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CYTOMEGALOVIRUS INFECTION AFTER KIDNEY TRANSPLANTATION: REAL PROGRESS AND PROSPECTS FOR PATHOGENESIS RESEARCH, PREVENTION AND TREATMENT

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Cytomegalovirus (CMV) infection plays an important role in clinical transplantology – it increases the risk of complications, graft failure, and patient death. The virus has both direct (direct damage to organs and tissues) and indirect immunomodulatory effects. Based on studies conducted, an international group of experts developed general principles for managing CMV infection after transplantation. This paper discusses risk factors, pathogenetic mechanisms by which CMV infection develops after kidney transplantation, the principles of diagnosis, treatment and prevention of this complication, and ways to overcome drug resistance in the virus. The prospects for the use of immunological monitoring, new antiviral drugs, as well as the possibility of using CMV vaccines, T-cell therapy, immunosuppressants (antiviral mTOR inhibitors) are discussed.

Keywords: cytomegalovirus infection, kidney transplant, graft failure, mortality, antiviral prophylaxis, mTOR inhibitors.

INTRODUCTION

Cytomegalovirus (CMV) belongs to the family of herpes viruses (*Herpesviridae*). It is the largest human herpes virus, measuring 150–200 nm in diameter [1, 2]. CMV contains at least 33 structural proteins and has a double-stranded DNA core. It is prevalent worldwide in the general population: CMV infections primarily occur in children, and the proportion of CMV seropositive adults reaches 70–90% [3, 4]. After primary infection, the virus does not undergo elimination. It rather persists throughout its lifespan in several types of cells – dendritic cells, megakaryocytes, CD14+ monocytes, CD34+ myeloid progenitor cells. This is why subpopulations of CMV-specific T lymphocytes exist in the infected body [5]. CMV does not usually cause a clinically manifest disease in immunocompetent individuals, although asymptomatic carriage of the virus may be associated with some inflammatory and age-related vascular diseases [6, 7]. Under a situation where the immune system is suppressed, for example, in HIV infection or after organ transplantation, CMV is reactivated and this is accompanied by damage to various body systems with a wide range of clinical manifestations and a real threat to the lives of patients [2, 8].

IMPORTANCE OF CMV INFECTION IN CLINICAL TRANSPLANTOLOGY. CLINICAL MANIFESTATIONS AND VIRUS REACTIVATION MECHANISMS

CMV infection can rightly be called the "number one infection" in transplantology because of its crucial role in morbidity and mortality of organ transplant recipients [2, 3, 9]. Apart from the direct effects of the virus, which is associated with its cytopathic effect, there are several "indirect effects" (general and transplant-specific) resulting from higher incidence of other types of infections, graft failure and death of recipients [10–12]. CMV infection and CMV disease are the direct effects of CMV.

According to the definition used by the International Consensus Recommendations and the American Society of Transplantation, CMV infection (asymptomatic replication of a virus, different from latent carriage of CMV) is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen [13]. CMV disease is a proven CMV infection with associated symptoms. It is further divided into viral syndrome (fever, malaise, leukopenia and/or thrombocytopenia) and tissue-invasive disease [13–15]. CMV disease can manifest itself as life-threatening pneumonitis, carditis, damage to any part of the gastrointestinal tract, pacreatitis, hepatitis, retinitis, tubulointerstitial nephritis, and less commonly as encephalitis and myeloradiculopathy [14, 16]. There have been reported separate cases of development of ureteral stenosis in renal transplant recipients in combination with tubulointerstitial nephritis caused by CMV [17].

Transplant-specific "indirect effects" of CMV are manifested in solid organ transplantation. They include chronic transplantation nephropathy and/or renal graft failure, accelerated recurrence of viral hepatitis C in liver transplant recipients, hepatic artery thrombosis in liver transplant recipients, cardiac allograft vasculopathy, and

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obliterative bronchiolitis in lung transplant recipients [11, 18–22]. A recent study confirmed that the appearance of CMV DNAemia having a viral load of ≥2000 copies/ml both in early (up to 3 months) and late onset in kidney transplant recipients is an independent risk factor for renal graft failure [23]. The general "indirect effects" of the virus consist of increased risk of bacterial and fungal infections, viral complications in general, acute rejection, post-transplant lymphoproliferative diseases, post-transplant diabetes mellitus, cardiovascular complications, accelerated aging and death [24–29].

