Successful Cost-Effective Prevention of Cytomegalovirus Disease in Kidney Transplant Recipients Using Low-Dose Valganciclovir

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Abstract

Objectives: Low-dose valganciclovir prophylaxis is still under investigation in renal transplant procedures. Our aim was to assess the cost effectiveness of 450 mg versus 900 mg valganciclovir prophylaxis in kidney transplant recipients.

Materials and Methods: In this prospective trial, 201 kidney transplant patients were randomized (1:1) to receive 450 mg/d (group 1, n = 100) or 900 mg/d (group 2, n = 101) valganciclovir prophylaxis for the first 6 months after transplant. Patients were studied for incidence of cytomegalovirus disease, leukopenia episodes, rejection episodes, and graft outcomes along with associated costs over 1 year. Costs (in US dollars) of treatment of rejection were also analyzed.

Results: Demographic features of the studied groups were comparable. We found that the cost of cytomegalovirus care in group 1 patients was significantly lower (by 50% at 6 months; P < .001), with less leukopenia episodes (P = .04), lower doses of granulocyte colony-stimulating factor (by 30% at 6 months; P = .03), higher doses of mycophenolate mofetil (P = .04), and less rejection episodes (P = .01) compared with group 2. In group 2, there were more episodes of cytomegalovirus infection (P = .052) and BK virus nephropathy (P = .04). Graft and patient outcomes were satisfactory in both groups.

Conclusions: Low-dose valganciclovir for cytomegalovirus prophylaxis after renal transplant is safer, effective and without breakthrough infection, and less costly than using the usual dose.

Key words: BK nephropathy, Outcome, Prophylaxis, Renal transplant

Introduction

Cytomegalovirus (CMV) infection is a common viral infection after kidney transplant,1 which causes noteworthy morbidity and mortality. Immunoglobulin G against CMV increases with age in the general population and in most donors and recipients before transplant.1,2 Cytomegalovirus infection can result in pneumonitis, encephalitis, hepatitis, and gastrointestinal disease, as well as many clinically important events such as fever and neutropenia.2 In addition, it is associated with a number of indirect effects in kidney transplant recipients, including reduced long-term patient survival, increased risks of other opportunistic infections, acute and chronic graft rejection, allograft dysfunction, and increased total cost of care.3,4

Lacking chemoprophylaxis, most CMV disease occurs during the first 3 months after transplant, when patients are receiving intensive immunosuppressive agents to prevent graft rejection,5,6 even with the absence of induction therapy and maintenance immunosuppression with cyclosporine, mycophenolate mofetil (MMF), and low-dose prednisone. In a study of 500 kidney transplant recipients, CMV antigenemia was detectable in over 60% of patients in the first 100 days after transplant.7

The risk of CMV infection and disease after transplant is strongly dependent on donor and recipient serostatus and the intensity of the immunosuppression regimen,2,8-12 with highest risk among CMV-seronegative recipients of CMV-seropositive donors.12
Originally, intravenous ganciclovir was effective for both CMV prevention and treatment, even with its oral formulation despite low bioavailability, and has been proven to be effective in high-risk donor-positive/recipient-negative patients. Valganciclovir with its favorable pharmacokinetic profile was developed to overcome the limitations of ganciclovir. A single once-daily 900-mg oral dose of valganciclovir provides comparable plasma exposures to those achieved with 5 mg/kg intravenous ganciclovir. At 60%, its bioavailability is up to 10-fold higher than that of oral ganciclovir. This dose has been effective in preventing CMV infection in kidney transplant recipients. Valganciclovir dose adjustment according to the estimated glomerular filtration rate (eGFR) is advisable. In a meta-analysis on CMV universal prophylaxis that included 12 trials with 900 mg valganciclovir (1543 patients) and 8 trials with 450 mg valganciclovir (1531 patients), the 900-mg dose showed no superior efficacy versus a control regimen (ganciclovir or preemptive) and equivalent efficacy to 450 mg valganciclovir (statistical power of 94% and 97%). However, 900 mg valganciclovir was significantly associated with 3 times increased risk of leukopenia and 2 times increased risk of rejection compared with 450 mg valganciclovir.

