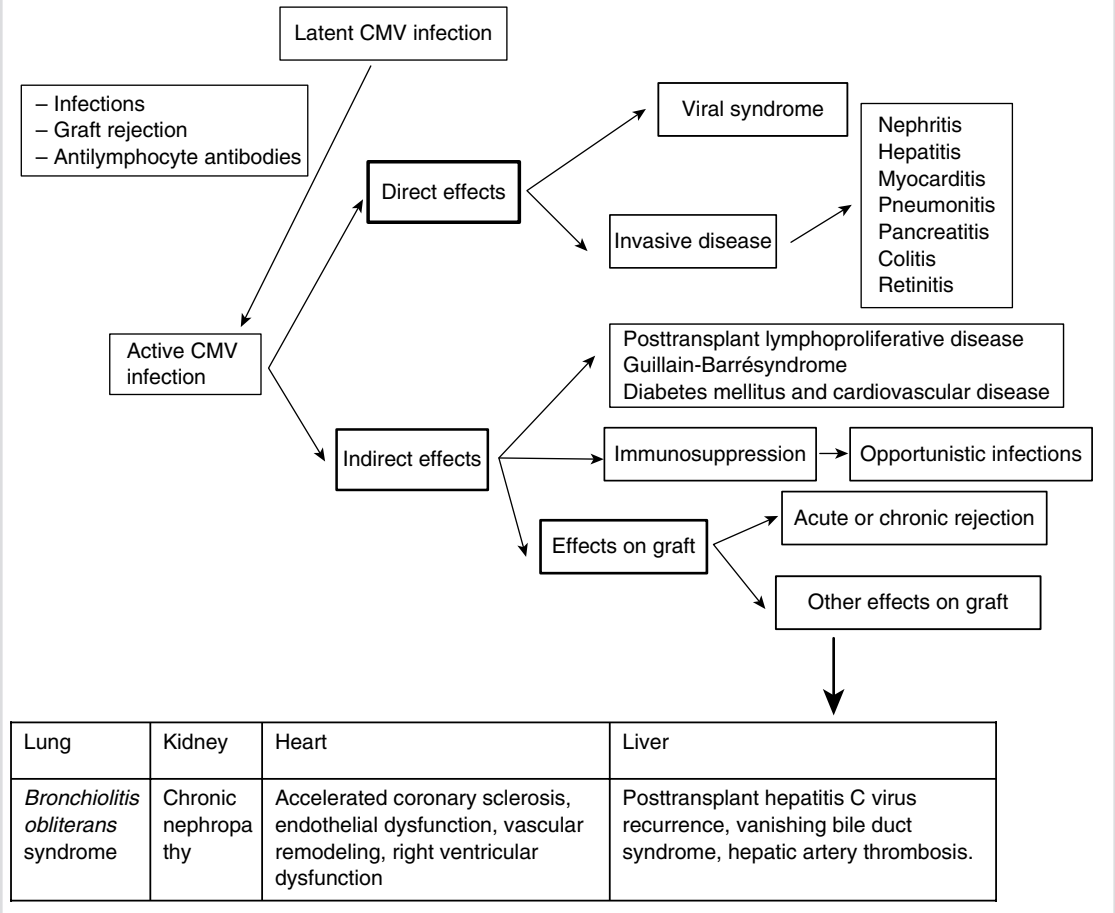
Effect of prophylaxis on CMV disease: universal prophylaxis versus preemptive therapy

There are two main strategies that can be used to prevent CMV disease: universal prophylaxis and preemptive therapy. Both strategies have advantages and limitations, and there is currently no conclusive data as to which should be used. Universal prophylaxis consists of administration of an active drug to all patients at risk of having CMV infection. Preemptive therapy consists of administration of an antiviral drug to patients with evidence of asymptomatic viral replication to prevent the development of symptoms (CMV disease). Although there are several marketed drugs that are effective against CMV (ganciclovir, valganciclovir, cidofovir, foscarnet, valacyclovir), these preventive strategies are currently based on the use of ganciclovir[2,7], either in its intravenous formulation or in the form of valganciclovir[8-10]. Oral bioavailability with this formulation is similar to that obtained with intravenous ganciclovir[11]. In high-risk heart transplant recipients (pretransplant serology: donor + and recipient –, D+/R–) and lung transplant recipients, the addition of CMV-specific immunoglobulins may increase the benefit obtained with ganciclovir[12-14].

