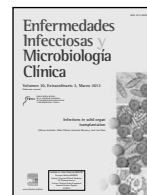




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Cytomegalovirus infection in solid organ transplantation

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ABSTRACT

Keywords:

Cytomegalovirus
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Cytomegalovirus infection remains a serious threat to solid transplant recipients. Despite advances in this field, there are still difficulties in the diagnosis of the disease and there are questions about the best and most cost-effective strategy to prevent infection and its direct and indirect consequences in the short and long term. All these points are discussed and updated in this chapter.

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Infección por citomegalovirus en trasplante de órgano sólido

RESUMEN

Palabras clave:

Citomegalovirus
Enfermedad
Infección
Órgano sólido
Trasplante

La infección por citomegalovirus sigue siendo una amenaza grave para los receptores de trasplante de órgano sólido. A pesar de los avances en este campo existen aún dificultades en el diagnóstico de esta enfermedad y dudas sobre cuál es la estrategia mejor y más coste-efectiva para prevenir la infección y sus consecuencias directas e indirectas a corto y largo plazo. Todos estos puntos se discuten y se actualizan en este capítulo.

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Introduction

Cytomegalovirus (CMV) infection constitutes a frequent cause of morbidity and mortality among solid organ transplant (SOT) recipients. CMV not only causes direct damage (in the form of viral syndrome or end-organ disease), but also exerts immunosuppressive and pro-inflammatory effects, and its sustained replication has been associated with the development of both acute and chronic allograft rejection, as well as with a greater incidence of some opportunistic infections. In the absence of prophylactic treatment, a variable proportion of SOT recipients suffer from one or more episodes of active infection during the first six months post-transplant, of whom up to 50% will progress towards a potentially fatal end-organ disease.

In this chapter, we briefly update the most important aspects related to the diagnosis, risk factors, prophylaxis and treatment of CMV infection in SOT recipients.

Diagnosis of CMV Infection and Disease

The presence of CMV in blood usually precedes the onset of clinical manifestations of CMV disease.¹ Thus, monitoring for the presence of either infectious virus or viral products in blood is a useful strategy for identifying patients at risk for developing CMV end-organ disease. Viral load monitoring in blood is, in addition, a useful tool for assessing the effectiveness of antiviral therapy and predicting the risk of development of CMV end-organ disease.² Surveillance of CMV load in tissue fluids, such as bronchoalveolar lavage (BAL), has also been proven to be a valuable strategy for assessing the risk of CMV pneumonitis in lung transplant recipients.³ Currently, the pp65 antigenemia assay⁴ and, most notably, molecular methods quantifying viral DNAemia are used in most centers for the surveillance of active CMV infection, and have largely replaced culture-based methods (viremia assays), and qualitative or semiquantitative PCRs.

The antigenemia pp65 assay

In this method, the lower matrix pp65 protein (UL83) is detected in peripheral blood polymorphonuclear leukocytes fixed onto a glass

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slide by cyto centrifugation, by means of immunofluorescence (IF) or immunoperoxidase methods.⁴ The number of pp65-positive cells provides a semiquantitative estimate of the systemic viral load. The turnaround time for the antigenemia assay is less than 5 h. The antigenemia assay has several drawbacks:⁵ 1) the test may not be useful during periods of severe neutropenia; 2) blood samples must be immediately processed upon arrival to the laboratory, and the test is laborious and cannot be automated; 3) the assay lacks adequate standardization; 4) the reading of the assay is subjective and 5) correlation between the rate of CMV replication and antigenemia levels is not always optimal, particularly in treated patients. A paradoxical increase in antigenemia in the face of decreasing levels of CMV DNAemia has been reported in SOT recipients experiencing primary CMV infections. In this setting, the antigenemia assay may provide misleading information that may prompt an unnecessary switch in antiviral therapy. The other drawbacks are that 6) clearance of antigenemia following initiation of pre-emptive therapy usually occurs earlier than that of DNAemia, so that the latter appears to be a more reliable marker of successful control of virus replication⁵ and 7) the antigenemia assay displays a low predictive value for the occurrence of gastrointestinal CMV disease.⁶

