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EVALUATION OF THE EFFECTIVENESS OF PROPHYLACTIC STRATEGIES FOR CYTOMEGALOVIRUS INFECTION IN PEDIATRIC KIDNEY RECIPIENTS

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Cytomegalovirus (CMV) infection is the most severe viral infection in renal transplant recipients, which can occur in the post-transplant period in both adult and pediatric recipients. Developing and applying an effective prevention and treatment strategy for pediatric renal graft recipients is a priority. **Objective:** to compare the effectiveness of the protocols used for the prevention of CMV infection in pediatric kidney transplant recipients. **Materials and methods.** The study enrolled 118 patients who underwent primary kidney transplantation at Shumakov National Medical Research Center of Transplantology and Artificial Organs. Based on retrospective analysis, all recipients were divided into two groups, depending on the prophylactic strategy after kidney transplantation. The follow-up period for pediatric kidney recipients ranged from 108 to 1803 (623.5 ± 379.5) days. CMV infection activity was monitored by polymerase chain reaction. **Results**. The frequency of CMV infection activation episodes at 3 and 6 months was independent of the prophylaxis strategy used. The recurrence rate of CMV infection one year after surgery was significantly lower ($p = 0.037$) with Strategy 2. No cases of CMV syndrome or CMV disease, graft dysfunction, or chronic rejection associated with CMV infection were reported. Increasing the dose of antiviral drugs in Strategy 1 did not increase the risk of cytotoxicity and nephrotoxicity, which are reversible (creatinine levels were not significantly different in the study groups at 3, 6, 12 months, $p = 0.542$, $p = 0.287$, $p = 0.535$, respectively). The incidence of kidney graft rejection did not increase in patients with lower doses of immunosuppressants in Strategy 2. **Conclusion.** Both prophylactic strategies are effective in pediatric kidney recipients. However, the choice of a strategy depends on the individual characteristics of the patient and requires a personalized approach.

Keywords: cytomegalovirus (CMV) infection, kidney transplantation, universal prophylaxis, pediatrics, nephrology, immunosuppression.

INTRODUCTION

Currently, protocols for prevention and treatment of CMV infection at various transplantation centers vary, but two strategies are acceptable according to international guidelines: universal prophylaxis and preemptive therapy [1]. Universal prophylaxis involves administration of antiviral drugs to all patients or a group of patients at risk. Antiviral drugs are usually started immediately after kidney transplantation for 3 to 6 months [2, 6]. However, under this strategy, there are increasing reports of CMV infection being resistant to therapy in solid organ recipients [3].

Several studies have identified CMV infection as a predictor of graft loss, worsening long-term outcomes, and as a cause of mortality in kidney allograft recipients. Tomas Reischig et al. identified CMV viremia as an independent risk factor for graft loss. The study included 180 transplant recipients: 87 (48%) patients received prophylaxis with valacyclovir and 45 (25%) with valganciclovir; for at least 100 days, 48 (27%) received preventive therapy. At 12 months after CMV transplantation, CMV DNAemia developed in 102 (57%) patients with 36 (20%) having a viral load of ≥2,000 copies/ml. Multivariate Cox analysis identified CMV DNAemia as an independent risk factor for graft loss (hazard ratio 3.42; $p = 0.020$); however, after stratification by viral load, only CMV DNAemia ≥2,000 copies/ml (hazard ratio 7.62; $p < 0.001$) remained significant. Kidney transplant recipients having CMV DNAemia with a higher viral load irrespective of the time to onset are at increased risk for graft loss. Glomerular allograft pathology was associated with chronic humoral rejection (in the absence of donor-specific antibodies in the study recipients) [13].

