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Comparison of prophylactic versus preemptive treatments in the management of cytomegalovirus infection in renal transplant recipients

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Abstract. *To prevent acute or chronic rejection in renal transplant recipients, immunosuppressive treatments are applied. However, immunosuppressive treatments increase the risk of cytomegalovirus (CMV) infection. The aim of this study was to evaluate the differences in efficacy and cost of prophylactic and preemptive treatment strategies applied in respect of CMV infection to renal transplant recipients.*

Methods. *Patients who underwent renal transplantation in our center between 2010 and 2015, were retrospectively analyzed. The patients were allocated in two groups as those who received prophylaxis or preemptive treatment. A record was made of the kidney function tests (KFT), CMV PCR copy numbers, the presence of CMV infection, antiviral treatments received, and the costs were calculated of the tests and treatments. The groups were compared in respect of CMV infection and costs.*

Results. *A total of 71 patients with a median age of 38 years (range, 19-74 years) were included in the study. The prophylaxis group included 43 patients and the preemptive group included 28 patients. CMV infection was detected in 7 (16.3%) of the prophylaxis group and 2 (7.1%) patients of the preemptive group ($p=0.467$). The cost per month of the tests and treatment was lower in the preemptive group than in the prophylaxis group ($p<0.001$).*

Conclusion. *No significant difference was determined between the prophylactic and preemptive treatment protocols in respect of the CMV infection in the intermediate-risk group renal transplantation recipients. Preemptive treatment was seen to be a more cost-effective method than prophylactic treatment in Turkey.*

Keywords: *cytomegalovirus infection, renal transplantation, preemptive treatment, prophylactic treatment, valganciclovir.*

Conflict of interest statement. The authors declare no competing interest.

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Порівняння профілактичного та превентивного лікування цитомегаловірусної інфекції у реципієнтів ниркового трансплантату

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Резюме. Для запобігання гострого або хронічного відторгнення ниркового трансплантату застосовують імуносупресивне лікування. Однак імуносупресивні лікарські засоби підвищують ризик інфікування цитомегаловірусом (ЦМВ). Метою цього дослідження було оцінити ефективність та вартість профілактичних та попереджувальних стратегій лікування ЦМВ інфекції у реципієнтів ниркового трансплантату.

Методи. Ми провели ретроспективний аналіз до якого включили пацієнтів з нирковим алотрансплантатом, які лікувались у нашому центрі між 2010 та 2015 роками. Хворі були розподілені у дві групи як ті, хто отримував профілактичне або превентивне лікування. Аналізували швидкість клубочкової фільтрації (ШЛФ), вірусне навантаження за результатами ПЛР тестування, наявність ЦМВ-інфекції та отримане протівірусне лікування. Витрати на лікування включали вартість тестування та метод терапії. Групи порівнювали щодо інфікування ЦМВ та вартості лікування.

Результати. У дослідження включено 71 пацієнт з середнім віком 38 років (діапазон, 19-74 роки). До групи профілактики увійшло 43 пацієнта, в превентивну групу - 28 пацієнтів. ЦМВ-інфекція виявлена у 7 (16,3%) пацієнтів групи профілактики та у 2 (7,1%) пацієнтів превентивної групи ($p = 0,467$). Вартість лікування була нижчою у превентивній групі у порівнянні з групою профілактики ($p < 0,001$).

Висновки. Суттєвої різниці між протоколами профілактичного та превентивного лікування щодо ЦМВ інфікування серед реципієнтів ниркового трансплантату не визначено. Тим не менш, у Туреччині превентивне лікування є більш рентабельним ніж профілактичне лікування.

Ключові слова: цитомегаловірусна інфекція, трансплантація нирок, превентивне лікування, профілактичне лікування, вальганцикловір

Introduction. In organ transplantation, effective immunosuppression must be applied to prevent organ rejection [1, 2]. However, effective immunosuppression causes the development of opportunistic infections [1, 2]. One of these opportunistic infections is cytomegalovirus (CMV) [1, 3]. Symptomatic CMV infection can be observed in 15%-20% of renal transplant recipients [4, 5]. Following transplantation from a CMV seropositive donor to a CMV seronegative recipient (D+/R-), the rate of CMV infection increases to as high as 60% [4]. Therefore, in general, prophylactic treatment for CMV infection is administered to recipients in the high and moderate risk groups [6]. Over recent years, as the CMV PCR diagnostic method has started to be used to rapidly and correctly reveal CMV viral replication, a preemptive treatment strategy has come to prominence [7, 8]. Prophylactic treatment is antiviral therapy applied for 3-6 months from 10 days after transplantation [9]. Preemptive treatment is antiviral treatment starting from the determination of asymptomatic CMV infec-

tion following weekly periodic (for 6 months) CMV PCR [6].