There is numerous evidence showing that both universal prophylaxis and preemptive therapy are effective to prevent CMV disease[15,16]. A large number of studies have evaluated the efficacy of both strategies (Tables 1 and 2), including comparative studies of universal prophylaxis versus preemptive therapy (Table 3). However, there are doubts about the efficacy of preemptive therapy to prevent indirect effects because this strategy does not fully prevent viral replication[17]. In a recent meta-analysis that analyzed 17 trials with a total of 1980 patients[18], it was found that both universal prophylaxis and preemptive therapy were effective compared with placebo in preventing CMV disease. However, only universal prophylaxis was associated with a reduction in opportunistic infections and mortality (Table 4). In another meta-analysis, Hodson, et al.[19] showed the benefits of universal prophylaxis in preventing CMV disease, in reducing overall mortality, and in preventing numerous opportunistic infections (bacterial, protozoal, and viral) (Fig. 2).

Prevention of late CMV disease

The development of CMV disease beyond the first three months posttransplant



Lung	Kidney	Heart	Liver
Bronchiolitis obliterans syndrome	Chronic nephropa thy	Accelerated coronary sclerosis, endothelial dysfunction, vascular remodeling, right ventricular dysfunction	Posttransplant hepatitis C virus recurrence, vanishing bile duct syndrome, hepatic artery thrombosis.

Figure 1. *Direct and indirect effects of CMV* (adapted from Fishman, et al.[5] and Pérez-Sola, et al.[4]).

(late disease) after cessation of prophylaxis is a worrying phenomenon[20]. Its atypical presentation in periods when the patient is far from the transplant center can make diagnosis difficult. Some authors have related late-onset CMV disease with an alteration in immune reconstitution dependent on CMV-specific T lymphocytes against the virus during periods of universal prophylaxis[15,17,21,22]. However, the studies that attempted to confirm this hypothesis obtained contradictory results[23-26], and future investigations should clarify this issue.

We currently lack evidence to determine which is the best strategy to prevent the occurrence of late CMV disease. One option is to accept the risk and to treat CMV if it occurs. Another option is to complement the prophylaxis period with a protocol of virologic surveillance and preemptive therapy until the end of the first year posttransplantation. This option poses serious logistic problems in patients who live far from the transplant center. Furthermore, determination of viral load by polymerase chain reaction (PCR) has little predictive value after day +100 posttransplant[27]. Therefore, this strategy is probably most useful in patients at high risk of late disease such as D+/R– and lung transplant patients[22,28]. Objective criteria are currently being sought to define the risk of late disease, including the development of specific immu-

Table 1. Summary of the principal studies evaluating the efficacy of universal prophylaxis versus placebo or no treatment