For preemptive therapy, patients are routinely referred for CMV infection testing, and therapy is initiated as soon as active viral replication becomes apparent. According to the guidelines for preventive therapy, treatment is continued until two consecutive negative antigenemia tests

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are obtained. Patients with CMV infection should receive intravenous ganciclovir or oral valganciclovir for at least 14 days until symptoms disappear [2]. Each strategy has its disadvantages and advantages. The disadvantage of preemptive therapy is the condition of high compliance of pediatric recipients and their parents. Universal prophylaxis reduces the number of CMV episodes, the recurrence rate, and the severity of the disease course, but it is associated with nephrotoxicity and cytotoxicity. Clinical reports have demonstrated positive results with universal prophylaxis. However, there are clinical reports of the occurrence of CMV infection in long-term post-transplant recipients who received prophylaxis with valganciclovir [1, 10, 12, 14]. In a study by Andre C. Kalil in evaluating the safety and efficacy of universal valganciclovir prophylaxis among solid organ recipients, one in 25 recipients (n = 1831) had CMV infection with late onset (OR = 8.95, 95% CI 1.07 to 74.83; p = 0.04) [4]. This study also identified the most common side effect of valganciclovir – absolute neutropenia.

A number of other studies have focused on the successful use of proliferative signal inhibitors as part of basic three-component immunosuppressive therapy for the prevention and treatment of cytomegalovirus infection [15]. Patients receiving everolimus (EVR) demonstrated a significant increase in the number of CMV-specific effector CD8+ and CD4+ T cells compared to patients receiving cyclosporine (CsA) and mycophenolate mofetil (MMF) [5]. The efficacy and safety of the combination of tacrolimus (TAC) and EVR was recently confirmed in the TRANSFORM study [5]. The efficacy of this protocol for cytomegalovirus infection is also explained by the possibility of reducing TAC levels when EVR is used, which allows for an increase in the number of effector CMV-specific cells. Taking into account the existing side effects of valganciclovir, risks of adverse immunological events with decreased immunosuppression, risks of preventive therapy in pediatric recipients, due to the impossibility of ensuring a high compliance in this category of patients, the development of an optimal protocol for prevention of CMV infection in pediatric recipients is still open for discussion.

Objective: to conduct a comparative analysis of the effectiveness of the protocols used for prevention of CMV infection in pediatric kidney recipients.

CLINICAL OBSERVATIONS AND STUDY METHODS

The study included 118 patients transplanted from January 2018 to July 2021 at Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow. Among them were 63 (53.3%) boys and 55 (46.7%) girls aged 1 to 17 (10.6 ± 5) years, with body weight from 7 to 71 (29.5 ± 14.7) kg, who received a kidney from a deceased (n = 37) and a living related (n = 81) donor. The follow-up period ranged from 108 to 1803 (623.5 ± 379.5) days. The minimum follow-up period was 3 months.

Based on analysis of patient histories and outpatient records, all recipients were divided into two groups, depending on their prophylaxis strategy after kidney transplantation (Strategy 1 and Strategy 2). The Strategy 1 group included 71 pediatric recipients after primary kidney transplantation between 2018 and 2021. The operated children included 30 (42.3%) girls and 41 (57.7%) boys, aged 1 to 17 (10 ± 5) years, with a body weight of 8 to 57 (28 ± 14.7) kg, who received a transplant from a deceased (n = 23) and from a living related (n = 48) donor. The recipients received universal prophylaxis for CMV infection, which was represented by valganciclovir dose according to Asberg method for 6 months; if viral replication was detected, valganciclovir was administered in a therapeutic dose.

The Strategy 2 group included 47 pediatric recipients after primary kidney transplantation between 2018 and 2021. The operated children included 25 (53.2%) girls and 22 (46.8%) boys aged 2 to 17 (11.6 ± 5) years, with a body weight of 7 to 68 (30.9 ± 14.9) kg, who received a transplant from a deceased (n = 14) and from a living related (n = 33) donor. The recipients received universal prophylaxis for CMV infection, which included valganciclovir dose according to Asberg method for 6 months; when viral replication was detected, immunosuppressive therapy was reduced (i.e., reduction in the number of components in the treatment regimen, reduction in immunosuppressant dose, etc).

CMV was monitored by quantitative polymerase chain reaction (PCR) testing of the virus DNA in the blood. In the first month after kidney transplantation, monitoring was performed every week, then every month; 6 months after transplantation, CMV monitoring was performed every 3 months.