These two approaches are similar in respect of CMV infection but studies have shown differences in respect of side-effects [7, 9-12]. However, these studies have been conducted with limited numbers of patients, and there has been variability in the follow-up periods and the antivirals used. Very few studies have compared prophylactic and preemptive treatments in respect of cost-effectiveness in CMV infection. This study aimed to evaluate the differences in efficacy and cost of prophylactic and preemptive treatment strategies applied in respect of CMV infection to renal transplant recipients.

Material and Methods. A retrospective evaluation was made in patients who were diagnosed, followed up and treated with renal transplantation in the Nephrology Department of Gazi University Hospital between 01.01.2010 and 01.01.2015. A database was created with data collected from patient files and computer records of demographic data, the etiology of chronic renal failure (CRF), hemodialysis and/or peritoneal dialysis applied, immunosuppressive treatments received, CMV IgG and IgM, CMV PCR, BUN, and creatinine values. In addition, CMV IgG and CMV PCR data of all recipients and donors before transplantation were obtained from the records. The patients included in the study were renal transplantation recipients aged >18

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years. Patients were excluded from the study if they withdrew from follow up, if data records were incomplete, if they had not taken the antiviral treatment regularly, or if regular CMV PCR measurements had not been taken. A total of 108 patients who met the criteria were included in the study.

The patients were evaluated as two groups, those applied with preemptive treatment and those applied with prophylactic treatment. Patients in the prophylaxis group were treated with 900mg/day valganciclovir for 3 months following renal transplantation (anti-thymocyte globulin [ATG] was applied for 6 months). CMV PCR test was not performed unless there was any deterioration in renal function of the patients in the prophylaxis group. Patients in the preemptive group were applied with regular weekly CMV PCR testing for 6 months, and if CMV PCR copy number reached 400 or more, antiviral treatment was started and continued until reaching clearance of CMV DNAemia in 2 consecutive measurements (CMV PCR copy number <50). Since late reactivation is not uncommon calculations were made of the costs of the antiviral treatments applied in the two-year follow-up period, the CMV PCR tests, and the hospital costs related to CMV infection or disease, and thus the mean monthly testing and treatment costs were calculated. Drug prices in our country change annually. The drug cost of the patients was calculated from the current price of that year. Similarly, CMV PCR test prices also change annually. While calculating the CMV PCR cost of the patients, it was calculated from the current price of that year. Treatment and examination costs of inpatients due to CMV infection were calculated at current prices at that time.

Cytomegalovirus infection was defined by the detection of CMV DNAemia (CMV PCR >400 copy). The patients with asymptomatic CMV DNAemia or latent infection were also included in the CMV infection group.

Ethical approval for the study was granted by the Ethics Committee of Gazi University (decision No: 524, dated: 16.10.2015).

Statistical Analysis. Data obtained in the study were analyzed statistically using Statistical Package for the Social Sciences software. Descriptive statistics were stated as number and percentage for categorical variables and mean (M) \pm standard deviation (SD) or median (Me) with minimum and maximum values for continuous variables. The conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. In the comparisons of categorical variables, the Pearson Chi-square test and Fisher's Exact test were used. For parametric data, the Student's t-test was applied. All the statistical analyses were applied two-way and a value of $p < 0.05$ was accepted as statistically significant.

Results. A total of 71 patients with a median age of 38 years (range, 19-74 years) were included in the study. The prophylaxis group included 43 patients and the preemptive group, 28 patients. Except for anti-thymocyte globulin (ATG) use, the clinical characteristics and demographic data of the patients were similar in both groups. ATG was not administered to any patient in the preemptive group (Table 1).

All the renal transplantation recipients and donors were serologically CMV IgG+ and CMV PCR negative. All the renal transplant recipients were in the intermediate-risk group in respect of CMV infection (D+/R+).