It is well known that CMV infection is a risk factor for acute renal graft failure due to the immunomodulatory effect of the virus [30, 31]. Recent studies have shown that CMV activity may be associated with microcirculatory damage to the renal transplant due to donor-specific antibodies, i.e., with humoral rejection. In patients with CMV infection, specific γδ T lymphocytes are more frequent within glomeruli and peritubular capillaries from antibody-mediated acute rejections than within those from T cell-mediated acute rejections. In addition, a persistently increased percentage of circulating cytomegalovirus-induced γδ T cells correlated inversely with the 12-month estimated GFR only in kidney transplant recipients with donor-specific antibodies [32].

Previously, when there were no monitoring and prevention strategies yet, incidences of CMV infection/disease in kidney transplant recipients were very high: 60% for CMV infection and 30% for CMV disease [33]. Currently, the incidence of active CMV infection in renal transplant recipients has fallen considerably, but remains clinically significant. After transplantation, CMV infection can develop under two scenarios – as a primary infection (when the virus is transmitted along with the transplanted organ to a seronegative patient) or as reactivation of a recipient's latent CMV infection. In the "natural" course (without the use of prophylaxis), primary CMV infection/reactivation is clinically manifested most often in the first 3 months after kidney transplantation. However, in rare cases, a case of a transplant recipient presenting with CMV primoinfection 12 years after renal transplant has been reported [34].

Reactivation of latent CMV after transplantation is a complex, not fully understood process. However, systemic inflammatory response, mediated by several factors, such as immunosuppression, coinfection with other herpesviruses, acute graft rejection, sepsis, and even surgical intervention clearly play a key role in CMV reactivation [35]. Reactivation is associated with suppression of cellular immune response, especially CD8+ cells, as well as with the impact of several cytokines promoting transition of the virus from a latent state to an active phase. Tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) play the most important role in CMV reactivation process [36, 37]. In late CMV disease, which may develop after completion of specific prophylaxis, higher IL-10 plasma levels are predictive of this disease [38]. Experiments have shown that CMV in the replication process needs an mTOR kinase (mammalian target of rapamycin), which is part of the mTORC1 and mTORC2 complexes. Both complexes are activated during development of CMV infection in humans, while mTORC1 is involved in the production of all classes of proteins of the virus. Inactivation of the 4EBP1 protein (eukaryotic initiation factor 4E-binding protein) by the mTORC1 complex is critical for successful CMV replication. At the same time, the effect of mTOR inhibitors in the early phase of infection inhibits translation of viral proteins, which confirms the antiviral effect of this group of drugs [39, 40]. Using the model of human macrophages, it has also been shown that in the late infection phase, mTOR activation is also essential for CMV replication and synthesis of virus proteins such as pUL-44 and pp65 [41].

The risk of developing CMV infection in the post-transplant period depends on factors associated with the virus itself and factors associated with the patient's body. The former include heterogeneity of CMV (various strains), possibility of co-infection with other viruses, the effect of immune evasion, and replication dynamics. The later includes the nature of immunosuppressive therapy, including the use of high doses of calcineurin inhibitors (CIN), especially the subpopulations of CD4+, CD8+ cells, NK-cells and B-cells of the recipient, the ratio of the CMV-specific serological status of the donor and recipient, gene polymorphisms of certain cytokines and cell receptors (interleukin IL-28B, toll-like TLR9 receptors and DC-SIGN lectin receptors) involved in the antiviral immune response [35, 42, 43]. Of the drugs used to induce immunosuppression, antithymocyte globulin and alemtuzumab increases the incidence of CMV infection [44].

The CMV IgG serostatus of the donor and recipient (D/R) is of great clinical importance. The highest risk of developing CMV disease is in cases where the donor is seropositive and the recipient is seronegative (D+/R–), that is, the virus is likely to be transmitted with the donor organ to a patient who does not have CMV immunity. With the D+/R+ or D–/R+ combination, the risk is considered moderate (the risk is slightly higher for D+/R+). When both donor and recipient are seronegative (D–/R–), there is minimal risk of CMV infection in kidney transplant recipients [35]. In rare cases, CMV can be transferred to a recipient from a seronegative donor (D–) if the donor was evaluated during the "serological window", when donor infection has already occurred, but antibodies have not yet appeared [45].

DIAGNOSIS OF CYTOMEGALOVIRUS INFECTION

Evaluation aimed at preventing and detecting CMV infection can be conveniently divided into pre-transplant and post-transplant evaluation.