Pre-emptive antiviral therapy based on antigenemia results is usually started in the presence of >100 pp65 positive cells/200,000 polymorphonuclear leukocytes (PMNLs) in SOT recipients at intermediate or low risk for CMV end-organ disease (kidney, liver and heart D+/R+). However, a much lower antigenemia threshold (≥ 1 pp65 positive cell/200,000 PMNLs confirmed twice in a week) has been adopted for high-risk recipients (D+/R-, and pancreas, intestinal and lung recipients irrespective of paired CMV-serostatus of donor and recipients).⁷ Nevertheless, cut-off antigenemia levels triggering the initiation of pre-emptive therapy vary widely among centers, and currently there is insufficient evidence to strongly recommend any of these.⁸ Antigenemia testing in SOT patients with active CMV infection must be performed once a week in low risk patients and twice a week in high risk patients, although studies defining the optimal monitoring schedule are lacking.

Molecular methods

Molecular assays based on quantitative detection of viral DNA by real-time PCR are currently the primary choice for the surveillance of active CMV infection in the SOT setting, because of their extreme sensitivity, simplicity, accuracy, reproducibility, and dynamic linear measuring range, and short turnaround time.⁹ A large number of in-house and commercial real-time PCR assays have been developed and evaluated for monitoring CMV infection in SOT recipients. The limit of detection and the linear measuring range of these assays range from 20 to 700 CMV DNA copies/ml, and from 1.5-2 log₁₀ to 5-7 log₁₀ CMV DNA copies/ml, respectively, depending on the type of specimen (whole blood vs. plasma) used for the analysis. Commercial tests show improved reproducibility when compared to in-house tests. Interassay and interlaboratory variation in CMV DNA loads for commercial assays are usually between 0.1 and 0.6 log₁₀, due to higher magnitudes at low viral loads.¹⁰ Thus variations in CMV DNA loads measured in two consecutive determinations should not be viewed as true increases (or decreases) unless they are >0.5 log₁₀. Overall, in-house and commercial real-time assays perform adequately, but they differ greatly in their analytical performance, so that direct comparison of viral loads measured by the different procedures is infeasible. However, within each laboratory, viral load values are linear. There are substantial differences in the nucleic acid extraction efficiency between automated systems, and in CMV DNA loads measured using different commercially available QRT-PCR assays, which may impact therapeutic decisions and should be taken into consideration for the interpretation of data from clinical studies.¹⁰ To date, the lack of universally accepted standards for CMV DNA

quantitation makes viral load values obtained in different centers using different PCR assays and extraction methods not directly comparable. Future studies using the 1st WHO International Standard for CMV for Nucleic Acid Amplification (NAT)-Based Assays are warranted to normalize CMV DNA loads measured using different extraction methods and QRT PCR assays.

There is some controversy as to what constitutes the optimal clinical specimen (whole blood, peripheral blood leukocytes-PBLs- or plasma) for monitoring CMV DNAemia. CMV DNA loads tend to be higher in PBLs or whole blood than in plasma, although they show a significant correlation.¹ It can be concluded that whole blood and plasma are equally suitable for the surveillance of active CMV infection in SOT recipients.

Real-time PCR assays are more sensitive than the antigenemia assay, thus turning positive earlier and becoming negative later during active CMV infection.¹⁰ Overall, a significant correlation is found between the number of pp65 positive cells and the CMV DNA load, although discrepancies (negative antigenemia concomitant with intermediate to low DNAemia levels) are common, particularly after initiation of pre-emptive therapy.¹⁰

Several DNAemia levels, ranging from 1,000 to 5,000 copies/ml of plasma or from 1,000 to 300,000 copies/ml of whole blood, have been proposed for initiation of pre-emptive therapy in SOT recipients at low or intermediate risk for CMV end-organ disease.⁷ To date, however there are no consensus criteria for the initiation of pre-emptive therapy in SOT recipients on the basis of quantitative PCR monitoring strategy.⁸