The following parameters were evaluated in the study: clinical and demographic characteristics of the recipients, incidence and characteristics of CMV events, incidence of acute allograft rejection, renal function, patient and graft survival, and nephrotoxicity and cytotoxicity of the prophylaxis protocol. Renal function after transplantation was assessed using the Schwartz formula.

Biopsy-confirmed cellular and antibody-mediated rejection were classified according to the Banff-2017 classification.

Statistical analysis was performed using IBM STATISTICS 20 (IBM SPSS Inc., USA) StatTech v. 2.2.0 (developer LLC Stattech, Russia), an application software package for calculations.

RESULTS

Among the observed kidney recipients, Strategy 1 was used in 60% (n = 71) of cases and Strategy 2 was used in 40% (n = 47). A comparative analysis of the

demographic data of the kidney recipients depending on the selected Strategy found that the age of the children in the Strategy 1 group was significantly lower than that in the Strategy 2 group (p = 0.010) (Table 1).

There were no significant differences in sex and body weight in pediatric kidney recipients, which indicates the homogeneity of the studied groups.

Comparative analysis showed no differences between the groups in terms of graft variant, haplotype compatibility, DR locus and number of mismatches (p ≥ 0.05), although the proportion of related grafts compatible by haplotype and DR locus was higher in the Strategy 2 group.

Table 1

Comparative analysis of demographic data of kidney recipients

Indicator	Strategy 1 (n = 71)	Strategy 2 (n = 47)	p
Gender: boys, n (%) girls, n (%)	 41 (57.7%) 30 (42.3%)	 22 (46.8%) 25 (53.2%)	0.256
Age, years	1 to 17 (10 ± 5)	2 to 17 (11.6 ± 5)	**0.010***
Body weight, kg	8 to 57 (28 ± 14.7)	7 to 68 (30.9 ± 14.9)	0.420

* – differences in indicators are statistically significant (p < 0.05).

Table 2

CMV infection activation in pediatric recipients 3 and 6 months after kidney transplantation

Detection time, months	CMV infection, n (%)	Category		p
		Strategy 1	Strategy 2	
3	no replication	34 (54.0%)	29 (46.0%)	0.141
	replication detection	37 (67.3%)	18 (32.7%)	
6	no replication	36 (55.4%)	29 (44.6%)	0.191
	replication detection	26 (68.4%)	12 (31.6%)	

* – differences in indicators are statistically significant (p < 0.05).

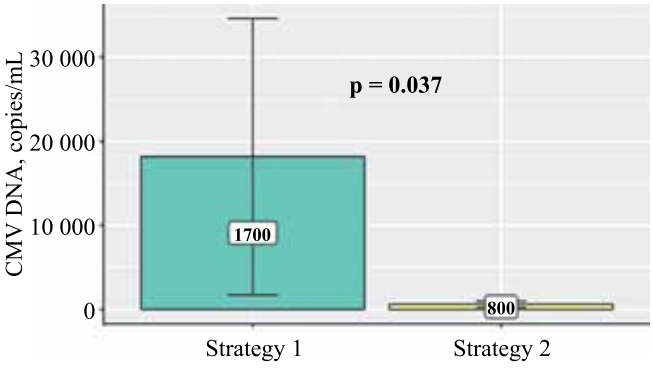

Fig. 1. Comparative analysis of median CMV DNA levels in pediatric kidney recipients with Strategy 1 (n = 71) and Strategy 2 (n = 47) 3 months after transplantation

No clinical manifestations of CMV infection, either as CMV syndrome (0%) or CMV disease (0%), were reported in pediatric kidney recipients when Strategy 1 and Strategy 2 were used for CMV infection prevention.

CMV infection activation in the form of asymptomatic viremia in pediatric recipients 3 months after kidney transplantation in Strategy 1 was detected in 37 (52%) recipients. In Strategy 2, asymptomatic CMV viremia was detected in 18 (38%) recipients 3 months later (Table 2).