At the pre-transplant stage, both the organ donor and the potential recipient are evaluated, since as mentioned above, the matching/difference between the CMV serostatus (D/R) in the donor and recipient plays a major role in assessing the risk of developing CMV infection after kidney transplantation and determining the need for prevention or preemptive therapy. To assess the serostatus, detection of IgG antibodies to CMV is used. This is achieved through highly sensitive and highly specific immunological methods. In this case, detection of IgM or IgM and IgG in total should not be used, since such tests have insufficient specificity [46, 47]. If the donor and recipient are seronegative (D–/R–) during the pre-transplant evaluation, serology should be repeated at the time of kidney transplantation because the serological status may change, which affects the choice of tactics for CMV infection prevention [15].

After kidney transplantation, serological tests are not essential in diagnosis of CMV infection and CMV disease. Detection of antibodies, however, can be used in establishing current susceptibility to CMV in patients who are seronegative before transplantation and who have not yet had an active CMV infection after surgery. For example, seroconversion within three months after the end of a 100-day antiviral prophylaxis in D+/R– patients reduces the risk of late-onset CMV disease [48]. Cultivating the virus from blood is not used to identify transplant recipients with CMV infection due to the low sensitivity of the method, while cultivating it from urine and saliva cultures are not used due to low specificity [49].

The basis for diagnosis of CMV infection after transplantation consists of quantitative nucleic acid amplification testing (QNAT) methods, most often – quantitative real-time polymerase chain reaction (real-time PCR), due to its high efficiency and possibility of standardization [11]. The new International Consensus Guidelines contain consensus statements and recommendations on diagnosis and management of CMV infection. Below are the most important ones [15].

– We recommend using QNAT calibrated to the WHO standard for diagnosis, surveillance to guide preemptive antiviral treatment, and for therapeutic monitoring due to the ability to harmonize and standardize these tests. Results must be reported as IU/mL and termed as DNAemia rather than viremia. If QNAT is not available, antigenemia is a less desirable alternative (strong recommendation, high-quality evidence).
– We recommend either plasma or whole blood specimens as a biological sample for QNAT, with an appreciation for the differences in viral load values, viral kinetics and assay performance characteristics (strong recommendation, high-quality evidence). Neither the specimen type nor the assay should be changed when monitoring patients.
– Despite reporting in IU/mL, we recommend that viral load values are not directly compared across centers and/or laboratories unless identical testing reagents and procedures can be assured or equivalence has been documented (strong recommendation, high-quality evidence).
– We recommend that only changes in viral load exceeding 0.5 $\log_{10}$ IU/mL (threefold) are considered to represent clinically significant differences in DNAemia (strong recommendation, low-quality evidence).
– Although harmonization of QNAT has improved, universal thresholds for therapy or treatment endpoints have not been established and current published thresholds remain assay-specific. Accordingly, we recommend that centers establish their own thresholds and audit clinical outcomes to verify the thresholds used (strong recommendation, moderate-quality evidence).
– We do not recommend surveillance of CMV DNAemia during routine prophylaxis.
– We recommend when monitoring response to antiviral therapy, that QNAT is performed weekly (strong recommendation, moderate-quality evidence).
– With the use of highly sensitive QNAT (lower limit of quantification <200 IU/mL), we suggest discontinuing therapy after 1 result is less than the lower limit of quantification. If this approach is used, confirmatory testing should be done 1 week after discontinuing therapy. If the assay is not highly sensitive, then 2 consecutive undetectable (negative) results are needed to discontinue therapy (weak recommendation, moderate-quality evidence).
– We recommend histology coupled with immunohistochemistry for the diagnosis of tissue-invasive disease. Histopathologic examination of tissue should routinely include immunohistochemistry for CMV (strong recommendation, moderate-quality evidence).

With an appreciation for the fast dynamics of replication of the virus during development of CMV infection, the results of quantitative evaluation of CMV DNA should be available within 24–48 hours after sampling for timely clinical decisions, and this should be considered in the laboratory operating mode.

There were concerns that monitoring therapeutic response using highly sensitive DNA quantification tests to monitor the effectiveness of antiviral therapy may lead to unreasonably longer antiviral therapy. However, it turned out that in practice, the total duration of treatment was not prolonged in kidney transplant recipients with CMV

infection, although the time to reach an undetectable viral load was longer [50].