Diagnosis of CMV end-organ disease

Clinical and laboratory criteria for the diagnosis of CMV infection have been published.¹¹ The presence of clinical signs and symptoms consistent with CMV disease, compatible signs in complementary tests (X-ray examination, endoscopy or ophthalmoscopy) and detection of CMV in the appropriate clinical specimen by direct culture, histopathological testing, immunohistochemistry or in situ hybridization allow for the diagnosis of CMV disease. PCR testing of tissue samples has a low positive predictive value, but a high negative predictive value for the diagnosis of pneumonitis and gastrointestinal disease. CMV DNA can be detected in bronchoalveolar lavage (BAL) in the absence of CMV disease. A correlation between the viral load in BAL and the presence of CMV pneumonitis has been demonstrated in lung transplant recipients,⁷ though no threshold permitting a definitive diagnosis has been established. PCR testing is however the first-choice laboratory assay for the diagnosis of CMV retinitis and peripheral and central nervous system diseases. Detection of CMV in blood in the presence of a compatible clinical picture does not allow for definitive diagnosis of CMV disease.

Testing for CMV resistance to antivirals

The emergence of CMV drug-resistant strains is uncommon in the SOT setting and has been associated with prolonged courses of antiviral therapy in concomitance with profound immunosuppression. Resistance to ganciclovir is due to mutations in either the UL97 phosphotransferase gene, or in the UL54 gene, which codes for DNA polymerase, or in both. Ganciclovir resistance occurs more frequently as a result of mutations within the UL97 gene than in the UL54 gene. UL97 mutations leading to *in vivo* resistance are located within two highly conserved regions among clinical isolates, the putative ATP-binding (codons 460 and 520) and substrate recognition (codons 590 to 607) sites.¹² Mutations in the UL54 gene may confer resistance to ganciclovir, foscarnet and cidofovir, and occur throughout the catalytic domain of the polymerase, spanning codons 301 (exonuclease I region) to 989 (domain V).¹² There are two types of methods used for assessing the susceptibility of CMV to antiviral

drugs. Phenotypic tests measure the ability of CMV to grow in the presence of a range of concentrations of the antiviral drug, and are performed by means of the classical plaque reduction test, *in situ* enzyme-linked immunosorbent assay, DNA reduction assay or flow cytometry-based assay.¹² Phenotypic methods have a long turnaround time, so results are not available in time to be clinically useful. Genotypic assays are designed to detect known mutations that confer drug resistance, and are performed by direct sequencing of PCR-amplified target genes from patient samples. Genotypic PCR-based assays show good correlation with phenotypic methods, and are the first choice in routine clinical practice. In addition, they are more sensitive than phenotypic methods for detecting mixtures of mutant and wild-type strains, with as little as 10% to 20% of a mutant virus in a background of wild-type virus.¹² Interpretation of results from genotypic tests is not always straightforward. Without confirmation from phenotypic testing and marker transfer studies, it is infeasible to try to distinguish between new mutations that potentially confer resistance and mutations associated with natural polymorphisms.

Risk Factors for Cytomegalovirus

General aspects

CMV infection occurs between 30% and 80% of patients undergoing TOS, although its incidence and the presence of symptomatic disease vary depending on the type of transplant, the presence of risk factors and prevention strategies.¹³

When primary infection occurs in SOT recipients, the lack of specific immunity allows for significant viral replication and is usually associated with the development of symptomatic CMV disease. In the case of CMV reactivations in previously seropositive patients, the receptor's humoral and cellular immunity decreases the dynamics of virus replication, thus decreasing the incidence and severity of the disease, which develops in 10% to 20% of patients. On reinfection, *in situ* reactivation of CMV in the transplanted organ is usually produced, leading to disease in up to 30% of patients.

