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Gokhan Ertugrul[1], Tumay Yanaral[2]

Efficacy of short term valganciclovir in a standard-dose for cytomegalovirus prophylaxis in living donor kidney transplantation: a single-center report

[1] Medipol University Hospital Organ Transplantation Center, Istanbul, Turkey.
[2] Medipol University Faculty of Medicine, Department of Anesthesiology, Istanbul, Turkey.

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Abstract. *Immunosuppressive drugs predispose the kidney transplant recipient to reactivation of cytomegalovirus (CMV) infections. Prophylaxis given to these patients is very important for the prevention of opportunistic CMV infections.*

The objective of this study was to evaluate the short term and standard-dose valganciclovir prophylaxis for CMV infections in living donor kidney transplantation.

Methods. This study is retrospective one. Between April 2014 and April 2019 100 patients after living donor kidney transplantation with results CMV PCR-DNA and prophylactic treatment were studied retrospectively at Medipol University Medical Faculty Hospital Organ Transplantation Department, Istanbul, Turkey.

Results. The mean age was 38.3±15.6 years. 68 (68%) patients were males and 32 (32%) patients were females. All patients were treated with 900 mg daily and 90 days valganciclovir prophylaxis. Mean follow-up was 29.1±15 months. There were not detected CMV infections during the follow-up period.

Conclusions: Short term and standard-dose valganciclovir prophylaxis appears to be successful prevention CMV infections in living donor kidney transplantation.

Keywords. *Living donor kidney transplantation, CMV infections, valganciclovir, prophylaxis.*

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Correspondence should be addressed to Gokhan Ertugrul1: mdgertugrul@gmail.com

Гохан Ертугрул[1], Тумай Янарал[2]

Ефективність короткочасного застосування стандартної дози вальганцикловіру для профілактики цитомегаловірусної інфекції у реципієнтів ниркового трансплантату від живого донору: звіт одного центру

[1]Центр трансплантації органів університетської клініки, Стамбул, Туреччина
[2]Медичний факультет університету Медіполь, кафедра анестезіології, Стамбул, Туреччина.

Резюме. *Застосування імуносупресивних лікарських засобів у реципієнтів ниркового трансплантату часто призводить до реактивації цитомегаловірусної (ЦМВ) інфекцій. Профілактична терапія ЦМВ-інфекції є важливою складовою лікування таких пацієнтів.*

Метою цього дослідження було оцінити ефективність короткочасної профілактики ЦМВ-інфекції за допомогою стандартної дози вальганцикловіру у реципієнтів ниркового трансплантату від живого донору.

Методи. 100 пацієнтів, які перенесли трансплантацію нирки від живого донору у центрі трансплантації органів Медичного університету, Стамбул, Туреччина, у період з квітня 2014 року по квітень 2019 року були проаналізовані ретроспективно.

Результати. Серед включених до аналізу пацієнтів будо 68 (68%) чоловіків та 32 (32%) жінок з середнім віком 38,3 ± 15,6 років. Усі хворі отримували профілактичну терапію вальганцикловіром у дозі 900 мг щодня протягом 90 днів. Тривалість спостереження склала 29,1 ± 15 місяців. Під час спостереження ЦМВ-інфекцій не виявлено.

Висновки. Короткострокова стандартна доза вальганцикловіру є ефективною у профілактиці ЦМВ-інфекції у реципієнтів ниркового трансплантату від живого донору.

Ключові слова: *трансплантація нирки від живого донору, ЦМВ-інфекція, вальганцикловір, профілактика.*

Introduction. Cytomegalovirus (CMV) infection significantly increases recipient morbidity and mortality after kidney transplantation [1]. The most important risk factor is high dose immunosuppression and antithymocyte globulin (ATG) induction for CMV infections [2]. Approximately 60% of the adult population has been exposed to CMV and are potential carriers of infection [3, 4].

In current scientific literature, the standard dose and duration of valganciclovir (VGV) for the CMV prophylaxis is 900 mg once daily for 6 months [5]. VGV mainly is used in the treatment of high-risk patients (preoperative donor CMV (+) / recipient CMV (-) and in induction with ATG) [6].

The aim of this study was to evaluate the short term and standard-dose valganciclovir prophylaxis for CMV infections in living donor kidney transplantation.

Material and Methods. Between April 2014 and April 2019 100 patients after living donor kidney transplantation with results CMV PCR-DNA and prophylactic treatment were studied retrospectively at Medipol University Medical Faculty Hospital Organ Transplantation Department, Istanbul, Turkey.

Gokhan Ertugrul
e-mail: mdgertugrul@gmail.com

Immunosuppression. All patients received ATG intraoperatively and continued its administration for 2 days postoperatively. All patients received standard immunosuppressive therapy with calcineurin inhibitors (tacrolimus or cyclosporine), Mycophenolate Mofetil or Mycophenolate Sodium to be used in the first year and Prednisolone to be used in the first three months. Targeted tacrolimus level was between 8-10 nanogram/milliliter (ng/mL). Targeted cyclosporine A level was between 100 and 200 ng/mL.

CMV Infection Prophylaxis. Patients were given 900 mg/day valganciclovir for CMV prophylaxis for the first 90 days. Patients were investigated on weekly basis during the first month after discharge, on bi-weekly basis during the second month, and monthly in the following months. CMV PCR-DNA was sent from patients who were considered to have CMV reactivation (creatinine elevation) and renal biopsy was performed if necessary. CMV viraemia was defined as CMV-PCR >1000 copies/mL and CMV infection as positive PCR in combination with clinical symptoms.