It should be emphasized that diagnosis of tissue invasive CMV disease is confirmed via detection of the virus in the tissues. The "gold standard" is to identify the cytopathic effects of CMV or virus antigens in biopsy specimens [13]. Evaluation of DNA in body tissues, for example, in biopsy specimens of the intestinal mucosa (including as a supplement to immunohistochemical studies) can be successfully used, although this method has not yet been standardized [51]. It is important that in the case of gastrointestinal CMV infection in solid organ transplant recipients and in pneumonitis in lung transplant recipients, there may be no DNAemia, or the quantity of DNA in the blood may be very small [52, 53]. The central nervous system (CNS) is rarely affected by CMV disease in solid organ transplant recipients. In the absence of data from special studies, detection of CMV DNA in cerebrospinal fluid can be considered as a confirmation of CNS viral infection. The diagnosis of CMV-retinin is based primarily on ophthalmological findings, although a positive QNAT in vitreous fluid may be helpful in guiding the diagnosis of retinitis [15].

PREVENTION OF CMV INFECTION IN KIDNEY TRANSPLANT RECIPIENTS

Since CMV infection occurs with high incidence after kidney transplantation and has a pronounced negative effect on the outcome of kidney transplantation, preventing this infection from developing is of paramount importance. The main approaches to preventing CMV infection in transplant recipients consist of preventive (preemptive) antiviral therapy and universal prophylaxis. There is a third, combined, approach – observation after completion of prophylaxis. This is also called a "hybrid approach" [11].

Universal prophylaxis involves administration of a specific antiviral drug to all patients at risk, starting from the 10th day after transplantation with continued continuous administration for a certain period (usually 3 or 6 months for kidney transplant recipients) [2, 3]. The following drugs were previously used and actively studied for prevention: acyclovir, valaciclovir, intravenous ganciclovir, oral ganciclovir (currently not available), and valganciclovir. It was further shown that ganciclovir is more effective in preventing CMV infection in kidney transplant recipients than acyclovir [54]. Valacyclovir in high doses has also been shown to be effective in preventing this complication [55], but its practical use is somewhat limited by the undesirable effects of high-dose therapy.

Currently, valganciclovir, a drug with proven effectiveness when orally administered, is most often used for universal prevention. Moreover, prevention for 6 months proved to be more effective in D+/R– kidney transplant recipients than a 3-month course [56]. It is important that introduction into clinical practice of valganciclovir prophylaxis in patients of medium risk (D+/R+ or D–/R+) was associated with considerable reduction in the incidence of significant CMV DNAemia [57]. The effectiveness of the prevention of active CMV infection with valganciclovir in the post-transplant period in kidney transplant recipients has also been confirmed by Russian and Belarusian authors [58, 59]. It is important to remember the need to select valganciclovir dose in accordance with the GFR level in a specific patient, since in patients with reduced renal function, the dose and/or frequency of administration of the drug should be lower than in normal renal function. When it comes to using a standard dose in patients with renal failure, serious adverse events may develop, primarily associated with leukopenia/neutropenia [60].

With all the positive effects of universal prevention, this approach comes with an important clinical problem – possibility of late-onset CMV disease after completion of a preemptive course. Apparently, the risk of late-onset CMV disease is associated with the absence of a virus-specific cellular immune response in patients with ongoing immunosuppression [61]. Risk factors for late-onset CMV infection/disease include certain types of transplantation (lung transplantation), high immunosuppression, graft rejection, D+/R– serostatus, GFR level less than 45 ml/min at the time of completion of prophylaxis [62–64]. This problem was what led to the emergence of a "hybrid" approach to the prevention of CMV infection. Although not all authors support this since data on the effectiveness of active surveillance after prophylaxis are somewhat contradictory [65, 66]. However, this combination approach may be applied for patients at significantly higher risk of late-onset CMV disease. In these cases, the viral load should be determined weekly for 8 to 12 weeks after the end of prophylaxis [15].

Preemptive therapy for CMV infection involves monitoring the viral load at regular intervals (blood CMV DNA must be determined at least once a week) for early detection of virus replication and conducting antiviral therapy if a predetermined DNA threshold is reached, even before clinical symptoms appear. Obviously, threshold values may vary for groups of different risks. For example, the threshold values of CMV DNAemia for D+/R– patients should be lower than for the D+/R+ group, since in the first case, viral load is doubled much faster and there might not be enough time to start preemptive therapy in the preclinical stage [67]. Preemptive therapy has some obvious advantages, which include lower incidence of late-onset CMV infection, selective treatment, reduction in the cost of therapy and the incidence of toxic effects when using antiviral drugs [2, 11, 15]. However, this tactic has obvious disadvanta-

ges: there are no common threshold values for the viral load, which serve as an indication for starting therapy (as mentioned above), logistics challenges associated with the need for weekly examination of the patient and a very fast start of treatment when the threshold viral load is reached, inconsistent or negative data on the effectiveness of preventing "indirect effects" of CMV and the impact on the survival of transplants and recipients compared with universal prophylaxis [68, 69].