In accordance with an IMPACT study, valganciclovir prophylaxis was recommended for 200 days posttransplant, as it was more efficacious than a 100-day course in preventing CMV disease. There were some limitations to this study, including uncontrolled immunosuppressive regimens, no analyses of HLA matching despite some reports showing that poor HLA-B and HLA-DR matching significantly reduce the incidence of CMV infection in solid-organ transplant recipients, and restriction to only high-risk kidney transplant recipients. In addition, data on discontinuation of antiemetabolites, drug-induced leukopenia, and CMV viremia were not assessed. Although total granulocyte colony-stimulating factor (G-CSF) use was reported, there was no detailed assessment of its use. However, information provided by the IMPACT study may have helped in better understanding the clinical consequences of valganciclovir-related adverse effects.

Before our study, we observed more leukopenia and rejection episodes after implementing the recommendation to extend high-dose anti-CMV prophylaxis to 6 months after transplant. We hypothesized that low-dose valganciclovir (450 mg/d instead of 900 mg/d) for 6 months may have the same prophylactic effect against CMV disease with less leukopenia attacks and the related consequences. In this study, our aim was to assess the cost effectiveness of 450 mg versus 900 mg valganciclovir for kidney transplant recipients.

**Materials and Methods**

From 2010 to 2013, we enrolled 201 kidney transplant patients in this prospective randomized study. Patients were randomized into 2 groups according to valganciclovir dose: group 1 included 100 patients with low-dose valganciclovir (450 mg/d) and group 2 included 101 patients with full-dose valganciclovir (900 mg/d) for 6 months posttransplant. All patients provided signed informed consent. This study was conducted in full accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and adhered to local and national regulatory requirement and laws. Informed consent was obtained from all individual participants included in the study.

Eligible patients were only kidney transplant recipients who could tolerate oral valganciclovir within 1 week posttransplant and were not allergic to valganciclovir. We excluded from the study patients with leukopenia (< 3500 cells/μL) before starting valganciclovir and pregnant women. Doses were given according to eGFR calculated according to the Cockcroft-Gault formula for adults. According to the eGFR, the dose of valganciclovir was modified so that a full prophylactic dose was given to patients of group 2 and 50% of this dose was given to patients of group 1.

Our immunosuppression protocol consisted of 5 doses of antithymocyte globulin (Sanofi US, Bridgewater, NJ, USA) for high-risk patients (patients with retransplants, prior pregnancies, blood transfusion, HLA-antibody positive, and or more than 4 HLA mismatches) or 2 doses of IL-2 receptor blocker (basiliximab; Novartis, Inc., Basel, Switzerland) for low-risk patients. Maintenance therapy consisted of prednisolone, MMF, and a calcineurin inhibitor (CNI). The dose of CNI was gradually decreased until the lowest dose by the end of year 1 was guided by the 12-hour trough level. We kept the cyclosporine levels between 200 and 250 ng/mL during month 1, then between 150 and 200 ng/mL for several months,
between 125 and 150 ng/mL for 2 months, and then from 75 to 125 ng/mL until the end of year 1. Similarly, we kept tacrolimus trough levels between 8 and 10 ng/mL during the first 3 months and then from 5 to 8 ng/mL thereafter. Maintenance immunosuppression with a sirolimus-based regimen was used for rejection-free patients with low immunologic risk 3 months after transplant.

Acute cellular rejection was treated with intravenous methylprednisolone sodium succinate (1 g/d for 3 d) and or thymoglobulin (1 mg/kg for 7-10 d) for steroid-resistant rejection. Acute antibody-mediated rejection was treated with plasma exchange, intravenous immunoglobulin G (2 g/kg), and rituximab. All rejection episodes were biopsy proven according to Banff criteria. Patients who received thymoglobulin as antirejection were treated with a secondary prophylaxis for 1 month, whereas those who developed viremia during this period were given a therapeutic dose for 3 weeks followed by prophylaxis for 3 months. Patients were monitored daily during hospital stay and then at each outpatient visit with complete blood analyses, serum creatinine, creatinine clearance, liver function tests (bilirubin, liver enzymes, and albumin), and drug levels. Cytomegalovirus DNA was tested by polymerase chain reaction (PCR) at the time of transplant and at 1, 2, 3, 6, 9, and 12 months post-transplant. Patients with significant CMV PCR titer (whenever CMV copies were detected by quantitative PCR) and who showed any sign of CMV disease were treated with therapeutic doses of valganciclovir or intravenous ganciclovir according to the clinical situation. Treatment was given for 3 weeks followed by secondary valganciclovir prophylaxis at 900 mg/day for 3 months. Cytomegalovirus syndrome was defined as CMV viremia and at least 1 of the following: a fever ≥ 38°C, new-onset severe malaise, leukopenia (< 4000 cells/μL), atypical lymphocytes of ≥ 5%, thrombocytopenia (< 100 000 cells/μL), or elevation of liver transaminases levels to ≥ 2-fold of upper limit of normal.22

