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CMV Infection in CMV-Seropositive Kidney Transplant Recipients

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1. Introduction

Cytomegalovirus (CMV) infection is a major cause of morbidity in kidney transplant recipients. CMV seropositivity is common in the general population, with a reported prevalence ranging from 30 to 97% (Paya, 2001; Preiksaitis et al., 2005). After primary infection, CMV establishes life-long latency. During the past 2 decades, major advances in the management of CMV infection of transplant patients have been achieved with new diagnostic techniques and the use of antiviral agents.

Most transplant centers have protocols for the diagnosis and monitoring of CMV, while strategies for the treatment of clinically significant infections as well as prophylactic and preemptive therapy have become common practice. Such strategies address both clinically significant disease and the indirect effects of CMV infection, increased risk of allograft rejection and other infections.

Several guidelines been published within the last few years regarding the management of CMV in transplant patients, diagnostic procedures, and prevention by prophylaxis or preemptive therapy.

The following definitions are commonly used in the transplant literature and are consistent with the American Society of Transplantation (AST) and The Transplantation Society (TTS) recommendations for use in clinical trials (Humar & Michaels, 2006; Kotton et al., 2010):

- CMV infection: evidence of CMV replication regardless of symptoms
- CMV disease: evidence of CMV infection with attributable symptoms. CMV disease can be further categorized as either a viral syndrome with fever and/or malaise, leucopenia, and thrombocytopenia, or as tissue-invasive disease (e.g., pneumonitis, hepatitis, retinitis, and gastrointestinal disease).

A number of review articles on CMV-associated problems in kidney transplantation can aid the clinician working with these patients. These reviews include information on its clinical signs and symptoms, indirect effects, diagnosis, prevention, and treatment protocols. However, the manifestations of CMV infection vary among patients, in part depending on their CMV serostatus. In fact, the prevalence, clinical manifestations, and effects of CMV depend on the patient's serostatus. In this overview, we summarize the current status of CMV, focusing primarily on adult kidney transplant patients who are CMV donor positive/recipient positive (CMV D+/R+).

2. Epidemiology and pathogenesis

CMV is a widespread pathogen that causes an asymptomatic or mild mononucleosis-like primary infection, which usually occurs in early childhood or adolescence. The prevalence of CMV seropositivity ranges from 40 to 100% worldwide, with lower rates in Europe, parts of North America, and Australia, and higher rates in Africa and Asia (Ho, 1990). In regions with higher rates of CMV seropositivity, rates of CMV disease after kidney transplantation may be lower, as populations with immunity to CMV are less likely to have active disease (Kanter et al., 2009).

Like other herpes viruses, CMV can establish latency. After primary infection, the virus may persist at specific sites in the host without any detectable viral infection (Sinclair & Sissons, 2006). Sporadic reactivation events may occur, but they are generally controlled by cell-mediated immunity, cytotoxic T-cells, and NK cells. Blood leukocytes, and mononuclear cells in particular, are generally the sites of latency, but viral DNA has been detected in bone marrow hematopoietic progenitors, epithelial cells, and endothelial cells.

The latent virus can thus be easily transmitted from a transplant donor to recipient by either the leukocytes, or possibly even tissue cells, of the kidney. Transplant patients' cell-mediated immunity is impaired and cannot control the virus, resulting in reactivation of the donor virus in CMV-seronegative recipients without immunity to CMV (D+/R-), as well as in CMV-seropositive (R+). Other recipients undergo reactivation of their own latent virus. CMV is thought to be a risk factor for other viral infections, as well as invasive fungal and bacterial infections in transplant recipients (Fishman & Rubin, 1998).

Without prophylaxis, CMV infections occur in the majority of kidney transplant patients, primarily during the first 3 months, when immunosuppression is most powerful. The risk factors for CMV disease in transplant recipients include CMV seropositive donor/CMV seronegative recipient (D+/R-) and the intensity of immunosuppressive therapy. It has been reported that CMV donor positive/recipient positive status was not a risk factor for CMV replication or disease in kidney transplant recipients (Bataille et al., 2010).

