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ARAŞTIRMA / RESEARCH

Efficacy and safety of low-dose valganciclovir prophylaxis among renal transplant recipients

Renal transplant alıcılarında düşük doz valgansiklovir profilaksisinin etkinliği ve güvenilirliği

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Abstract

Purpose: Cytomegalovirus (CMV) infection is one of the most common infections observed following kidney transplantations. Transplantations between cytomegalovirus (Immunoglobulin G)-seropositive donor and CMV-seropositive recipient (D+/R+) are considered to be of moderate risk. In our study, we investigated the efficacy of low-dose (450 mg/g) valganciclovir in CMV chemoprophylaxis in renal transplant patients over their first post-transplant year.

Materials and Methods: A total of 68 consecutive patients aged over 18 years who underwent renal transplantation between January 2016 and June 2019 were included in this retrospective study. All patients were administered valganciclovir 450 mg/g, for 100 days. The efficacy of low-dose valganciclovir was determined by whether the patients developed a CMV disease during their first post-transplant year.

Results: Only one patient (n=1/68) (1.5%) developed CMV disease. CMV DNA titer was positive on post-transplant day 134 of the patient who had unexplained loss of GFR. CMV disease-related acute rejection, graft loss, leukopenia, post-transplant diabetes mellitus, opportunistic infection, or patient loss was not observed.

Conclusion: There are many studies comparing CMV prophylaxis with low and standard dose (450 vs. 900 mg/g) valganciclovir treatment in transplant patients. The results of this study show that low-dose valganciclovir is sufficient for the prophylaxis of CMV disease in D+/R+ medium-risk patients without leading to any side effects. Further clinical studies with larger patient participation are needed.

Keywords:. Renal transplantation, cytomegalovirus, valganciclovir

Öz

Amaç: Sitomegalovirüs (CMV) infeksiyonu, böbrek nakli sonrasında en sık görülen infeksiyonlardan biridir. Sitomegalovirüs (Immunglogulin G) -seropozitif donör ve CMV-seropozitif alıcı (D+/A+) arasında yapılan nakiller orta riskli kabul edilmektedir. Çalışmamızda renal transplantasyon yapılmış hastalarda nakil sonrası 1 yıllık dönem için düşük doz (450 mg/g) valgansiklovirin CMV kemoprofilaksindeki etkinliğini araştırdık.

Gereç ve Yöntem: Ocak 2016 ile Haziran 2019 tarihleri arasında böbrek nakli yapılmış 18 yaş üzerinde ardışık 68 hasta retrospektif olarak çalışmaya dahil edildi. Tüm hastalara 100 gün süreyle 450 mg/g valgansiklovir tedavisi verildi. Düşük doz valgansiklovirin etkinliği hastaların posttransplant 1 yıl içerisinde CMV hastalığı geçirip geçirmemeleri dikkate alınarak belirlendi.

Bulgular: Sadece bir hastada (n=1/68) (%1,5) CMV hastalığı gelişti. Nakil sonrası 134. günde nedeni açıklanamayan GFR kaybı olan hastanın CMV DNA titresi pozitif geldi. Tüm grupta CMV hastalığı ilişkili akut rejeksiyon, graft kaybı, lökopeni, PTDM, fırsatçı infeksiyon veya hasta kaybı gelişmedi.

Sonuç: Literatürde transplant hastalarında CMV profilaksisi için düşük doz (450 mg/g) valgansiklovir tedavisinin standart doz (900 mg/g) ile karşılaştıran çok sayıda araştırma mevcuttur. Çalışmamızda düşük doz valgansiklovirin D+/A+ orta riskli hastalarda CMV hastalığının profilaksisi için yeterli olduğu ve yan etkiye yol açmadığını gördük. Bu konu ile ilgili geniş hasta katılımlı klinik çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Renal transplantasyon, sitomegalovirüs, valgansiklovir

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INTRODUCTION

Cytomegalovirus (CMV) infection is one of the most common infections in kidney transplant patients. CMV disease is diagnosed with the presence of CMV in plasma by quantitative nucleic acid amplification test (QNAT) or polymerase chain reaction (PCR)-pp65 test along with CMV infection-related clinical symptoms and signs. CMV disease / infection may lead to multisystem diseases and clinical conditions such as graft rejection, post-transplant diabetes mellitus (PTDM), opportunistic infections, and leukopenia[1]. Due to immunosuppressive therapies used in kidney transplant recipients, the risk of CMV disease is particularly high in the first three post-transplant months[2]. The risk of CMV infection is determined by CMV serology of the donor and the recipient and the intensity of immunosuppressive therapy used during transplantation. While transplants carried out between CMV (immunoglobulin G)-seropositive donors and CMV-seronegative recipients (D+/R-) pose the highest risk for CMV infection, D+/R+ and D-/R+ transplants are under moderate risk and D-/R- transplants carry low risk[3].