Leukopenia episodes during the treatment phase were monitored for time after transplant, MMF dose reduction, valganciclovir dose reduction, and requirement for G-CSF treatment. When leukopenia developed, a supportive G-CSF dose was given to increase the absolute neutrophil count. Persistent leukopenia (not responsive to 3 doses of G-CSF) was managed by extra doses of G-CSF and reduction of valganciclovir dose, MMF (or other antimetabolites), trimethoprim/sulfamethoxazole, and other agents that could contribute to leukopenia and could be stopped temporarily.11 Associated infections were recorded if they necessitated hospital admission. Details of patients who developed CMV disease or rejection episodes during the study period were recorded.

Cost assessment
We obtained cost data from our hospital records, which were measured in US dollars. In our cost-effectiveness analysis, outcomes were measured in nonmonetary units (eg, number of rejection-free grafts, number of patients with a functioning graft, and survival outcomes). In this study, patient survival, graft survival, and the number of rejection-free patients were chosen as clinical outcome parameters. Direct costs associated with acquisition of immunosuppressive medications, valganciclovir, ganciclovir, G-CSF, diagnosis of rejection, and hospitalization were included. Total costs of these resources were calculated for each treatment group (total patient cost). Next, total costs were divided by the number of patients who had used this resource in each treatment group (average cost per patient). Drugs used to treat adverse events were also included in the analyses. Hospitalization costs were calculated based on the daily full-cost according to the type of ward (ie, in intensive care unit or regular ward). The hospital costs included the cost of health-related services (eg, pathology, and medical tests), blood transfusion bank, hospital pharmacy, and incidental services (including meals, laundry, and special waste removal). For each type of rejection, the resource use categories comprised hospitalization, diagnostic tests, and prescribed drugs used to treat the rejection episode.

Statistical analyses
Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 20.0, IBM Corporation, Armonk, NY, USA). Sample size was calculated to accept marginal error of 6.6% (95% confidence interval) in a normally distributed population. Variables and means were compared using paired sample t test, independent sample t test, chi-squared test, Fisher exact test, and analyses of variance as appropriate. Results are expressed as means ± standard deviation, and differences were
considered significant at $P \leq .05$. Graft and patient survival rates were summarized using Kaplan-Meier curves and tested for significance using the 2-sided log-rank test.

**Results**

The 2 study groups were comparable regarding demographic data (Table 1; $P > .05$). Most kidney recipients (97.5%) were seropositive and received grafts from seropositive donors (97.5%). The number of patients who were maintained on tacrolimus was significantly higher in group 1, whereas those who were maintained on cyclosporine were significantly higher in group 2 (Table 1; $P = .001$). Both the mean dose of cyclosporine (350 ± 75 vs 325 ± 75 mg/d at baseline, 225 ± 50 vs 250 ± 75 mg/d at 6 mo, and 125 ± 25 vs 125 ± 50 mg/d at 1 y) and the trough levels (225 ± 50 vs 200 ± 50 ng/mL at baseline, 125 ± 25 vs 125 ± 25 ng/mL at 6 mo, and 100 ± 25 ng/mL at 1 y) were comparable in both groups. Similarly, the mean dose of tacrolimus (5 ± 1.3 vs 5.5 ± 1.2 mg/d at baseline, 4 ± 1 vs 4.5 ± 1.0 mg/d at 6 mo, and 2.2 ± 0.8 vs 2.4 ± 1.1 mg/d at 1 y) and the trough levels (9.2 ± 1.2 vs 9.0 ± 1.1 ng/mL at baseline, 7.2 ± 1.3 vs 7.4 ± 1.2 ng/mL at 6 mo, and 6.1 ± 1.2 vs 6.4 ± 1.1 ng/mL at 1 y) were comparable in both groups at the different time intervals ($P > .05$).