3. Clinical impact of CMV infection

3.1 Direct effects

Symptoms of CMV disease are largely nonspecific, such as fever, fatigue, body aches, and myelosuppression. In some patients, CMV disease is manifested as tissue-invasive disease. The gastrointestinal tract is the most common site for tissue-invasive CMV disease, independent of the type of allograft transplant (Faure-Della Corte et al., 2010), which can cause abdominal pain and diarrhea. In severe cases, CMV ulceration of the gastrointestinal tract can lead to hemorrhage and perforation. Other organs that may manifest tissue-invasive disease include the liver, lungs, heart, pancreas, and kidneys, and may present with allograft dysfunction easily misdiagnosed as acute or chronic rejection (Couzi et al., 2010).

3.2 Indirect effects

CMV is associated with a variety of indirect effects due to the virus' ability to modulate the immune system (Couzi et al., 2010). Kidney transplant recipients with CMV infection or disease are more likely to develop opportunistic infections from other viruses (e.g., human herpesvirus [HHV]-6, HHV-7, and Epstein-Barr virus-related post-transplant lymphoproliferative disease) (Razonable & Paya, 2003; Razonable et al., 2003), bacteria (e.g.,

Nocardia spp.) (Peleg et al., 2007), and fungi (Husni et al., 1998). In addition to infections, patients with CMV infection are more likely to experience acute and chronic rejection. CMV infection has also been described as an independent risk factor for atherosclerosis in kidney transplant recipients (Hodson et al., 2005). In addition, new-onset diabetes mellitus has been reported in patients with CMV infection or disease after kidney transplantation (Hartmann et al., 2006; Rodrigo et al., 2006). Research has shown that the development of γ - δ T cells in response to CMV is associated with a lower risk of malignancy after kidney transplantation (Couzi et al., 2010). CMV infection is associated with a higher rate of allograft failure and death in kidney transplant recipients, in part due to increased opportunistic infections as well as acute and chronic allograft rejection (Razonable & Paya, 2003; Sagedal et al., 2007). In one study, CMV persistence in the allograft was associated with reduced allograft function and survival after kidney transplantation (Helantera et al., 2006). In regard to treatment, primary antiviral prophylaxis appears to be more effective in preventing the indirect effects of CMV than pre-emptive therapy (Hodson et al., 2005; Kalil et al., 2005).

4. Diagnosis

The diagnosis of CMV infection and disease has evolved considerably. Historically, the diagnosis of CMV disease was made by histopathology, which requires an invasive procedure to obtain samples. Serologic assays appear to have limited clinical utility after transplantation, and should not be used to diagnose acute disease in kidney transplant recipients (Humar et al., 2005).

For years, culture-based methods (tissue culture and shell vial centrifugation culture) were used for CMV diagnosis. Tissue cultures can take weeks, however, and the shell vial centrifugation assay is less sensitive than molecular assays (Mazzulli et al., 1999). Nonetheless, tissue cultures are useful to grow CMV isolates in the laboratory for phenotypic antiviral resistance testing, although the latter technique has been replaced predominantly by genotypic resistance testing.

The pp65 antigenemia assay is a semi-quantitative fluorescent assay based on detection of infected cells in the peripheral blood. This assay has far higher sensitivity and specificity than culture-based methods (Mazzulli et al., 1999), and is comparable in sensitivity to CMV PCR (Caliendo et al., 2000). Though not fully quantitative, it can provide an estimate of the magnitude of viral load from the number of infected cells. Molecular diagnostic tests detect DNA or RNA, are qualitative and quantitative, and the majority are highly sensitive for CMV.

Quantitative measurement of CMV-DNA levels has become popular at many centers. Commonly used assays include PCR testing of plasma or whole blood, which is commercially available. Whole blood assays often have higher viral loads than plasma assays. In general, the highest viral loads are associated with tissue-invasive disease, while the lowest are seen with asymptomatic CMV infection (Kim et al., 2011). In addition to the absolute value of viral load, the rate of rise is also an important factor (Emery et al., 2000). Of note, it is possible for patients with tissue invasive disease (especially gastrointestinal or retinal disease) to occasionally have undetectable blood viral loads.

Both the pp65 antigenemia assay and quantitative CMV viral load testing can be utilized in preemptive protocols, to diagnose of CMV disease, and to guide management (Caliendo et al., 2000; Emery et al., 2000; Kim et al., 2011). A major problem of these assays is the lack of

standardization. A recent multicenter comparison of viral load assays demonstrated up to a 1000 folds variation among them. Standardization may be achieved in the future with quantitative viral load assays (Pang et al., 2003).