Comparative analysis showed no statistical significance in the incidence of CMV infection 3 months after kidney transplantation (p = 0.141). In the Strategy 1 group, the median CMV DNA level was 1700 [600; 11,000] copies/ml, and in the Strategy 2 group, it was 800 [600; 1875] copies/ml. Strategy 1 had a higher median CMV DNA level than Strategy 2 (p = 0.037) (Fig. 1).

Most of the kidney recipients had an episode of active CMV infection in the early postoperative period, i.e., developed within 14 days after kidney transplantation. Comparative analysis showed no statistical significance in CMV infection incidence 3 months after kidney transplantation (p = 0.141).

By the end of the study, 103 recipients had reached a follow-up period of 6 months, which was 87.3% of the total number of patients included in the study. Six months after transplantation in Strategy 1, asymptomatic CMV viremia occurred in 26 (41.9%) of the 62 recipients. In Strategy 2, 12 (29.3%) of 41 recipients also had CMV viremia at 6 months. In the Strategy 1 group, the median CMV DNA level was 0 [0; 615] copies/ml, and in the Strategy 2 group, it was 0 [0; 508] copies/ml (p = 0.178). A comparative analysis of the incidence of CMV infection activation in pediatric recipients six months after kidney transplantation was performed in the study groups. Although the comparative analysis showed no statistically significant differences between the groups (p = 0.191), CMV replication incidence in Strategy 1 group was almost double that in Strategy 2 (Table 2).

By the end of the study, 78 kidney recipients had reached the 12-month follow-up period, which was 66.1% of the total number of patients included in the study. Twelve months after transplantation, 14 (27.5%) of 51 recipients in Strategy 1 developed CMV infection, while 2 (7.4%) of 27 developed same in Strategy 2. The Strategy 1 group had a median CMV level of 0 [0; 600] copies/ml, the Strategy 2 group had 0 [0; 0] copies/ml (p = 0.028). A comparative analysis of the incidence of CMV infection activation in pediatric recipients 12 months after kidney transplantation was performed in the study groups.

The comparative analysis showed that activation of CMV infection in pediatric recipients 12 months after

transplantation occurred more frequently with Strategy 1 (p = 0.037) (Fig. 2).

We analyzed the number of recurrent CMV infection depending on the chosen strategy of CMV infection prevention in children after kidney transplantation for the whole period of observation (Table 3).

No statistically significant difference (p = 0.281) could be found in the number of CMV reactivation episodes between the two strategies. However, as shown in Table 3, the total number of relapses was higher in Strategy 1 recipients.

Evaluation of adverse events

We analyzed the presence of cytopenia (leukopenia, neutropenia, thrombocytopenia) after 3 and 6 months and found no statistically significant differences between the groups (p = 0.396, p = 0.738, respectively). At 12 months after transplantation, cytopenia was not detected in any of the study groups. Serum creatinine levels in kidney recipients did not statistically differ at different times after transplantation (3, 6, 12 months) regardless of the CMV prophylaxis strategy used (p = 0.542, p = 0.287, p = 0.535, respectively).

Assessment of adverse immunological events

There were no cases of graft rejection associated with activation of CMV infection in recipients during prophylaxis.

Fig. 3 shows a comparison of survival without adverse events (mortality, rejection, return to hemodialysis) in kidney recipients depending on the cytomegalovirus infection prophylaxis strategy.

A comparative analysis of one-year survival without adverse events (mortality, rejection, return to hemodialysis) in kidney recipients depending on CMV infection prevention strategy showed no statistical difference (p = 0.537).

DISCUSSION

CMV infection remains one of the most common viral infectious complications in solid organ recipients, affecting the course of the post-transplant period [9, 10, 14]. CMV infection in pediatric kidney recipients has been shown to be associated with indirect effects. CMV infection can cause acute and/or chronic damage, graft rejection, and consequently affect poor graft survival, which are attributed to indirect effects. Any effort to prevent CMV will help improve long-term outcomes. The first milestone in the fight against CMV infection was the advent of antiviral drugs and the use of prophylactic strategies. To this day, they are the CMV prevention cornerstones, but they are not enough to prevent the virus from replicating [11].