All patients were followed for 12 months. During the treatment phase, 1 patient died in group 1 due to acute myocardial infarction and 2 patients in group 2 had lost their grafts (1 because of recurrent oxalosis and the other because of severe rejection and renal vein thrombosis). After 6 months, 1 patient in each group was lost to follow-up.

As shown in Table 2, more patients were treated for CMV disease in group 2 than in group 1, but this did not rank to significance ($P = .052$). Patients in group 2 showed significantly more leukopenia episodes ($P = .04$), a higher mean dose of G-CSF ($P = .03$), and earlier development of CMV reactivation ($P = .01$). We observed that the number of patients who needed MMF dose reduction was significantly higher in group 2 ($P = .04$). This was reflected partially by the

| Table 2: Drug Modifications and Effects on Infections, Hospitalizations, Transplant Outcomes, and Associated Costs in Both Groups |
|---|---|---|---|
| Group 1 | Group 2 | $P$ Value |
| No. of positive CMV-PCR requiring treatment | 2 | 8 | .052 |
| Mean time of CMV disease after transplant, mo | 11.5 ± 0.7 | 4.9 ± 2.7 | .01 |
| Compliance of patients to therapy, % | 100% | 100% |
| Organ involved by CMV/viremia | 0/2 | 0/8 |
| Treatment given to affected patients (ganciclovir/valganciclovir) | 2 | 1/7 |
| CMV status (donor and recipient positive) | 2 | 8 |
| Mean leukopenia episodes per patient | 0.59 ± 0.81 | 0.85 ± 0.95 | .04 |
| Mean MMF dose per patient, g/d | 1.41 ± 0.62 | 1.07 ± 0.65 |
| Total cost per day for all patients | $514 | $108 |
| MMF cost (patient cost/d) | $4.9 ± 2.1 | $3.75 ± 2.2 | .04 |
| No. of patients requiring MMF dose reduction | 3 (3%) | 10 (9.9%) | .04 |
| Valganciclovir daily cost per patient | $31 | $62 |
| Total cost for 6-mo treatment | $6200 | $12400 | < .001 |
| No. of patients requiring valganciclovir (positive) | 26 (26%) | 37 (36.6%) | .07 |
| Mean total G-CSF dose, µg | 36.4 ± 87 | 69.5 ± 133.8 | .03 |
| No. of patients required G-CSF treatment (%) | 22 (22%) | 37 (36.6%) | .03 |
| Mean cost of G-CSF dose | $127 | $243.3 |
| Total cost for G-CSF | $2794 | $9002 | .03 |
| BK virus nephropathy, No. of patients | 0 | 3 | .035 |
| No. of associated infections needing hospitalization | 54 | 54 |
| Cost of hospitalizations for associated infections | $2435 | $2435 |
| Mean basal serum creatinine | 126 ± 54.8 | 137 ± 96 | .31 |
| Mean eGFR at 1 year (ml/min) | 70 ± 26.8 | 70 ± 26.8 |
| Mean serum creatinine level at 1 year (µmol/L) | 106 ± 27 | 118.4 ± 51.8 | .07 |
| Mean eGFR at 1 year (ml/min) | 75.4 ± 22.2 | 74 ± 27.2 | .72 |
| Graft survival at 1 year, No. (%) | 100 (100%) | 99 (98%) | .498 |
| Patient survival at 1 year, No. (%) | 99 (99%) | 101 (100%) | .498 |

*Abbreviations: CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; G-CSF, granulocyte colony-stimulating factor; group 1, low-dose valganciclovir; group 2, full-dose valganciclovir; MMF, mycophenolate mofetil; PCR, polymerase chain reaction.*

Costs are in US dollars.
mean daily cost per patient, which was significantly higher in group 1 by 1.25 US dollars ($P = .04$).