5. Antiviral prophylaxis and preemptive therapy

There are very few randomized trials comparing preemptive therapy with prophylaxis in the prevention of CMV in kidney transplant recipients with CMV D+/R+ status. Reasons for this include variation among transplant programs, different end-point definitions, non-standardized testing methodologies, and different patient populations.

Two strategies are commonly used for CMV prevention: antiviral prophylaxis and preemptive therapy. Antiviral prophylaxis involves giving antiviral therapy to all 'at-risk' patients (or a specified subset) beginning in the early post transplant period for a defined duration, such as 3 to 6 months. In preemptive therapy, patients are monitored regularly by laboratory assay (often weekly) for early evidence of CMV replication. Patients with detectable replication are then treated with antiviral therapy to prevent symptomatic disease.

Each approach has advantages and disadvantages that must be considered in the context of the patient and the allograft (Table 1) (Fishman et al., 2007; Torres-Madriz & Boucher, 2008). Preemptive therapy may decrease drug costs and toxicity, but requires excellent logistic coordination in order to obtain, receive, and act on results in a timely fashion, which can be difficult if patients live far from the transplant center. In addition, due to a lack of standardized diagnostic testing, optimal threshold values for the initiation of preemptive therapy have not been defined. Antiviral prophylaxis has the theoretical advantage of preventing reactivation of other viruses such as HHV-6 and may thus be more likely to prevent the indirect effects of CMV. Meta-analyses have demonstrated that antiviral prophylaxis is associated with decreased graft loss, decreased opportunistic infections, and improved survival (Kalil et al., 2005; Small et al., 2006). Late-onset CMV disease is a potential limitation of prophylaxis.

	Prophylaxis	Preemptive therapy
Efficacy	Yes	Yes
Ease	Relatively ease to coordinate	More difficult to coordinate Test thresholds not Standardized
Late onset disease	A potential problems	Much less commonly seen
Cost	Higher drug costs	Higher laboratory costs
Toxicity	Potential for greater toxicity (myelosuppression)	Potential for less drug toxicity with shorter courses of antivirals
Indirect effects (e.g. graft loss, mortality, and opportunistic infections)	Consistent and positive impact based on meta-analyses and limited comparative trials	Very limited data that preemptive therapy affects indirect effects

Table 1. Prophylaxis versus preemptive therapy.

5.1 Antiviral prophylaxis

Drugs that have been evaluated for antiviral prophylaxis include ganciclovir, valganciclovir, acyclovir, valacyclovir, and immune globulin preparations (Table 2). All doses should be adjusted based on renal function. Ganciclovir is available in both oral and intravenous formulations. The literature contains several large, multicenter, randomized trials of prophylaxis with oral ganciclovir, valganciclovir, and valacyclovir (Hodson et al., 2008). Valganciclovir is a valine ester pro-drug of ganciclovir with better bioavailability (50–60%) than oral ganciclovir (6–9%) (Perrottet et al., 2009).

Acyclovir has less activity against CMV and is not recommended specifically for prophylaxis. The efficacy of prophylaxis with either CMV immune globulin (CMVIG) or intravenous immune globulin (IVIG) in kidney organ transplant recipients has been investigated in relatively few trials (Hodson et al., 2007), the majority of which have been randomized, but not blinded. Further research is needed to delineate the benefit of adding immune globulin to current CMV prophylaxis regimens.

Drug	Usual adult prophylaxis dose	Comments on use and major toxicity
Valganciclovir	900mg once daily	Ease on administration; leukopenia
Oral ganciclovir	1g three times daily	Low oral bioavailability; high pill burden
IV ganciclovir	5mg/kg once daily	Intravenous access; leucopenia
Valacyclovir	2g four times daily	High pill burden; neurological effects

Table 2. Currently available drugs for CMV prophylaxis.

5.1.1 Late onset CMV disease

The major problem with CMV prophylaxis continues to be late-onset CMV disease, defined as disease occurring after discontinuation of antiviral prophylaxis. For 3-month prophylaxis regimens, this typically occurs between 3 and 6 months post transplant, but occasionally occurs later. Late onset CMV disease can be difficult to diagnose, especially in patients who live far away from their primary transplant program. Late onset CMV disease contributes to morbidity and has been associated with higher overall mortality (Limaye et al., 2004).