Universal prophylaxis			
Author, year, organ	**Serological status, mean follow-up time, number of patients**	**Drugs**	**Results**
Balfour, 1989, kidney[71]	Any serological status, 1 year, 104	Acyclovir 84 days vs. placebo	Reduction in CMV disease. No reduction in overall or CMV mortality
Gavaldá, 1997, liver[72]	R+, 12 months, 73	Acyclovir 104 days vs. no intervention.	No reduction in CMV disease. No reduction in overall mortality
Saliba 1993, liver[73]	R+, 3 months, 120	Acyclovir 84 days vs. no intervention	Reduction in CMV disease
Cohen, 1993, liver[75]	R+, D+/R–, 18 months, 65	Ganciclovir 14 days vs. no intervention	No reduction in CMV disease or overall mortality was shown
Gane, 1997, liver[60]	Any serological status, 12 months, 304	Ganciclovir 88 days vs. placebo	A reduction in CMV disease was shown. No reduction in mortality for any cause or CMV mortality was shown
Merigan, 1992, heart[76]	R+, D+/R–, 4 months, 149	Ganciclovir 28 days vs. placebo	A reduction in CMV disease was shown. No reduction in mortality for any cause was shown
Lowance, 1999, kidney[47]	R+, D+/R–, 12 months, 616	Valacyclovir 87 days vs. placebo	A reduction in CMV disease was shown. No reduction in mortality for any cause or CMV mortality was shown
Flechnner, 1998, kidney[77]	R+, D+/R–, 12 months, 79	Oral ganciclovir vs. oral acyclovir 84 days	In D+, ganciclovir was more effective than acyclovir
Badley, 1997, liver[78]	Any serological status, 12 months, 167	IV ganciclovir 14 days + subsequent oral acyclovir vs. oral acyclovir 119 days	Ganciclovir + acyclovir was more effective to prevent CMV infection and disease than acyclovir alone in all groups
Martin, 1994, liver[79]	Any serological status, 6 months, 139	IV ganciclovir 14 days + subsequent oral acyclovir vs. oral acyclovir 84 days	In R+, a reduction in CMV disease was shown with the first strategy
Winston, 1995, liver[80]	Any serological status, 4 months, 99	IV ganciclovir vs. IV acyclovir + oral acyclovir 100 days	Prevention of CMV infection and disease was more effective in the first group
Winston, 2003, liver[81]	R+, 12 months, 219	IV ganciclovir 14 days + oral ganciclovir vs. IV ganciclovir 14 days + oral acyclovir 100 days	Prevention of CMV disease was superior in the first group
Paya, 2004, kidney, liver, heart, kidney-pancreas[7]	D+/R–, 12 months, 364	Oral valganciclovir vs. oral ganciclovir 90 days	There were no significant differences between the two groups (except for a higher incidence of CMV invasive organ disease in the valganciclovir group in liver transplant)
Duncan, 1994, lung[58]	R+, D+/R–, 12 months, 25	IV ganciclovir vs. IV ganciclovir 21 days + oral acyclovir 90 days	Greater reduction in CMV disease and *bronchiolitis obliterans* syndrome in the first group during the first year, with equal incidences at two years
Rubin, 2000, kidney, liver, heart[82]	D+/R–, 12 months, 155	IV ganciclovir 10 days + oral ganciclovir vs. IV ganciclovir 10 days + oral acyclovir 94 days	Prevention of CMV disease was more effective in the first group than in the second group
King, 1997, liver[83]	D+/R–, 6 months, 56	IV ganciclovir + IG vs. placebo + IG 4 weeks	No significant differences were found
Aguado, 1995, heart[84]	R+, 6 months, 31	IV ganciclovir 14 days vs. IG	The first group achieved a significant reduction in the incidence of CMV disease

CMV: cytomegalovirus; R+: cytomegalovirus seropositive recipient; D+: cytomegalovirus seropositive donor; R–: cytomegalovirus seronegative recipient; IV: intravenous; IG: cytomegalovirus-specific immunoglobulin.

Table 2. Summary of the principal studies evaluating the efficacy of preemptive therapy versus placebo or conventional therapy (treatment when the disease appears, without a prophylactic strategy)

Preemptive therapy			
Author, year, organ transplanted	**Serological status, mean follow-up time, number of patients**	**Drugs used**	**Results**
Hibberd, 1995, kidney[54]	R+, 6 months, 113	Ganciclovir 9 days after antithymocyte globulin vs. no treatment	A reduction in CMV disease was shown. No reduction in mortality for any cause or CMV mortality was shown
Torre-Cisneros, 2002, liver[85]	D+/R–, R+, 6 months, 64	Oral ganciclovir vs. no treatment 7 weeks	The first group showed a significant reduction in the incidence of CMV disease. There were no significant differences in mortality or rejection
Paya, 2002, liver[86]	R+, D+/R–, 4 months, 69	Oral ganciclovir 56 days vs. placebo	Preemptive use of ganciclovir significantly reduced the incidence of CMV disease, but not the incidence of acute rejection
Rayes, 2001, liver[87]	Any serological status, 4 months, 60	Oral ganciclovir 14 days vs. standard care	Preemptive therapy did not reduce the incidence of CMV disease
Brennan, 1997, kidney[74]	R+, D+/R–, 12-18 months, 36	IV ganciclovir 14 days vs. standard care	Preemptive therapy was not shown to significantly reduce the incidence of CMV disease, organ rejection or mortality compared to conventional therapy
Sagedal, 2003, kidney[88]	R+, D+/R–, 12 months, 80	Oral ganciclovir 27-70 days vs. standard care	Preemptive therapy significantly reduced the incidence of CMV disease compared to conventional therapy. There were no differences in late disease, mortality or rejection between both groups

CMV: cytomegalovirus; R+: cytomegalovirus seropositive recipient; D+: cytomegalovirus seropositive donor; R–: cytomegalovirus seronegative recipient.