Regarding valganciclovir costs, costs were lower (by almost half) in group 1, as the number of patients who needed valganciclovir dose reduction because of adverse effects was seen more frequently in group 2; however, this did not rank to significance ($P = .07$).

The number of patients who need G-CSF was significantly higher in group 2 (37 vs 22 patients), with significantly higher mean dose in group 2 versus group 1 (243.3 vs 127 MU) and significantly higher cost (almost triple) in the same group (Table 2; $P < .05$).

Despite the significantly higher number of associated BK virus nephropathies observed in group 2 ($P = .03$), we found that other associated infections (those necessitating hospitalization) were comparable in both groups (Table 2; $P = .23$). Regarding graft function (as shown by serum creatinine levels and eGFR at 6 and 12 mo posttransplant), we found no significant differences between the 2 groups ($P > .05$). Patient survival (99% vs 100%) and graft survival (99% vs 97.02%) were comparable in both groups (Table 2; $P = .49$).

Table 2 shows details of patients with CMV disease. Despite most patients having intermediate risk (donor and recipient positive; $P > .05$), there was a significant delay in the development of CMV disease after transplant in group 1 ($P = .01$). Moreover, we observed significantly higher numbers of acute rejection episodes in group 2, especially mixed acute rejection ($P < .05$). This was reflected by the cost associated with such episodes. It is worth noting that the cost of T-cell-mediated rejection (steroid resistant) was significantly higher in group 1 (4275 vs 1425 US dollars, needing treatment with thymoglobulin after steroid pulse; $P = .045$), whereas the cost associated with acute antibody-mediated rejection treatment was comparable between groups (125 426 vs 143 344 US dollars, needing treatment with 10 sessions of plasmapheresis, a single dose of 125 g of intravenous immunoglobulin G, and a single dose of rituximab; $P = .4$). However, the cost associated with treating mixed episodes of acute rejection was significantly higher in group 2 (360 424 vs 148 072 US dollars; $P < .001$).

**Discussion**

The prevalence of past exposures to CMV, as indicated by a positive immunoglobulin G, varies markedly throughout the world and is close to 100% in adults in many developing countries such as the Philippines and Uganda. Most of our kidney transplant recipients and their donors showed intermediate risk for CMV infection as they were seropositive for CMV, which is comparable to other studies. The use of full-dose valganciclovir (900 mg/d with normal graft function) for 200 days is the recommended anti-CMV prophylaxis for kidney transplant recipients. Low-dose valacyclovir with CMV immunoglobulin was as efficacious in preventing CMV disease as other published regimens, including those with full-dose valacyclovir and valganciclovir. There was a low incidence of CMV disease beyond 6 months. Outcomes could be improved by ensuring
appropriate dose adjustments after changes in renal function. Selective low-dose valganciclovir may provide similar protection against CMV compared with universal oral ganciclovir. Prolongation of prophylaxis beyond 100 days should be explored.

Because of its favorable pharmacokinetic profile, our data suggest that valganciclovir can be used in the early period after kidney transplant and that 450 mg daily provides ample drug exposure for effective CMV prophylaxis in kidney transplant patients.

Despite proven efficacy of prolonged CMV prophylaxis using valganciclovir at 900 mg/day, some centers use 450 mg/day because of reported success and cost savings. Gabardi and associates recently reported in a retrospective study that low-dose and high-dose valganciclovir regimens provide similar efficacy in preventing CMV disease in high-risk renal transplant recipients, with a reduced incidence of leukopenia associated with the low-dose regimen and no difference in resistant CMV. They added that low-dose valganciclovir may provide a significant cost benefit.

We aimed to assess the cost effectiveness of low-dose valganciclovir prophylaxis (450 mg/d) compared with high dose (900 mg/d) among our renal transplant recipients in this prospective randomized trial. The 2 groups of patients were equivalent regarding demographic data, apart from the type of CNI-based regimen used with significantly higher number of tacrolimus-treated patients in group 1 and higher numbers of cyclosporine-treated patients in group 2. This higher number of patients in group 2 with a cyclosporine-based regimen was surprising, with its relatively lower immunosuppressive potency, although this did not rank to significance.