Potential options for dealing with late-onset CMV disease are as follows: (1) careful clinical follow-up with treatment as soon as symptoms occur, and (2) virologic monitoring after completion of prophylaxis, such as periodic measurement of antigenemia or viral load for 8 to 12 weeks. However, studies evaluating the utility of post-prophylaxis monitoring have demonstrated poor sensitivity and specificity in predicting CMV disease (Humar et al., 2004). Weekly monitoring may be required to increase sensitivity.

5.2 Preemptive therapy

Preemptive therapy involves monitoring for early evidence of CMV replication followed by early treatment to prevent symptomatic disease (Paya, 2001; Preiksaitis et al., 2005). Preemptive therapy has the potential advantage of targeting patients at higher risk, thereby decreasing drug costs and toxicity. A sound preemptive strategy includes careful selection of the patient, the optimal laboratory test, the duration of monitoring, and the type, dose, and duration of an antiviral agent.

The best laboratory test to monitor is either a viral load test or a pp65 antigenemia assay. Site-specific and assay-specific threshold values for initiation of preemptive therapy should be locally validated prior to institution of a preemptive protocol. The optimal monitoring strategy is approximately once weekly testing for 12 weeks post transplant.

Once viremia is detected, treatment should be initiated with either oral valganciclovir (900 mg twice a day) or intravenous ganciclovir (5 mg/kg twice a day). Therapy should be continued until viremia is undetectable. A randomized trial found that these agents had equal efficacy for treatment of mild to moderate CMV disease (Asberg et al., 2007). As the aim of preemptive therapy is to treat low-level asymptomatic viremia, oral valganciclovir is preferable to intravenous ganciclovir for logistical issues. Further studies are required to determine comparative efficacy of preemptive therapy versus prophylaxis, especially regarding the indirect sequelae of CMV.

5.3 Comparison of antiviral prophylaxis and preemptive therapy

Only relatively small trials have compared universal prophylaxis with preemptive therapy. In a study comparing oral ganciclovir prophylaxis with preemptive intravenous ganciclovir in kidney transplant patients, prophylaxis reduced the incidence of CMV infection over 12 months by 65% (13/73 versus 33/65 patients) and improved 4-year graft survival (Kliem et al., 2008). A trial of 98 kidney transplant patients randomly assigned to preemptive therapy or prophylaxis with valganciclovir for 100 days showed that both strategies were effective in preventing symptomatic CMV infection (Khoury et al., 2006). Another study that compared preemptive therapy with universal prophylaxis found significantly higher rates of biopsy-proven acute rejection in the preemptive therapy group (Reischig et al., 2008).

Recently, 2 studies reported directly opposed results in CMV-seropositive kidney transplant recipients receiving antiviral prophylaxis or preemptive treatment with valganciclovir. One study found no difference between groups in the incidence of CMV syndrome (4% vs. 5%; $P=0.67$), CMV disease (0% vs. 2%; $P=0.45$), or acute rejection (10% vs. 5%, $P=1.00$) (McGillicuddy et al., 2010). The other study found that CMV reactivation 1 year post-transplant in 67.4% and 28% of preemptive and prophylactic groups, respectively ($P<0.001$). In addition, the study found a significantly greater incidence of CMV disease in the preemptive group than in the prophylactic group (9.8% vs. 2.68%, $P=0.021$) (Weclawiak et al., 2010). Several meta-analyses found that although preemptive therapy was effective in reducing the relative risk of CMV, all-cause mortality was not altered (Hodson et al., 2005; Kalil et al., 2005; Small et al., 2006).

Guidelines regarding prophylaxis management favor the use of prophylaxis over preemptive therapy in intermediate-risk, CMV-seropositive transplant recipients, based on the available data suggesting better graft survival and clinical outcomes. (Humar & Michaels, 2006; Kotton et al., 2010) Individual transplant centers must weigh the risks and benefits of each approach, based on the frequency of CMV disease in their center, their ability to monitor recipients, cost of antiviral medications and diagnostics, local rates of late onset CMV disease, and the incidence of other opportunistic infections, graft loss, rejection, and mortality.