Separately, the role of immunosuppressive therapy regimens in possible prevention of CMV infection should be discussed. In 2011, a combined analysis of three clinical trials of the use of various doses of everolimus in combination with cyclosporin A in *de novo* renal transplant recipients was published. A considerable decline in CMV infection/syndrome in the everolimus group versus the mycophenolate group, especially in non-prophylactic patients, was confirmed [70]. Several studies, systematic reviews, and meta-analyzes performed over the past few years have also shown a significant decrease in the incidence of CMV infection/disease in recipients treated with mTOR inhibitors. Here, this decrease was observed not only in adult kidney transplant recipients, but also in pediatric kidney transplant recipients, as well as in liver, heart and lung transplant recipients [71–77]. A meta-analysis of 28 randomized, controlled trials with 6,211 participants found that the risk of CMV infection was reduced by 46% ($p < 0.001$) in patients receiving mTOR inhibitors without CNI (calcineurin inhibitor), and 57% ($p = 0.007$) in patients taking mTOR inhibitors with reduced CNI doses compared to patients who received standard CNI doses [78]. Finally, TRANSFORM, the largest multicenter randomized study of the efficacy and safety of *de novo* everolimus-based therapy in kidney transplant recipients, which included 2,037 patients, showed that the incidence of CMV infection was significantly lower when everolimus is used in combination with reduced CNI doses than when mycophenolates and standard CNI doses are used – 3.6% versus 13.3%; incidence of BK virus infection was also lower – 4.3% versus 8% [79].

The results obtained are quite logical considering the role of mTOR kinase in CMV replication, as was mentioned above [39–41]. Besides, significant increase in CMV-specific effector-type CD8+ and CD4 T-lymphocytes was found in everolimus-treated renal transplant recipients 6 months and 24 months after surgery compared with cyclosporin A or mycophenolate treated recipients. This may also offer partial explanation for the low incidence of CMV infection with mTOR inhibitors [80].

In view of the above, one may ask: is it necessary to prevent CMV infection in patients receiving mTOR inhibitors? In a major meta-analysis published back in 2012, which showed significant reduction in the risk of CMV infection in mTOR-inhibitor treatment either alone or in combination with reduced CNI doses, it was suggested that standard mTOR inhibitor-based antiviral prophylaxis may be dispensable [81]. It was further found that the use of mTOR inhibitors protected R+ (CMV-seropositive) kidney transplant recipients from CMV even when polyclonal anti-lymphocyte globulin (high immunosuppression) was used in the absence of prophylaxis. However, early discontinuation of mTOR inhibitors increased the risk of CMV infection [82]. Apparently, in CMV-seropositive patients, the very use of *de novo* mTOR inhibitors can be a method for preventing CMV complications, so far as patients are carefully monitored. As for highest-risk D+/R– recipients, it is more advisable to adhere to the traditional approach (prophylaxis or preemptive strategy) until more complete data on the protective effect of mTOR inhibitors against CMV in this group of patients is obtained. Analysis have shown that the use of everolimus and tacrolimus in combination with induction therapy with no prophylaxis for CMV infection in renal transplant recipients provides clinical efficacy comparable to that of mycophenolates and tacrolimus (also with antibody induction), but is characterized by higher cost efficiency due to lower treatment costs [83].

Here are some of the consensus statements and recommendations of the International Consensus Guidelines regarding kidney transplantation [15].

– We recommend either universal prophylaxis or preemptive therapy We recommend either universal prophylaxis or preemptive therapy for prevention of CMV disease (strong recommendation, high-quality evidence).
– For D+/R−, we recommend the use of either prophylaxis or preemptive therapy after kidney and liver transplant. For programs or patients unable to meet the stringent logistic requirements required with a preemptive therapy strategy, prophylaxis is preferred.
– For seropositive recipients (R+) after kidney or liver transplant, we recommend either strategy (strong recommendation, high-quality evidence).
– We suggest prophylaxis may be preferred in donor and/or recipient seropositive patients whose risk for CMV may be increased, including those on recent antilymphocyte therapy, potent immunosuppression including desensitization or ABO incompatible protocols (including those on rituximab, bortezomib, eculizumab, and plasmapheresis/immunoadsorption), and those with HIV; a longer duration of prophylaxis (ie, 6 months) may be more effective (weak recommendation, moderate-quality evidence).
– For D+/R− kidney recipients, prophylaxis for 6 months is preferable (strong recommendation, high-quality evidence).
– When a prophylaxis strategy is used for prevention in R+ patients (with either D+ or D−), a majority of