Table 1

Demographic and clinical data of the included patients

Analyzed data	Total (n=71)	Prophylaxis Group (n=43)	Preemptive Group (n=28)	p-value
Male	43 (60.6)	26 (60.5)	17 (60.7)	0.983
Female	28 (39.4)	17 (39.5)	11 (39.3)	
Age (years), median (range)	38 (19-74)	38 (21-74)	38 (19-61)	0.572
Etiology– n (%)				
HT	14 (19.7)	6 (14.0)	8 (28.6)	0.220
GN	13 (18.3)	7 (16.3)	6 (21.4)	
DM	5 (7.0)	3 (7.0)	2 (7.1)	
ADPKD	4 (5.6)	3 (7.0)	1 (3.6)	
Other	21 (29.6)	18 (42)	3 (10.7)	
Unknown	14 (19.8)	6 (14.0)	8 (28.6)	
Hemodialysis, n (%)	50 (70,4)	32 (74.4)	18 (64.3)	0.361
Peritoneal dialysis, n (%)	14 (19,7)	9 (20.9)	5 (17.9)	0.750

Table 1 continuation

Analyzed data	Total (n=71)	Prophylaxis Group (n=43)	Preemptive Group (n=28)	p-value
Immunosuppressive treatment, n (%)				
ATG	21 (29.6)	21 (48.8)	0 (0)	<0.001
Simulect	21 (29.6)	15 (34.9)	6 (21.4)	0.225
MMF	63 (88.7)	39 (90.7)	24 (85.7)	0.704
Tacrolimus	67 (94.4)	42 (97.7)	25 (89.3)	0.293
Cyclosporin	8 (11.3)	5 (11.6)	3 (10.7)	0.905
mTOR	5 (7.0)	5 (11.6)	0 (0)	0.149
Other	15 (21.1)	8 (18.6)	7 (25.0)	0.519

Abbreviations. HT: Hypertension, DM: Diabetes Mellitus, GN: Glomerulonephritis, ADPKD: Autosomal Dominant Polycystic Kidney Disease, ATG: Anti-thymocyte Globulin, MMF: Mycophenolate mofetil

CMV infection was determined in 7 (16.3%) patients in the prophylaxis group and in 2 (7.1%) patients in the preemptive group. No statistically significant difference was observed between the groups in respect of

CMV infection ($p=0.467$). The monthly cost of testing and treatment was determined to be statistically significantly lower in the preemptive group than in the prophylaxis group ($p<0.001$) (Table 2).

Table 2

Comparison of the Prophylaxis versus Pre-emptive groups according to the presence of CMV-infection and monthly treatment costs

	Prophylaxis Group (n=43)	Pre-emptive Group (n=28)	p-value
CMV Infection present, n (%)	7 (16.3)	2 (7.1)	0.47
Monthly cost – TL (ss)	98 ± 65.7	58 ± 30.1	<0.001

Abbreviations. CMV: Cytomegalovirus, TL: Turkish Liras

CMV reactivation occurred in one of the patients in the pre-emptive treatment group in the 2nd month after transplant, while the other occurred in the 3rd month. In 7 patients in the prophylaxis group, CMV reactivation occurred at the 2nd, 3rd, 5th, 6th, 7th, 9th, and 40th months after transplantation, respectively.

The comparison between the preemptive group and the prophylaxis subgroup not administered with ATG according to the presence of CMV infection and treatment costs is shown in Table 3.

Table 3

Comparison of the Prophylaxis (ATG -) versus Pre-emptive groups according to CMV-infection presence and monthly treatment

	Prophylaxis Group (n=22)	Pre-emptive Group (n=28)	p-value
CMV infection present – n(%)	3 (13.6)	2 (7.1)	0.45
Monthly cost – TL (ss)	112 ± 83.8	58 ± 30.1	0.003

Abbreviations. CMV: Cytomegalovirus, TL: Turkish Liras

No statistically significant difference was determined between the two groups in respect to the CMV infection ($p=0.45$). The monthly cost of testing and

treatment was determined to be statistically significantly lower in the pre-emptive group than in the prophylaxis group ($p=0.003$).