6. Treatment of established CMV disease

Intravenous ganciclovir has been used to successfully treat CMV disease in kidney transplant recipients in over 30 uncontrolled, non-randomized, therapeutic trials (Preiksaitis et al., 2005) and is has been considered the mainstay of therapy. The typical dose of

intravenous ganciclovir is 5 mg/kg twice daily. The duration of therapy in trials varied from 2 to 4 weeks. Valganciclovir at a dose of 900 mg twice daily achieves levels similar to intravenous ganciclovir treatment. In a randomized controlled trial comparing 3 weeks of oral valganciclovir to intravenous ganciclovir for the treatment of mild to moderate CMV disease in 321 organ transplant patients, the vast majority of whom were kidney transplant recipients, both drugs had similar efficacy for the eradication of viremia 21 days post-treatment (Asberg et al., 2007). However, in the per-protocol population, a significant number of patients had persistent viremia at day 21, suggesting that longer courses of therapy are appropriate in some patients.

CMV disease should be treated for at least 2 weeks or until the following criteria are met: clinical resolution of symptoms and virologic clearance below a threshold negative value.

Intravenous ganciclovir is preferable to oral valganciclovir in patients with severe or life-threatening disease, or in patients with impaired gastrointestinal absorption (e.g., significant diarrhea). Acyclovir and oral ganciclovir are not effective in treating CMV disease in transplant recipients. While oral ganciclovir has been shown to prevent CMV disease, it is not recommended as a treatment due to concerns about emergence of ganciclovir-resistant CMV strains in the presence of CMV replication.

It is unclear whether addition of IVIG or CMVIG to existing treatment regimens has a benefit for solid organ transplant recipients, but it can be considered for patients with CMV pneumonitis or other severe disease.

Overall, molecular diagnostic tests can be used to tailor the duration of antiviral therapy based on clearance of CMV viral load or antigenemia. This risk of relapse is lower in patients who have no detectable CMV viral load at the end of therapy than for those with a detectable CMV viral load (Asberg et al., 2009; Humar et al., 2002). Therefore, patients with evidence of CMV viremia should be maintained on therapy until viremia (measured either by antigenemia or nucleic acid testing) has dropped below the negative threshold value for a given test, a value that remains poorly defined in ultra-sensitive assays. After completion of treatment, a 1 to 3 month course of secondary prophylaxis may be considered depending on the clinical situation. An alternative option is close clinical and/or virologic follow-up after discontinuation of treatment.

7. Conclusion

Although, new therapeutic procedures and the use of modern diagnostic methods have reduced the incidence of severe infections, CMV remains a common disease that negatively influences kidney transplant outcomes. In addition to viral factors and pharmacological immunosuppression, the roles of innate and adaptive immune deficiencies are now being recognized in its pathogenesis.

Prevention of CMV with antiviral prophylaxis and preemptive therapy are both effective, but have distinct disadvantages. The direct and indirect effects of CMV may be reduced by prophylaxis with antiviral agents, though late onset primary infections may complicate the post-transplant course. Furthermore, many CMV-seropositive recipients who will never develop CMV reactivation are exposed to drugs during prophylaxis. On the other hand, preemptive therapy is based on the frequent laboratory monitoring of viral load, and some patients develop a symptomatic infection before the diagnosis of CMV viremia.

Large randomized clinical trials are needed to establish a casual relationship between CMV reactivation and graft injury. In particular, they should analyze long-term graft survival and

compare prophylaxis with preemptive therapy in D+/R+, with particular attention to patients receiving preemptive therapy who have no episodes of positive antigenemia and therefore are not receiving anti-CMV treatments.

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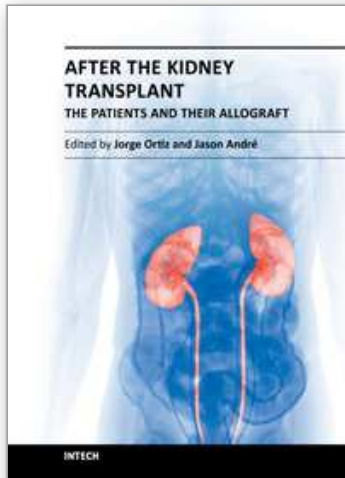
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There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipient's tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

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