Table 3. Summary of the principal studies evaluating the efficacy of preemptive therapy versus universal prophylaxis

Preemptive therapy vs. universal prophylaxis			
Author, year, organ transplanted	**Serological status, mean follow-up time, number of patients**	**Drugs used**	**Results**
Singh 1994, liver[89]	Any serological status, 6 months, 47	IV ganciclovir 7 days (preemptive therapy) vs. oral acyclovir 168 days (universal prophylaxis)	The group with preemptive therapy showed a significant reduction in CMV disease compared to group with acyclovir prophylaxis
Khoury, 2006, kidney[90]	R+, D+/R–, 12 months, 98	Oral valganciclovir 21 days (preemptive therapy) vs. oral valganciclovir 100 days (universal prophylaxis)	No differences were found in the incidence of CMV disease. Higher incidence of late viremia in the prophylaxis group
Jung, 2001, kidney[91]	Any serological status, 12 months, 70	Oral ganciclovir 14 days (preemptive therapy) vs. oral ganciclovir 90 days (universal prophylaxis)	No significant differences were found between both groups

IV: intravenous; R+: cytomegalovirus seropositive recipient; D+: cytomegalovirus seropositive donor; R–: cytomegalovirus seronegative recipient.

Table 4. Results of the meta-analysis performed by Kalil, et al.[18]

	CMV organ disease	CMV organ disease in D+/R–	CMV organ disease in patients treated with anti-lymphocyte antibodies	Graft rejection	Death	Bacterial and fungal infections
Universal prophylaxis	OR: 0.20 (95% CI: 0.13-0.31)	81% reduction (95% CI: 60-90%)	80% reduction (95% CI: 56-91%)	OR: 0.74 (95% CI: 0.59-0.94)	OR: 0.62 (95% CI: 0.40-0.96)	51% reduction (95% CI: 33-64%)
Preemptive therapy	OR: 0.28 (95% CI: 0.11-0.69)	64% reduction (95% CI: 92% reduction – 52% increase)	56% reduction (95% CI: 86% reduction – 41% increase)	OR: 0.47 (95% CI: 0.24-0.91)	OR: 0.94 (95% CI: 0.32-2.76)	No significant reduction

OR: odds ratio; CI: confidence interval; R+: cytomegalovirus seropositive recipient; D+: cytomegalovirus seropositive donor; R–: cytomegalovirus seronegative recipient; CMV: cytomegalovirus.

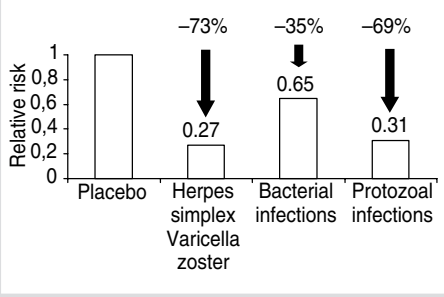


Figure 2. *Effect of CMV prophylaxis on concomitant infections* (adapted from Hodson, et al.[19]).

nity or the production of gamma interferon[29]. However, a study has shown that seroconversion during the prophylaxis period is not predictive of late CMV disease[30]. Finally, we cannot exclude the possibility of extending prophylaxis until six months post-transplantation[31]. This practice is widely used in many lung transplant groups[32,33]. Other authors think that it is not justified in lower-risk patients, arguing that it only serves to delay the onset of CMV disease. The results of an ongoing clinical trial (Impact Study) where valganciclovir is used in D+/R– kidney transplant recipients may be useful to test this hypothesis.

Effect of universal prophylaxis on the development of resistance

There is some concern over the possibility that prolonged use of ganciclovir may increase the emergence of CMV strains resistant to the drug. Although we cannot ignore the fact that resistant strains are a real problem, current evidence suggests that it is a rare phenomenon, especially when valganciclovir is used. This was shown in the virologic analyses of a comparative study of valganciclovir versus ganciclovir in D+/R– patients[7], and also in another large prospective multicenter study, where CMV resistant strains only caused 2-3%

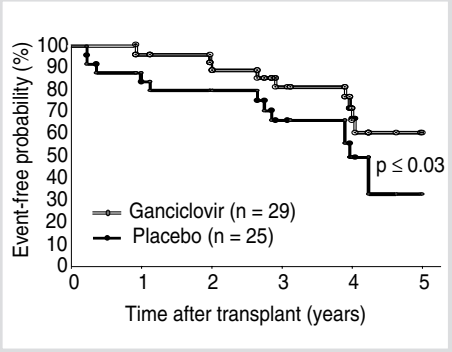


Figure 3. *Incidence of cardiovascular events in patients not treated with calcium blockers* (adapted from Valantine, et al.[39]).