In SOT recipients, the risk of CMV disease is the result of the balance between the degree of viral replication and the recipient's level of cellular competence and humoral immune response. There have been several studies analyzing clinical risk factors for development of CMV disease, mostly in order to detect a subgroup of SOT recipients that are obvious candidates for specific preventive strategies.

Factors related to the immune status of recipient and donor

Seronegative recipients receiving an organ transplant from a seropositive donor (D+/R-) is considered a major risk factor for CMV disease in all types of transplants,¹⁴ including pancreas combined with kidney.¹⁵ Late CMV infection is a special complication that occurs mainly when this group of patients receive long term prophylaxis during the first months, although recent information suggests that, among this risk group, those undergoing re-transplant could be at higher risk for developing late CMV disease.¹⁶

Seronegative recipients with seronegative organ transplant donors (D-/R-) have a risk of infection below 10%, with a lower incidence of disease (around 5%). The main risk factor in these patients is blood transfusion without leukocyte filter from a seropositive donor.¹⁷

Factors related to the type of transplanted organ

The onset of CMV disease is more common, and usually more severe in the intestine, pancreas and lung transplant than in liver, heart and kidney.¹⁴ Without prophylaxis, the incidence of CMV infection in pancreas transplantation is between 50% and 75%. In

D+/R- patients, the rates of disease are around 10%-40%.¹⁵ Rates of CMV disease are also between 25%-40% in intestinal transplant recipients.¹⁸ Finally, in lung transplant recipients, the incidence of CMV disease without prophylaxis ranges from 20% to 35%.¹⁹ This higher incidence of CMV disease in intestinal, pancreatic and lung transplantation is partially due to the more abundant lymphoid tissue and macrophages in these grafts, with a higher burden of latent CMV replication. For the same reason, multiple transplants (reno-pancreatic, cardio-pulmonary) are also at greater risk than single organ transplants. On the other hand, immunosuppressive treatment schedules in these types of transplants are particularly aggressive, which clearly contributes to the higher incidence of CMV disease.

Factors related to immunosuppressive treatment

The immunosuppressive drugs used to prevent rejection dampen the humoral and cell-specific immune response, allowing uncontrolled replication of latent virus. The effect on CMV replication is especially intense when using high doses of methylprednisolone or agents (such as antilymphocyte globulin [ALG] and antithymocyte globulin [ATG]), antilymphocyte antibodies (such as OKT3), mycophenolate mofetil and azathioprine.²⁰ The use of antilymphocyte globulins or monoclonal antibodies, apart from its depleting effect on lymphocytes, is associated with the production and secretion of cytokines (particularly tumor necrosis factor [TNF]), which triggers the inflammatory cascade and intensely stimulates CMV replication, leading to an increase of 3-4 times the rate of CMV infection especially in seropositive patients.²¹ Anti CD25 monoclonal antibodies, basiliximab and daclizumab have not been associated with increased risk of CMV infection or disease. However, alemtuzumab is considered a relevant risk factor for CMV disease when used as induction therapy, but mostly when used for the treatment of transplant rejection in all types of SOT.²² It is important to note that its administration causes lymphopenia for up to one year, which especially affects T lymphocytes.

Regarding anti-calcineurin drugs, some studies suggest that cyclosporine confers a higher risk for CMV replication and CMV disease than tacrolimus,¹⁴ although such differences have not been clearly explained. Tacrolimus is known to be 30 to 100 times more potent than cyclosporine *in vitro*, but maximal calcineurin activity inhibition *in vivo* has been shown to be significant with cyclosporine, which could lead to a higher effect in T-cells function.

The use of mycophenolate in renal transplantation has also been associated with increased risk of CMV disease, particularly in the gastrointestinal tract,²³ although other studies were unable to demonstrate such an effect.²⁴

The mTOR inhibitors (sirolimus and everolimus) used in kidney and heart transplantation have been associated with a protective effect against CMV infection and even CMV disease.¹⁴ The basis of this protective effect is not clear. Mammalian target of rapamycin (mTOR) kinase is a key regulator for protein synthesis in cells and intracellular viruses as CMV are depend heavily on cellular protein synthesis to support the synthesis of their constituent proteins and genomic replication. It is therefore conceivable that inactivation by rapamycin kinase impairs CMV viral replication.