Moreover, the mean number of leukopenia episodes per patient was significantly lower in group 1 with low-dose valganciclovir (P = .04), which was matched with that reported by Brum and associates who noted that low-dose valganciclovir for CMV prophylaxis appeared to be as effective as a high-dose treatment with less frequent leukopenia and neutropenia episodes.

We found that nearly one-third of patients (22% in group 1 and 36.6% in group 2) required G-CSF for treatment of leukopenia, with mean dose of G-CSF being significantly higher in group 2 (P = .03). This finding was similar to that reported previously by Brum and associates who showed that high-dose valganciclovir prophylaxis was associated with significantly increased frequency of leukopenia (20.3%) compared with low-dose valganciclovir prophylaxis, especially among patients on MMF-tacrolimus regimens. They added that there was no increase in CMV infection among patients with low-dose valganciclovir.

Gabardi and associates concluded that a high rate of CMV disease was noted among the donor-positive/recipient-negative population, especially when antithymocyte globulin was used as induction.

In our study, the incidence of CMV was 2% in group 1 and 7.9% in group 2, which is less than that reported in other studies, possibly because of heavier immunosuppression. The total number of leukopenia episodes was significantly higher in group 2, which could be related to the full valganciclovir effect (P = .04). Leukopenia episodes were associated with significant MMF dose reduction in the same group (P = .04; Table 2), higher rejection episodes, more significant mandatory doses of G-CSF, and more holding of valganciclovir, which interrupted the prophylactic effect of the drug against CMV. Moreover, Hartmann and associates reported that, when G-CSF was used, a mean of 3.1 doses was needed to successfully manage leukopenia. We had achieved our target with a relatively lower mean G-CSF dose (36.4 µg in group 1 and 69.5 µg in group 2), possibly because of heavier immunosuppression of kidney-pancreas transplants. This was confirmed by the higher number of patients with CMV disease (P = .052).

Our results did not match results shown by Gabardi and associates who reported no difference in rates of biopsy-proven acute rejection. This difference could be explained by frequent discontinuation of MMF, frequent leukopenia episodes, and more potent induction therapy. However, this group reported significantly lower mean white blood cell counts at months 5 and 6 months after transplant with similar premature valganciclovir discontinuation rates, which could be explained by differences in immunosuppressive
regimens. Moreover, the group reported similarity in their 2 groups regarding renal function and graft loss and no breakthrough/resistant CMV infection, which matched our results. However, breakthrough CMV infection has been shown to develop with low-dose valganciclovir prophylaxis.35

In our study, we observed that the 2 groups were comparable regarding induction therapy (Table 1; \( P = .30 \)). Despite patients in group 1 receiving significantly higher mean daily MMF dose (Table 2), with significantly more tacrolimus-treated patients (being associated with more leukopenia than cyclosporine),36 the number of patients who needed MMF dose reduction was significantly higher in group 2 due to frequent leukopenia episodes, possibly due to the effects of higher valganciclovir dose (\( P = .014 \)).

The mean daily cost per patient was significantly higher in group 1 by 1.25 US dollars (\( P = .04 \)). However, the risk of acute rejection was higher in group 2 possibly due to lower MMF exposure. It is worth noting that costs associated with treating T-cell-mediated rejection, especially steroid resistant episodes, was significantly higher in group 1 (\( P < .05 \)); cost of management of antibody-mediated rejection was comparable in both groups (\( P > .05 \)), but the cost of mixed acute rejection treatment and the total cost of rejection episode management were significantly more in group 2 (\( P < .05 \); Table 3).

Therefore, the use of low-dose valganciclovir was cost effective in CMV prophylaxis in view of reducing the cost of leukopenia management, the total cost of rejection management, and the cost of valganciclovir itself. Our results matched a retrospective analysis by Bhat and associates.37

Concerning graft function, which was represented by eGFR, we found no significant differences between the 2 groups at baseline, at the end of treatment phase, and at the end of the study (Table 2; \( P = .71 \)).

Conclusions

Low-dose valganciclovir for CMV prophylaxis after renal transplant is safer, effective without breakthrough infection, and less costly than using usual dose amounts.

References