Statistical Analysis. Normally distributed continuous variables were given as mean ± standard deviation, and categorical variables were given as percentage and number.

Results. Mean age was 38.3 ± 15.6 years, 68 (68%) patients were males and 32 (32%) patients were females. The mean body mass index was 25.2 ± 5.6 kg /m2. The 27 (27%) patients were done preemptive transplantation. The indications for kidney transplantation were; 37 (37%) patients had unknown cause of end-stage renal failure, 32 (32%) had diabetes mellitus, 14 (14%)

had hypertension, 12 (12%) had chronic glomerulonephritis, 3 (3%) patient had polycystic kidney disease and 2 (2%) other causes (Alport syndrome, vesicoureteral reflux, etc.). In all these donors and recipients, preoperative CMV IgM was (-), CMV was IgG (+). During the first year of transplantation, the acute rejection rate constituted 9% (9 patients).

All patients were treated with ATG induction. Mean ATG dosages per kilogram were 1.57 ± 0.17 mg/kg. Mean cumulative ATG dosages per patient were 370 ± 140 mg.

Mean follow-up was 29.1 ± 15 months. During follow-up period four graft loss due to humoral rejection happened and 5 patients died. Graft survival rates for 1 and 5 years were 98% and 96%, respectively. Patient survival rates for 1 and 5 years were 98% and 95%, respectively. Five patients died with cardiovascular disease.

In our cohort, there was not detected CMV infection in follow up. Table 1 shows a comparison of our results with literature results.

Table 1

Comparison of our results with literature results

	Dose of Valganciclovir (mg/kg/day)	Duration of Prophylaxis (day)	CMV Infection (n/%)	ATG Induction (n/%)	Acute Rejection (n/%)
Halim et al [22]	900 mg/kg/day	180 days	1 (1%)	50 (51%)	24 (24.5%)
Gabardi et al [23]	900 mg/kg/day	180 days	26 (24.3%)	77 (72%)	14 (13%)
Stevens et al [24]	900 mg/kg/day	180 days	12 (26.7%)	5 (1.5)	4 (8.9%)
Our Study	900 mg/kg/day	90 days	-	100 (100%)	9 (9%)

Discussion. Viral infections are an important cause of graft dysfunction after kidney transplantation [7]. CMV infection may reduce graft survival and patient survival [8]. It is the most important viral agent that requires prophylaxis after renal transplantation. CMV infection is a serious condition that may occur especially during the first few months after kidney transplantation. The cytopathic effect of cytomegalovirus on glomerular cells was first described by Richardson et al [9]. CMV can cause glomerular vasculopathy, tubulointerstitial nephritis (rich in plasma cells), and graft dysfunction [10]. CMV conditions 20% of cause symptomatic disease [11, 12]. CMV 10-60% can be seen in patients not receiving prophylaxis [13, 14].

The immunosuppressive dose is the most important risk factor for the CMV infections [15, 16]. Especially, the risks increase in patients using high dose immunosuppressive and ATG induction (acute rejection etc.) [17]. Also, the other risk factors are a preoperative CMV IgM-IgG of donors and recipients. [18]. In our study, all these preoperative donors and recipients CMV IgM was (-), CMV IgG was (+). The first year of transplantation, the acute rejection rate was 9% (9 patients). All patients were treated with ATG induction. Mean ATG dosages per kilogram were 1.57 ± 0.17 mg.

CMV PCR-DNA and transplant kidney biopsies are used as the gold standard diagnostics of CMV disease [19]. Pathological finding (Owl-Eye Inclusions) are pathognomonic [20]. In our study, CMV PCR-DNA was assessed and trucut transplant kidney biopsy was performed in 9 patients with increased creatinine values. CMV-PCR<1000 copies/mL was not found anything in trucut transplant kidney biopsy for CMV infections.

Prophylaxis is very important for prevention the CMV infections. Intravenous Ganciclovir or oral VGV is used for CMV prophylaxis [21]. VGV is using low and high dose (450 mg/day and 900 mg/day) or short term and long term (3 months or 6 months) [22-24]. In our clinic, we use only VGV. Our standard protocol is a high dose (900 mg/ day) and short term (90 days) prophylaxis in all patients.

Using high dose and long term (900 mg/day – 6 months) of VGV reduces frequency of CMV infection, but leukocytopenia and thrombocytopenia are potential severe side effects of this prophylaxis [25, 26]. CMV replication induces a state of immunosuppression. CMV infection was significantly associated with bacterial, fungal, and parasitic infections [27]. In our study, leukopenia, thrombocytopenia, bacterial, fungal, and parasitic infections associated with CMV prophylaxis were not detected.

In our study, during the follow-up period CMV infection was not detected. Of course, in addition to valganciclovir effectiveness two factors can contribute in this result: first is low dose ATG induction, second is donor and recipient CMV IgG (+).

Conclusions. Short-term standard-dose valganciclovir prophylaxis appears to be successful prevention CMV infections in living donor kidney transplantation. However, physicians must take into account ATG induction dose and preoperative CMV IgM and IgG positivity.

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Author contributions. GE and TY collected, analyzed, interpreted the data, and wrote the manuscript. All authors read and approved the final manuscript.

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