Other factors

Some observational studies in liver and kidney transplantation have shown that reactivation and replication of other beta-herpesviruses, such as human herpesvirus 6 and 7, are associated with CMV disease.²⁵ Other recently described risk factors include donor age over 60 years, cadaveric renal transplantation, female gender in the recipient, extreme age of recipients, retransplantation, the need for multiple transfusions and prophylaxis or short early treatment.^{14,26}

In abdominal transplant recipients, intraoperative factors such as hypothermia, stress associated with surgery or critical situations, serious postoperative bacterial infections, the need of re-transplantation, fulminant hepatitis as a cause of liver transplantation and hepatitis C virus (HCV) have also been associated with increased CMV replication.

The outcome of the graft also seems to be relevant in the risk for developing CMV disease. Acute rejection is a well known risk factor in kidney transplantation²⁷ as has been reported with chronic graft malfunction.¹⁴ Finally, there is recent evidence showing how some defects in the host immune system may be associated with increased risk of CMV infection. These situations include some polymorphisms of the Toll-like receptor 2 and 4 and some deficits of complement factors, cytokines, chemokines and mannose-binding lectin.^{28,29}

Prevention of CMV Infection

General considerations

CMV prevention strategies have resulted in a decrease in CMV disease and CMV-related mortality. The main strategies for preventing CMV disease are universal prophylaxis and pre-emptive therapy.

Universal prophylaxis involves the administration of antiviral drugs to all patients at risk even in the absence of clinical or microbiological data of infection. The efficacy of this approach has been demonstrated in clinical trials that compare this strategy with non-prophylaxis or placebo.³⁰ In these trials, the drugs evaluated have been acyclovir, valacyclovir, oral and intravenous ganciclovir and oral valganciclovir. In early studies, acyclovir was inferior to oral ganciclovir.³¹ Valacyclovir has been associated with decreased risk of incidence of CMV disease in kidney transplant recipients.³² Moreover, valacyclovir was associated with delayed onset of CMV disease in these patients. A subsequent international clinical trial that included kidney, liver, pancreas and heart transplant recipients (all of them D+/R-) compared oral ganciclovir and valganciclovir.³³ The study demonstrated an equivalent efficacy of the two regimens for the prevention of CMV disease.

In pre-emptive therapy, treatment is administered to patients when asymptomatic CMV replication is detected by regularly monitoring of viral load or antigenemia in blood. The efficacy of this strategy has been evaluated in meta-analysis that included comparative studies between pre-emptive therapy and no treatment or placebo.³⁰

Universal prophylaxis versus pre-emptive therapy

Both prophylaxis and pre-emptive therapy have proven to be effective in preventing CMV disease. However, no randomized clinical trials have been conducted to compare both strategies in SOT recipients, and each has advantages and disadvantages. Universal prophylaxis has the advantage of potentially preventing the reactivation of other herpesviruses, as well as preventing indirect effects. In addition, this strategy does not require an assay to determine risk. However, one of the major concerns with universal prophylaxis is that prolonged exposure to antiviral drugs may increase the risk of resistance and toxicity related to antiviral treatment. Moreover, late CMV disease has been a significant finding in studies evaluating universal prophylaxis.³³ The advantages of pre-emptive therapy include decreased drug cost and associated toxicities. Nevertheless, adequate logistics at each transplant center are necessary to develop this approach. Moreover, optimal threshold values for antigenemia or viral load are not well established and may be different depending on the laboratory.