the experts felt that 3 months of antiviral medication should be used for routine kidney, pancreas, liver, and heart transplant recipients (strong recommendation, high/moderate-quality evidence).
- For those receiving more potent immunosuppression (antilymphocyte antibody therapy, desensitization protocols) or vascularized composite and intestinal transplant recipients, between 3 and 6 months of prophylaxis can be used (weak recommendation, low-quality evidence).
- In CMV D−/R−, antiviral prophylaxis against other herpes infections (varicella and herpes simplex) with acyclovir, famciclovir, or valacyclovir should be considered (strong recommendation, high-quality evidence).
- To avoid transfusion-transmitted CMV, we recommend the use of leukoreduced or CMV-seronegative blood products (strong recommendation, moderate-quality evidence) especially in the highest risk group, D−/R−.
- We do not recommend the routine use of low-dose valganciclovir (weak recommendation, low-quality evidence).
- CMV seropositive recipients receiving mTOR inhibitors have a significantly lower incidence of CMV infection/disease. We suggest the use of mTOR inhibitors as a potential approach to decrease CMV infection and disease in CMV seropositive kidney transplant recipients (strong recommendation, high-quality evidence) and in liver, heart, and lung transplant recipients (strong recommendation, moderate-quality evidence). Cytomegalovirus risk is only one of the factors to consider when deciding on the optimal immunosuppression regimen. The impact of mTOR inhibitors on CMV in D+R− recipients is less clear.

TREATMENT OF CMV INFECTION IN KIDNEY TRANSPLANT RECIPIENTS

The drug of choice for treatment of CMV disease is intravenous ganciclovir. In the VICTOR study, intravenous ganciclovir and oral valganciclovir showed similar efficacy in the treatment of CMV syndrome and invasive CMV disease in adult patients after transplantation of a kidney, liver, heart, and lung [84]. However, it should be borne in mind that in instructions for valganciclovir protocols registered in Russia, there is no "treatment of infection" indication. Only "prevention of CMV infection after solid organ transplantation" is indicated. In addition, with a life-threatening infection or with a virus in the gastrointestinal tract, the use of intravenous ganciclovir is definitely indicated. Acyclovir and valaciclovir are not recommended for treatment of CMV infection. Correctly selecting a dose of intravenous ganciclovir is of fundamental importance (Table).

Table

Dosage recommendations for intravenous ganciclovir in adult patients with impaired renal function (using Cockcroft–Gault formula) [85]

Creatinine clearance, mL/min/1.73 m^2	Initial dose, mg/kg	Maintenance dose, mg/kg per day
≥70	5.0 every 12 hours	5.0
50–69	2.5 every 12 hours	2.5
25–49	2.5 per day	1.25
10–24	1.25 per day	0.625
<10	1.25 mg/kg 3 times a week after hemodialysis	0.625 mg/kg 3 times a week

Clinicians should be aware of some differences in GFR calculation when using various formulas – Cockcroft–Gault, MDRD, CKD-EPI. Suboptimal doses of ganciclovir may contribute to the development of drug resistance, and doses exceeding therapeutic doses may cause toxicity [86, 87]. During treatment, clinical blood counts should be regularly monitored to promptly detect hematological complications. In the case of leukopenia during treatment, one should not immediately discontinue ganciclovir or sharply reduce its dose. It is necessary to start by discontinuing other drugs that can suppress bone marrow hematopoiesis and introducing colony-stimulating factors.

The intensity of immunosuppressive therapy can affect the outcome of CMV infection: bicomponent immunosuppression versus ternary and lower concentrations of calcineurin inhibitors in the blood are associated with eradication of the virus after 21 days of treatment [88]. For this reason, in patients with CMV infection without concomitant graft rejection, reduction of immunosuppression is suggested in the following settings: severe CMV disease, inadequate clinical response, high viral load and/or cytopenia [15].