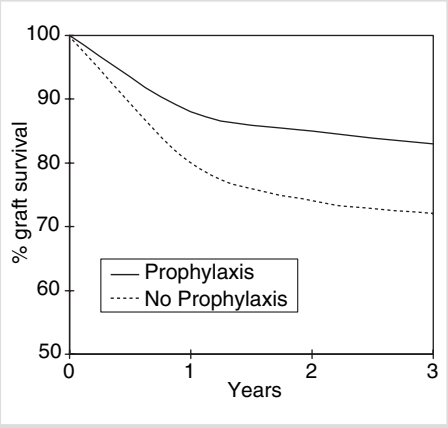


Figure 4. *Effect of CMV prophylaxis on cardiac graft survival in D+/R– patients. D+: cytomegalovirus seropositive donor; R–: cytomegalovirus seronegative recipient* (adapted from Opelz, et al.[41]).

of all cases of CMV disease in patients receiving valganciclovir prophylaxis[34].

This low incidence of resistance development in patients treated with valganciclovir could be explained by the higher drug exposure existing in patients treated with this drug at the doses established in the pivotal studies (900 mg every 24 hours)[34,35].

Effect of prophylaxis on the indirect effects of CMV infection

Heart transplant

Cytomegalovirus infection in heart transplant recipients has been associated with the development of cardiac allograft vasculopathy, decreased survival, and an increased incidence of lung infections. However, CMV prophylaxis is able to reduce the incidence of some of these effects[36-38].

In the *post hoc* analysis of a randomized, placebo-controlled trial, ganciclovir prophylaxis was shown to significantly reduce the relative risk of cardiac allograft vasculopathy after 4.7 years of follow-up in transplant patients who did not receive calcium blockers[39] (Fig. 3). There are doubts about the benefit provided by combined use of CMV-specific immunoglobulin in ganciclovir prophylaxis, although there are data supporting this practice[40]. Combined use of ganciclovir and immunoglobulin has been shown to reduce the incidence of rejection and increase survival at three years compared to ganciclovir alone[38]. Bonaros, et al.[37] also showed a significant reduction in CMV-associated mortality, cardiac allograft vasculopathy, and infections in general when prophylaxis with immunoglobulin plus ganciclovir was compared with immunoglobulin alone. Opelz, et al. also found a beneficial effect on graft survival in patients who received CMV prophylaxis[41] (Fig. 4).

Kidney transplant

Numerous studies have found an association between CMV infection and the development of acute or chronic rejection and cardiovascular disease[42-48]. In addition, CMV infection has been associated with an increased incidence of mortality and diabetes and a reduction in graft survival[43]. Death from

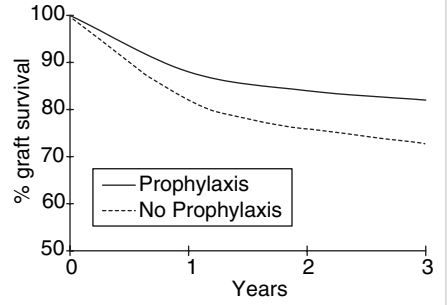


Figure 5. *Effect of CMV prophylaxis on kidney graft survival in D+/R– patients. D+: cytomegalovirus seropositive donor; R–: cytomegalovirus seronegative recipient* (adapted from Opelz, et al.[41]).

a cardiovascular cause was significantly higher in CMV-seropositive patients in a single-center retrospective study[45]. In another retrospective study, CMV disease was a risk factor for developing myocardial infarction or arrhythmias[46].

Valacyclovir prophylaxis may reduce the risk of biopsy-proven acute rejection in seronegative patients[47]. The beneficial impact of CMV prophylaxis on survival in patients older than 60 years observed in the study by Opelz, et al. was also striking. This author observed a survival rate at three years after transplantation of 83% in the 5426 patients who received prophylaxis versus 71% in the 2908 who received no prophylaxis ($p = 0.0008$)[41] (Fig. 5). A recent study has shown that the incidence of acute rejection in patients who received prophylaxis with ganciclovir was lower than in those who received acyclovir or no prophylaxis[49]. This reduction in the incidence of acute rejection may be related to an immunomodulatory effect associated with the use of certain antiviral drugs[50-52].

In a study of 36 renal transplant patients at high risk of CMV disease[53], preemptive therapy was not associated with a reduction in mortality or in the incidence of acute rejection compared to conventional therapy (treatment if symptoms appear). In a trial that compared the use of preemptive therapy with ganciclovir versus no treatment in patients who had received antithymocyte globulin, no significant differences were found in the incidence of death or opportunistic infections[54].