In general, the guidelines are consistent in that both universal prophylaxis and pre-emptive therapy are useful approaches for preventing CMV disease, even for patients in D+/R- situations.^{34,35}

However, for high-risk patients (lung, intestine, pancreas and pancreas-kidney transplantation), universal prophylaxis is generally recommended and is preferred in D+/R- patients where follow-up cannot be ensured.^{34,35}

The drugs approved for universal prophylaxis are intravenous ganciclovir (5 mg/kg/day) and valganciclovir (900 mg/day). In addition, oral valacyclovir (2 g/6 h) may be used in kidney transplant recipients.³² Oral ganciclovir has been traditionally indicated although it is not currently available.

The duration of prophylaxis should be between 3 and 6 months.³⁴ The decision to use 3 vs. 6 months will be based on the degree of immunosuppression and type of organ transplanted. In lung and intestine transplant recipients, a minimum of 6 months of prophylaxis is recommended.^{34,35} After completing universal prophylaxis, pre-emptive therapy is recommended for a period of 3-6 months.^{34,35}

In R+ patients, pre-emptive therapy is the preferred strategy except in high-risk patients (lung, intestine) and at centers where monitoring of viral load or antigenemia may be difficult.^{34,35} When this situation occurs, universal prophylaxis for 3 months should be employed. The use of anti-CMV prophylaxis is not recommended in D-/R- patients since these patients are at low risk of CMV disease.^{34,35}

In patients treated with anti-lymphocyte or monoclonal antibodies, antiviral prophylaxis (universal prophylaxis or pre-emptive therapy) must be initiated for 1 to 3 months. A similar approach may be used in patients who receive steroids for the treatment of rejection.^{34,35}

There are insufficient data to recommend the use of anti-CMV immunoglobulin in addition to antiviral drugs for prophylaxis in all transplant recipients. However, some centers use anti-CMV immunoglobulin in lung and intestine transplant recipients.³⁶

Treatment of CMV Disease

Ganciclovir has been the standard treatment for CMV disease in SOT recipients. More recently, an international randomized clinical trial showed that valganciclovir (an esterified derivative of ganciclovir with a bioavailability of 60% after oral administration) was non-inferior to intravenous ganciclovir in the treatment of CMV disease in this population.³⁷ In this study, 74% of the patients were renal transplant recipients and the majority of them had moderate disease. However, its results support the recommendation of valganciclovir for the treatment of CMV disease. This indication was further supported by the results of a subsequent study in which no long-term differences in the incidence of clinical and virologic recurrence was observed when valganciclovir was compared to intravenous ganciclovir.³⁸

Nevertheless, current available guidelines recommend the use of intravenous ganciclovir in children and in patients with severe or life-threatening disease.^{34,35} Moreover, intravenous ganciclovir should be used in those patients where valganciclovir is poorly tolerated or inadequately absorbed since data on the efficacy of oral treatment in such patients are scarce. In the subgroup of patients with mild or moderate CMV disease, valganciclovir (900 mg orally every 12 hours) and intravenous ganciclovir (5 mg/kg every 12 hours) are recommended as first-line treatment.³⁷

Foscarnet has been frequently used but its nephrotoxicity limits its use, especially in patients who are receiving calcineurin inhibitors. Oral ganciclovir cannot be used because it is not currently available commercially. Other oral drugs, such as acyclovir and valacyclovir, are not recommended for treating CMV disease.

Once the treatment is initiated, it is important to administer appropriate doses of ganciclovir or valganciclovir because suboptimal doses may cause clinical failure and promote the development of resistance.³⁹ On the other hand, the use of supratherapeutic doses

may result in nephrotoxicity. For this reason, monitoring of renal function during treatment is recommended, especially in those patients who receive concomitant nephrotoxic drugs.⁴⁰

Reducing the dose of ganciclovir or valganciclovir in patients who develop leukopenia during treatment is not recommended. In these patients, the use of a granulocyte colony-stimulating factor may be considered, particularly when absolute neutrophil counts are lower than 1000/mL.³⁴

The optimal length of treatment must be based on clinical evaluation and virologic monitoring by weekly antigenemia or quantitative PCR.^{34,35} The treatment must be continued until a negative antigenemia or PCR result is obtained. In high-risk patients, it is advisable to obtain two consecutive negative results before ending treatment. In any case, treatment must not be shorter than two weeks.^{34,35}