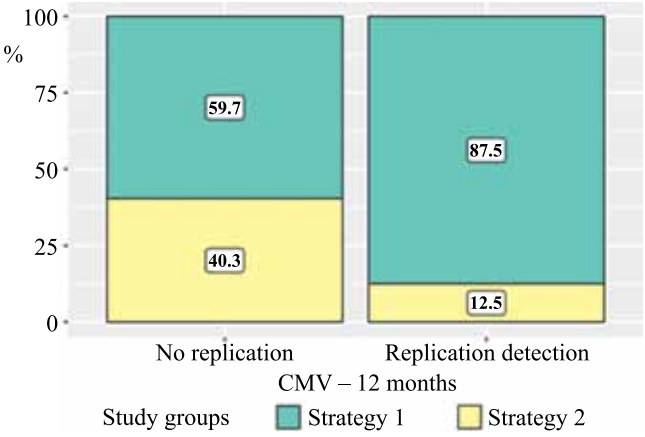

Fig. 2. CMV infection activation in pediatric recipients 12 months after kidney transplantation

Table 3

Analysis of recurrence rates of CMV infection depending on the strategy chosen

Category	Number of recurrent CMV infection, n						p
	0	1	2	3	4	6	
Strategy 1	37	8	6	5	5	1	0.281
Strategy 2	31	6	4	1	0	0	

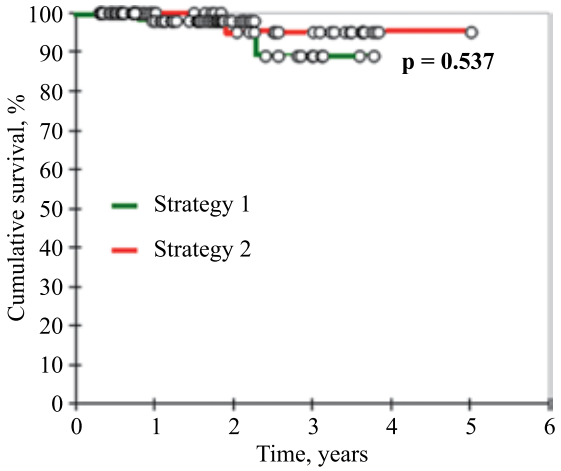

Fig. 3. Comparison of survival without adverse events (mortality, rejection, return to hemodialysis) in kidney recipients depending on the CMV prevention strategy

Over the past two decades, it has become clear that both innate and CMV-specific immunity play a crucial role in controlling CMV, necessitating the optimization of immunosuppressive therapy protocols. The present study conducted a comparative retrospective analysis of the clinical outcomes of kidney transplantation in 118 pediatric kidney recipients in order to develop individualized prophylaxis for cytomegalovirus infection. The results revealed that the viral load differed in the groups only 12 months after transplantation; no differences were detected in other time periods.

Comparative analysis showed that activation of CMV infection one year after transplantation occurred more often with Strategy 1, i.e., when prophylaxis was no longer used. The risk of recurrence was significantly lower with Strategy 2, which is logical against the background of reduced immunosuppression.

However, Strategy 2 must take into account the restrictive criteria for the acceptability of immunosuppressive therapy reduction – reduction of calcineurin inhibitor and the use of mTOR inhibitors – acceptable for recipients with low or moderate immunological risk, thus limiting the widespread use of this approach.

CONCLUSION

The presented experience in CMV prevention in kidney recipients has shown that the algorithms used for diagnosis and prevention of CMV infection and, when appropriate, algorithms for treatment of episodes of active CMV infection, demonstrate good clinical outcomes both in controlling recurrent CMV infection and preventing CMV disease and CMV syndrome, and in reducing the likelihood of developing indirect CMV effects affecting graft function, graft survival, and recipient survival.

The authors declare no conflict of interest.

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