Valganciclovir is the L-valyl ester of ganciclovir. It is used as a single dose daily by the oral route, and its absorption is much better than ganciclovir[4]. Leukopenia, diarrhea, and fever may develop due to valganciclovir. Dose modification should be performed according to glomerular filtration rate (GFR)[5,6]. There are studies reporting increased risk of leukopenia and rejection with high dose (900 mg/g) valganciclovir prophylaxis[7-10].

In our study, we investigated the efficacy of low-dose (450 mg/g) valganciclovir CMV chemoprophylaxis in D+/R+ medium-risk renal transplant patients over their first post-transplant year.

MATERIALS AND METHODS

Seventy-two consecutive patients aged over 18 years who underwent renal transplantation between January 2016 and June 2019 were included in this retrospective study. The study was approved by the Ufuk University, Faculty of Medicine, regional committee for ethics (protocol no: 20200124/2) in medical research and complied with Helsinki criteria.

Four of the high-risk D+/R- patients were excluded from the study since two of them was on 900 mg/g valganciclovir prophylaxis for 6 months; and the other two had GFR <60 ml/min and valganciclovir dose was adjusted to 450 mg/g. The final sample included 68 patients. When indicated anti-thymocyte globulin (ATG-Fresenius S) was administered at 100 mg/g dose for 3 days. Following total 1500 mg intravenous methyl-prednisolone all patients were administered prednisolone (0.8 mg/kg/day, orally). Prednisolone dose was tapered to 30 mg/day at 1 month, 20 mg/day at 2 months and 5 mg/day after 3 months. In the maintenance treatment phase, calcineurin inhibitor [tacrolimus (Tac); 0.1 mg/kg/day, 2 doses per day or cyclosporin-A (CsA); 6 mg/kg/day, 2 doses per day] and antiproliferative agent (mycophenolate mofetil; maximum 2 g/day or mycophenolate sodium; maximum 1440 mg/g) were used along with prednisolone. CsA and Tac doses were titrated as needed to achieve target blood levels. Valganciclovir prophylaxis was started in the first 10 post-transplant days considering GFR. The duration of treatment was determined as 100 days in D+R/+ patients and 6 months in D+/R- patients. In case of acute organ rejection, renal biopsy was performed and treatment [pulse methyl-prednisolone, *antithymocyte globulin* (ATG), plasmapheresis, and intravenous immunoglobulin treatments alone or in combination] were administered according to Banff criteria. Six of eleven patients who experienced with an acute rejection received ATG therapy for the treatment and they were given CMV prophylaxis for 3 months.

Routine laboratory tests [complete blood count, fasting blood glucose, creatinine, eGFR measurements, liver function tests (bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase levels) and drug levels were performed. CMV DNA titer was measured in all patients in the post-transplant 1st month. Further CMV DNA titer measurements were done in all hospitalized and outpatients who developed unexplained graft dysfunction, leukopenia, and/or febrile illnesses. CMV tests were performed according to the international consensus guidelines[1]; tissue-invasive disease and CMV syndrome were generally accepted as CMV disease. Local infections and organ dysfunctions presented via biopsy were evaluated as tissue-invasive disease. It was as CMV syndrome if CMV viremia was accompanied by one or more of the finding of fever, newly developed severe malaise, leukopenia, thrombocytopenia, atypical lymphocytosis, and elevation of liver enzymes. When CMV DNA titer was high enough to diagnose CMV disease, a therapeutic dose of

valganciclovir was administered. The side effect profile of valganciclovir was determined by routine clinical and laboratory tests.

The efficacy of low-dose valganciclovir was determined by considering whether the patients developed CMV disease within the first post-transplant year. Patient survival, PTDM, opportunistic infections, leukopenia, acute rejection (confirmed by biopsy in a 12-month period) and graft loss (dialysis or retransplant requirement in a 12-month period) were monitored as follow-up parameters.

Statistical analysis

Descriptive statistics have been conducted for reporting of demographic deatures and clinical outcomes.

RESULTS

Of the patients, 26% were female and 74% were male. The median age was 42 ± 14.3 years and the follow-up period was 24 ± 11 months. The underlying causes of end-stage renal disease were as follows 23 (33.8%) of the patients had chronic glomerulonephritis, 13 (19.1%) of the patients had hypertension, 9 (13.2%) of the patients had secondary amyloidosis, 8 (11.8%) of the patients had type 2 diabetes mellitus, 6 (8.8%) of the patients had atrophic kidney, 4 (5.9%) of the patients had nephrolithiasis, 1 (1.5%) of the patient had polycystic kidney disease, 1 (1.5%) of the patient had tubulointerstitial nephritis and 1 (1.5%) of the patient had vesicoureteral reflux; while no cause could have been detected in 2 (2,9%) of the patients. Dialysis type, number of tissue adaptation, type of transplantation, type of induction and maintenance immunosuppression treatment features of patients are shown in Table 1.