Pancreas-kidney transplant

Most pancreas-kidney transplant groups perform aggressive prophylaxis of CMV infection[2]. This means that there are no control groups in which to demonstrate a beneficial effect of prophylaxis on the incidence of acute rejection. Perhaps the best evidence can be obtained from a multicenter study of 205 pancreas-kidney transplant recipients between 1998 and 2000, which showed a significant increase in rejection-free survival at three years in patients who received prophylaxis with ganciclovir versus those who received acyclovir or no prophylaxis (61.4 vs. 42.4%; $p < 0.001$)[49,55].

Lung transplant

Lung transplantation has the highest risk of CMV infection[56]. Despite the prophylactic strategies developed, mortality associated with CMV remains significant[57]. *Bronchiolitis obliterans* syndrome, frequently associated with CMV infection, is one of the major causes of morbidity and mortality. Cytomegalovirus prophylaxis has been shown to reduce the incidence of rejection and *bronchiolitis obliterans* syndrome[5,57]. Ruttmann, et al., in a study of 68 high-risk lung transplant recipients (D+/R–, D+/R+), found a significant reduction in overall and specific mortality, CMV disease, rejection, and *bronchiolitis obliterans* syndrome, when the use of ganciclovir plus CMV-specific hyperimmune globu-

lin was compared with ganciclovir alone[57] (Table 5). Because of the high incidence of late replication, prolonged periods of prophylaxis may be required to show the beneficial effects on rejection.

In a study comparing universal prophylaxis with ganciclovir versus acyclovir[58], a lower incidence of *bronchiolitis obliterans* syndrome was found in the first group in the first year posttransplant, but this incidence was later equal in both groups.

Liver transplant

Although liver transplantation is considered to have an intermediate risk of CMV disease, it has been used as a model to show the relationship between viral reactivation and the occurrence of opportunistic infections, primarily bacterial and fungal[59]. The CMV infection has also been associated with increased mortality in these patients[60]. This virus has been associated with vanishing bile duct syndrome, which in turn increase the risk of fibrosis and graft dysfunction. The relationship between CMV infection and the development of chronic rejection in liver transplant patients is well known[61]. The possibility that CMV replication may accelerate the progression of posttransplant HCV reinfection cannot be excluded, although studies are needed to confirm this hypothesis because the results of some of the studies conducted to date are contradictory[62-65,92-94].

Cytomegalovirus prophylaxis has been shown to reduce the incidence of biopsy-proven chronic rejection[66] and to increase long-term graft survival[67]. In addition, the results of some studies provide evidence of the impact of prophylaxis of CMV infection on patient survival. In one of these studies[60], a randomized, placebo-controlled study, patients in the placebo group showed higher mortality than those who received oral ganciclovir.

Table 5. Results of study published by Ruttmann, et al.[57]

	Survival at 1 year	Survival at 3 years	CMV disease	CMV death	Absence of rejection at 1 year	Absence of rejection at 3 years	Absence of BOS at 1 year	Absence of BOS at 3 years
Ganciclovir	63.3%	40.0%	43.3%	16.7%	41.7%	35.8%	69.7%	54.3%
Ganciclovir + CMV-IG	81.6%	71.5%	13.2%	0.0%	52.5%	49.0%	91.0%	82.0%
	p = 0.013		p = 0.007	p = 0.014	p = 0.33		p = 0.024	

CMV: cytomegalovirus; CMV-IG: cytomegalovirus-specific immunoglobulin; BOS: Bronchiolitis obliterans syndrome.

Other benefits of CMV prophylaxis

There are studies that have observed a reduction in the incidence of human herpesvirus 6, 7, and 8, varicella zoster virus, and Epstein-Barr virus in patients who received CMV prophylaxis[68]. In an analysis of renal transplant patients that compared 108 post-transplant lymphoproliferative disease (PTLD) cases with 404 controls, prophylaxis with ganciclovir was associated with a significant reduction in PTLD risk. These effects were not shown when acyclovir was used[50]. Correct prophylaxis of CMV infection is currently considered one of the mainstays for prevention of PTLD in high-risk patients.

Some studies have found an association between seropositivity for CMV and a higher prevalence of type 2 diabetes mellitus[69] and atherosclerosis in patients with diabetes mellitus[70]. Cytomegalovirus prophylaxis may have a potential role in the prevention of diabetes mellitus in selected patients.

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