The mean BUN, creatinine, and GFR values of all the patients who developed CMV infection (n=9) were determined to be 29.89 ± 16.34 mg/dL, 1.61 ± 0.85 mg/dL, and 48.72 ± 28.23 mL/min/1.73m², respectively before CMV infection and 35.77 ± 15.90 mg/dL, 1.80 ± 0.91 mg/dL, and 47.11 ± 23.73 mL/min/1.73m² after infection developed. No statistically significant difference was determined between the pre-post CMV infection in respect of BUN, creatinine and GFR mean values (p=0.260, p=0.202, p=0.680, respectively). No statistically significant difference was determined between the preemptive and prophylaxis treatment groups in respect of pre-post CMV infection BUN, creatinine and GFR mean values (preemptive group: p=0.260, p=0.202, p=0.680, respectively, and prophylaxis group: p=0.566, p=0.658, p=0.779, respectively).

Discussion. In this study, we investigated the difference between prophylactic and preemptive treatment groups according to the development of CMV infection and cost-effectiveness. No difference was determined between the two groups according to the development of CMV infection. The study showed no statistical differences in the effectiveness of compared protocols. The monthly average testing and treatment costs were seen to be lower in the pre-emptive treatment group than in the prophylaxis group.

CMV infection or reactivation may be seen at rates of up to 60% in renal transplantation recipients [4]. The highest risk group is CMV IgG- patients with a CMV IgG+ transplanted organ (D+/R-) [13]. CMV IgG+ recipients are in the intermediate-risk group in respect of CMV infection, regardless of the CMV serology of the donor (D+/R+ or D-/R+). The lowest risk group comprises CMV negative recipients with a CMV negative transplanted organ (D-/R-) [1]. In a randomized, controlled trial by Reischig et al, the CMV infection rates were found to be 6% in the preemptive group and 9% in the prophylaxis group, with no difference determined between the groups [10]. In the same study, the vast majority of patients were found to be in the intermediate risk group in respect of CMV infection (D+/R+) [10]. Kielberger et al conducted a randomised controlled trial of patients with similar characteristics, and reported the CMV infection rate to be 6% in both the preemptive and prophylaxis groups, with no difference between the groups [14]. Similarly in the current study, the CMV infection rate was determined as 7.1% in the preemptive group and as 13.6% in the prophylaxis group not applied with ATG as immunosuppression. Consistent with the findings of the studies by Reischig

and Kielberger, no difference was determined between the current study groups in respect of CMV infection. Witzke et al conducted a randomized controlled study on intermediate-risk group patients and reported the CMV infection rate as 11.5% in the prophylaxis group and 39.7% in the preemptive group (p<0.001) [15]. In their study, the CMV PCR follow-up was applied once every 2 weeks [15]. In the current study, CMV PCR follow-up was applied weekly. The higher rate of CMV infection seen in the pre-emptive group in the Witzke study could be related to the long interval of CMV PCR follow-up.

In the study by Reischig et al, the cost of the preemptive treatment group was shown to be higher than those of the prophylactic treatment group [10]. As that study was conducted in 2009, the costs of the drugs and CMV PCR tests could have been different from current costs. Kielberger et al also found that costs were lower in the prophylaxis group than in the preemptive group [14]. In contrast to the Reischig et al study, the costs in our study were seen to be lower in the preemptive group than in the prophylaxis group, which was thought to be due to the lower current cost of the CMV PCR test in Turkey. In addition, the fact that different antivirals have been used in studies could have affected these results.

The present study has some limitations. As all the patients were in the intermediate-risk group for CMV infection, it is not possible to comment on the cost-effectiveness of preemptive treatment in other risk groups. Since the study did not include acute or chronic rejection patients' data and associated biopsy results, the preemptive and prophylaxis groups could not be compared. Moreover, sufficient information about side-effects also was not available in the medical records.

Conclusion. The results of the study showed that preemptive treatment with weekly CMV PCR follow-up was an effective method as an alternative to the prophylactic treatment method for renal transplant recipients in the intermediate-risk group. Although there may be differences from country to country, the preemptive treatment cost was seen to be lower.

Disclosure statement. The authors declare no conflict of interest

Authors Contributions.

Karaçin C: Writing manuscript, data collection;

Yaşar E: Data collection and analyzed clinical data of the patients;

Helvacı Ö: Data collection;

Güz G: Management of the research.

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