All patients were administered valganciclovir treatment of 450 mg/g for 100 days. No early discontinuation was observed among 68 patients included in the study due to intolerance towards or adverse effects (leukopenia, impaired liver function tests, diarrhea, or fever) of valganciclovir. CMV disease-related acute rejection, graft loss, leukopenia, PTDM, opportunistic infection or patient loss did not occur in any of the patients.

Only one (1.5%) patient developed CMV disease. CMV DNA titer was positive of this 64-year-old female patient who had unexplained loss of GFR on the 134th post-transplant day; the etiology of the end-stage renal failure was unknown. One of her kidneys was atrophic. ATG induction has been given for 3 days due to six mismatches. Valganciclovir treatment was given to patient until her CMV DNA titer was negative. No side effects and relapses were observed during the treatment.

Table 1. Patient demographics

Variable	All patients (n=68; %)
Gender, F/M	18/50 (%26/%74)
Age, median	42±14.3
Dialysis type	
Pre-emptive	33 (%48.5)
Hemodialysis	31 (%45.6)
Peritoneal dialysis	4 (%5.9)
Transplant type (live donor/cadaver)	65/3 (%95.6/%4.4)
Miss-Match Count	
0 MM	4 (%5.9)
1 MM	4 (%5.9)
2MM	9 (%13.2)
3 MM	25 (%36.8)
4 MM	10 (%14.7)
5 MM	9 (%13.2)
6 MM	7 (%10.3)
Transplant duration, months, median	24±11
Immunosuppression	
Tac+MMF	67 (%98.5)
CsA+MMF	1 (%1.5)
Induction treatment	
ATG	27 (%39.7)
Basiliximab	1 (%1.5)
No induction	40 (%58.8)
Biopsy-diagnosed rejection	11 (%16.2)

DISCUSSION

International consensus and guidelines recommend the use of antiviral prophylaxis for protection from CMV disease in renal transplant patients[11]. There are reports claiming higher incidence of drug interruption or discontinuation, dose reduction in antiproliferative treatment and more frequent need for G-CSF due to causes such as early period leukopenia and myelosuppression in patients receiving high-dose prophylaxis[8,12].

In the medical literature, there are studies comparing low-dose (450 mg/g) and standard-dose (900 mg/g) of valganciclovir for CMV prophylaxis in transplant patients[8,9,13]. In 478 medium-risk D+/R+ renal

transplant patients, low-dose (450 mg/g, n=398) and high-dose (900 mg/g, n=89) valganciclovir prophylaxis was administered for 3 months, where the 1-year follow-up CMV disease rate was 3.5% in the low-dose group and 3.4% in the high-dose group (p=1.0). In this study, the frequency of biopsy-proven acute rejection was 10.3% in the low-dose and 11.2% in the high-dose prophylaxis groups (p = 0.84) with a graft loss ratio of 5% and 6.7%, respectively. In addition, reported creatinine values were lower (1,4±0,8 vs. 1,6±0,7mg/dl, p=0.005) and eGFR values (52.9 ± 20 vs. 45.9 ± 19.8 ml/min, p = 0.011) were significantly higher in the low-dose group. On the other hand, the rates of opportunistic infections and diabetes mellitus were 20.6% and 7.3%, respectively, in the low-dose valganciclovir group and the difference was not statistically significant compared to the high-dose group[12]. Another study comparing 196 patients receiving low-dose (450 mg/g, n=98) and high-dose (900 mg/g, n=98) valganciclovir prophylaxis in the first 6 post-transplant months, the CMV infection rate was reported as 1% (p>0.05) in both groups at the 1-year follow-up. Additionally, 2% acute rejection, 8% PTDM, 1% graft loss and 98% patient survival rates were observed in the low-dose group and no statistically significant difference was observed when compared to the high-risk patients[13]. In a recent meta-analysis, patients receiving low-dose and high-dose valganciclovir were compared, and no statistically significant differences were observed with respect to CMV disease (p=0.36 for 1271 patients), acute rejection (p=0.19 for 1343 patients), graft loss (p=0.24 for 1271 patients), mortality (p=0.23 for 1271 patients), opportunistic infections (p=0.14 for 985 patients), and leukopenia (p=0.18 for 1082 patients)[14]. In our study, the rate of CMV disease was found to be 1.5% (n=1/68) in renal transplant recipients with low dose valganciclovir prophylaxis, similar to the rates in the literature[15]. CMV-related graft loss, opportunistic infection, leukopenia, or PTDM was not observed in our patient group.

The fact that our study sample consisted of patients who received only low-dose valganciclovir without a control group including patients receiving high-dose prophylaxis, collecting the data retrospectively, and the small sample size are limitations of this study.

In conclusion, we determined that low-dose valganciclovir was sufficient for CMV disease prophylaxis in D+/R+ medium-risk patients and did not cause any side effects. There is a need for larger scale clinical trials on this subject. Moreover, transplantation centers would encourage one another on low-dose prophylaxis by sharing their experiences and treatment outcomes.

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