As already noted, the viral load during treatment should be determined weekly in order to establish the optimal duration of treatment. Plasma CMV DNA retention at the end of treatment is a significant predictor of virological recurrence [84]; therefore, therapeutic doses of ganciclovir should remain until the clinical symptoms disappear and CMV DNA is eradicated. Eradication is detected when one result of CMV DNA determination is less than the lower limit of quantification (LLOQ) with the use of highly sensitive QNAT or when two consecutive negative results are obtained by less sensitive methods [15]. The use of a therapeutic dose of ganciclovir in any case should last for at least two weeks. Routine use of intravenous immunoglobulin in the treatment of CMV infection is not recommended, although it can be considered in severe cases of the disease. Secondary prevention, i.e. the use of prophylactic doses after completion of treatment is impractical, since it usually

does not reduce the incidence of recurrence [89–91]. However, it can be used in some cases involving very high risk of recurrence.

In patients with a previous use of ganciclovir or valganciclovir lasting for over 6 weeks, or with treatment failure lasting at least two weeks, or with DNAemia during prophylaxis, drug resistance may be suspected. Drug resistance is a change in the genome of a virus, which reduces its sensitivity to one or more antiviral drugs. Among solid organ recipients, the incidence of ganciclovir resistance is on average 5–12%, and when the recipients were given D+/R prophylaxis for 100 or 200 days, ganciclovir or valganciclovir resistance incidence was less – from 0 to 3% [92–94]. Genetic testing – sequencing of the virus genome – is recommended for clarifying the causes of resistance. The database of CMV mutations associated with drug resistance is constantly growing [95, 96]. Testing should include mutation studies of the UL97 and UL54 genes. UL97 kinase gene mutations occur during initial genetic testing in 90% of cases of resistance in patients who initially received ganciclovir and disrupts drug phosphorylation required for its antiviral effect [97]. UL54 DNA polymerase gene mutations are usually detected at a later period, causing resistance to ganciclovir and often cross-resistance to cidofovir and/or foscarnet.

Unfortunately, there are currently no data from controlled trials that would allow us to choose the optimal treatment tactics for drug resistance to CMV. So, the proposed algorithms are based on the opinion of a group of experts. If laboratory testing returns no evidence supporting drug resistance, emphasis should be given to optimization of factors associated with the patient's body and drug delivery, than switching antiviral medications [15]. Immunosuppressive therapy is reduced to the minimum possible volume. Some UL97 mutations are characterized by lower levels of ganciclovir resistance, and escalating the dose of ganciclovir (up to 10 mg/kg every 12 hours) in combination with optimizing the recipient's body condition if there is no severe CMV disease might be useful [98]. This is a double standard dose, therefore, it is necessary to monitor possible bone marrow suppression and adjust the dose according to renal function.

Switching to foscarnet (which is not available in Russia) is recommended in cases where the mutation causes high-grade resistance to ganciclovir or there are combined UL97 and UL54 mutations causing high-grade ganciclovir resistance and, as a rule, cross-resistance to cidofovir. Foscarnet salvage therapy is often effective, at least initially, but metabolic disruptions and nephrotoxicity of the drug can negatively affect the final results of treatment [99–101]. There is still insufficient information on the effectiveness of salvage therapy with cidofovir in CMV infection in solid-organ transplant recipients [102, 103]. The nephrotoxicity of this drug is dose dependent. Cidofovir can be used in cases where double resistance – to ganciclovir and to foscarnet – is detected, but without cidofovir resistance. However, amidst such treatment, there have been reported cases of rapid development of virus load recurrence and appearance of new mutations that have already caused cidofovir resistance [104–106]. Apparently, the phenomenon described is associated with previously undetected subpopulations of cross-resistance mutants selected during previous ganciclovir therapy. A high dose of ganciclovir can also be used in situations where CMV is resistant to foscarnet, has no high-grade resistance to ganciclovir.

Additional treatment options for CMV infection include the use of drugs that can boost the patient's immune system or have an antiviral effect inessential for this class of drugs. Introduction of anti-cytomegalovirus intravenous immunoglobulin and infusion of CMV-specific T-lymphocytes can boost the body's antiviral defense [107, 108]. Several drugs used for other purposes, namely, everolimus, sirolimus, leflunomide, artesunate (antiprotozoal drug), have an *in vitro* anti-CMV activity and can act synergistically with antiviral drugs [109–111]. However, one should be aware that the use of leflunomide and artesunate with CMV infection has been studied in isolated cases and in small series. Besides, the use of these drugs requires special control due to possible toxic effects on the liver.