The use of secondary prophylaxis (valganciclovir 900 mg/day from 1 to 3 months) varies among transplant centers.^{37,38} This strategy may be especially useful in patients with risk factors for recurrence (primary CMV infection, high basal viral load, persistence of viremia at the beginning of secondary prophylaxis, multi-organ disease, high-risk organs and increases in immunosuppression due to rejection).³⁸ In cases of severe and tissue-invasive disease without viremia, longer treatment periods are recommended, with clinical monitoring focusing on the detection of specific expressions of the disease.^{34,35} In patients with recurrent CMV disease, secondary prophylaxis after re-treatment must be extended.^{34,35}

Treatment of ganciclovir-resistant CMV disease

At present, some risk factors for the development of drug resistance have been identified. These include the lack of CMV immunity (D+/R-), prolonged exposure or suboptimum levels of ganciclovir, pancreas and lung transplantation, high-level viral replication and intense concomitant immunosuppressive treatment.⁴¹

Currently, there are no clinical trial data about the best alternative for treatment of ganciclovir-resistant CMV disease. In these cases, treatment must be based on resistance tests, patient immune conditions and disease severity. Resistance should be suspected when viral load or antigenemia or progressive clinical disease are detected during prolonged treatment. In this situation, a genotypic analysis of the UL97 and UL54 genes is indicated. However, in patients with severe CMV disease, it may be necessary to start empirical treatment until the results of genotypic analysis are available. There are many alternative empirical treatments, including higher doses of ganciclovir (to more than 10 mg/kg twice a day for normal renal function) in patients with mild disease, and combining ganciclovir and foscarnet⁴² or administering foscarnet separately to patients with severe CMV disease. If genotypic resistance tests demonstrate a major UL97 mutation (associated with a high degree of resistance), switching to foscarnet should be considered.^{34,35} Nevertheless, if the test detects a UL97 mutation with low grade of resistance, higher doses of ganciclovir may be useful. When UL54 mutation is present, the treatment should switch to foscarnet as this mutation is associated with resistance to ganciclovir and cidofovir. In any case, when resistance to ganciclovir is detected, immunosuppressive therapy should be reduced as much as possible.³⁵

Alternative therapies

Currently, the evidence about the efficacy of alternative treatments for CMV disease is scarce. Various drugs with anti-CMV effects, such as leflunomide⁴³ and artesunate,⁴⁴ have been used. Leflunomide has shown to clear CMV viremia in renal transplant recipients with ganciclovir-resistant CMV disease, but failure with this drug has

been documented in stem cell recipients. Maribavir, a recent antiviral drug, presents good oral bioavailability and does not present hematological, renal or hepatic toxicity. For this reason, it has been considered a promising alternative for the treatment of resistant-CMV disease.⁴⁵ However, a recent phase III trial performed in stem cell transplant recipients showed that the efficacy of prophylaxis with maribavir was similar to placebo.⁴⁶

The administration of anti-CMV immunoglobulin could improve host defenses against CMV, but there is currently insufficient evidence for its use in SOT recipients. Similarly, the adoptive transfer of T cells is being investigated for both the prevention and treatment of resistant CMV infection.⁴⁷

Prophylactic vaccination

Although several CMV vaccines are in development, none of them are available for use in SOT recipients. A live attenuated vaccine ("Towne strain") has shown to be safe and reduce the severity of CMV disease in renal transplant recipients in D+/R- situations.⁴⁸ However, this strategy does not prevent primary infection. The recombinant vaccine gB, administered with the adjuvant MF59, provides protection against primary infection in 50% of vaccinated patients.⁴⁹ Ultimately, a bivalent DNA vaccine (VCL-CB01), containing two gB and pp65-encoding plasmids, has been shown to develop neutralizing antibodies in both healthy CMV-seropositive subjects and CMV-seronegative patients.⁵⁰

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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