PROSPECTS FOR MONITORING, PREVENTING AND TREATING CYTOMEGALOVIRUS INFECTION IN SOLID ORGAN TRANSPLANT RECIPIENTS

In recent years, advances in clinical transplantology have been marked by significant successes in prevention and treatment of CMV infection in solid organ transplant recipients. This is associated with better immunological and molecular diagnosis of the disease, and expansion of the scope of knowledge about treatment of ganciclovir-resistant forms of CMV [112]. Nonetheless, management of CMV infection in kidney transplant recipients still has a series of unresolved problems, and there is a certain gap between scientific advances and real clinical practice. For example, no immunological monitoring method that could justify a personalized approach to prevention or preemptive therapy has been fully developed, universal DNAemia threshold for starting therapy has not been defined, the optimal duration of prevention has not been determined, and the issue of combating late-onset CMV infection has not been resolved [15]. The problem of overcoming ganciclovir resistance of the virus is also not resolved.

Immunological monitoring can be used to determine the individual risk of viral infection reactivation. *In vitro* interferon-gamma release (induced by stimulation of lymphocytes with CMV antigens) test have been de-

veloped. The commercially available QuantiFERON-CMV test is already being used and it has shown good prognostic value: the positive results of this test at the end of valganciclovir prophylaxis correlated with a low incidence of CMV disease in the future [113, 114]. More recently, the results of an interventional study of the efficacy of QuantiFERON-CMV test in patients undergoing the first episode of CMV reactivation have been published. In this study, patients who tested positive at the end of treatment for the first episode of CMV infection did not receive secondary prophylaxis, and only a single patient subsequently experienced an episode of asymptomatic DNAemia [115]. However, further research is required for widespread clinical use of this method.

As we have already noted, development of new drugs for treatment of CMV infection is extremely important due to emergence of ganciclovir resistance and high toxicity of alternative drugs – foscarnet and cidofovir. Brincidofovir, a lipid-conjugated analog of cidofovir, has higher oral bioavailability and less nephrotoxicity compared with cidofovir. However, the effectiveness of bricidofovir was low in the prevention of CMV infection in hematopoietic cell transplant recipients. Moreover, there is still extremely insufficient information on the use of the drug in solid organ recipients [116]. Maribavir is a viral UL97 kinase inhibitor. Although this drug has not been shown to be effective in preventing CMV infection in liver transplant recipients when taken 100 mg orally twice daily using it at higher doses has shown to be effective in treating resistant CMV disease in solid organ recipients [117, 118]. Maribavir ≥400 mg twice daily was quite active in the treatment of patients with refractory or resistant CMV infection in a phase 2 study, and the phase 3 study is ongoing [119]. Letermovir, a new non-nucleoside inhibitor of the CMV viral terminase complex, was approved by the FDA in 2017 for prevention of CMV infection in bone marrow transplantation. In this population, a randomized phase 3 trial showed letermovir to have superior efficacy than placebo in prevention of CMV disease. Here, myelotoxicity and nephrotoxicity were comparable to placebo [120]. Letermovir has been successfully used in a lung transplant recipient with a series of drug-resistant CMV infections; effective treatment of CMV viremia in kidney transplant recipients has also been reported [121, 122]. A clinical study comparing letermovir with valganciclovir for the prevention of CMV infection in kidney transplant recipients in a D+/R– situation is commencing (ClinicalTrials.gov ID: NCT03443869).

A promising area is the possibility of using T-cell therapy and CMV vaccines. Expansion of CMV-specific T-lymphocytes is achieved by exposing the cells to synthetic or viral CMV peptides after which T-lymphocytes are administered to the patient. This restores antiviral immunity and cures the CMV disease. T-lymphocytes can be autologous, but the process of obtaining them usually takes several weeks. That is why there is growing interest in ready-made HLA-compatible lymphocytes from cell banks. The emergence of commercially available banked CMV-specific T-lymphocytes can lead to an increase in the incidence of use of this modality of therapy in solid organ transplant recipients [123, 124]. CMV vaccines are of various types – live attenuated, recombinant/chimeric viral vectors, recombinant subunits, and DNA (gene) vaccines [125]. Generally, development of CMV vaccines has reached the phase of clinical trials in humans. However, vaccines are not yet available in real clinical practice.

Main focus should certainly be on prevention of CMV infection in kidney transplant recipients. For prevention of CMV infection, new effective antiviral drugs can be used, as well as active introduction of immunosuppressive agents with additional antiviral effects in clinical practice. In this regard, the use of *de novo* immunosuppressive protocols with an mTOR inhibitor everolimus in kidney transplant recipients, which significantly reduced the incidence of viral infections in the post-transplant period, including CMV infection, seems to be promising [79]. Since it is still far from ideal, further research is needed to optimize the prevention of CMV infection in clinical transplant practice.

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