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ORIGINAL ARTICLE

Tomas Reischig
Karel Opatrny Jr.
Mirko Bouda
Vladislav Treska
Pavel Jindra
Miroslava Svecova

A randomized prospective controlled trial of oral ganciclovir versus oral valacyclovir for prophylaxis of cytomegalovirus disease after renal transplantation

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T. Reischig (✉) · K. Opatrny Jr.
M. Bouda
Department of Internal Medicine I,
Charles University Teaching Hospital,
Alej Svobody 80, 30460 Pilsen,
Czech Republic
E-mail: reischig@fnplzen.cz
Tel.: +420-19-7103573
Fax: +420-19-7531110

V. Treska
Department of Surgery,
Charles University Teaching Hospital,
Pilsen, Czech Republic

P. Jindra
Department of Hemato-oncology,
Charles University Teaching Hospital,
Pilsen, Czech Republic

M. Svecova
Department of Virology,
Charles University Teaching Hospital,
Pilsen, Czech Republic

Abstract Oral ganciclovir and valacyclovir reduce the incidence of cytomegalovirus (CMV) disease after renal transplantation (RTx). Our study was designed to compare the efficacy, costs, and safety of oral ganciclovir and valacyclovir in the prophylaxis of CMV disease over the first 6 months after RTx. A total of 38 patients was randomized to 3-month treatment with either oral ganciclovir (1 g t.i.d., $n=14$, GAN group) or oral valacyclovir (2 g q.i.d., $n=12$, VAL group). A third group (C, $n=12$) received no prophylaxis. The patients were monitored by CMV-nested PCR in whole blood. No differences were found between the groups in their demographic characteristics, immunosuppressive protocols, or donor and recipient CMV serology. Thirty-six out of 38 (94.7%) recipients were CMV-seropositive. Over the 6-month post-RTx period, there were 13 episodes of CMV disease in eight (66.7%) patients of the C group compared with none in the GAN and VAL groups ($P=0.0005$, GAN vs C; $P=0.001$, VAL vs C). The incidence of CMV viremia was 30.8%, 50.0%, and 91.7% in the GAN, VAL, and C groups, respectively ($P=0.004$, GAN vs C; $P=0.07$, VAL vs C; $P=$NS, GAN vs VAL). Treatment failure (death, graft loss, CMV disease, or withdrawal from study) occurred in 14.3%, 0% and 66.7% in the GAN, VAL, and C groups, respectively ($P=0.014$, GAN vs C; $P=0.001$, VAL vs C; $P=$NS, GAN vs VAL). The average CMV-associated costs per patient (in 2001 euros) were $2,449 \pm 1,178$, $2,485 \pm 581$, and $4,259 \pm 4,616$ in the GAN, VAL, and C groups, respectively. Ganciclovir and valacyclovir were well tolerated, with ganciclovir having had to be withdrawn shortly in one patient only because of thrombocytopenia. In conclusion, oral ganciclovir and valacyclovir are equally safe and effective in the prophylaxis of CMV disease after RTx. Both are cost-effective and help reduce CMV-associated costs by some 40% compared with patients without prophylaxis.

Keywords Renal transplant · Cytomegalovirus prophylaxis · Ganciclovir · Valacyclovir

Introduction

Despite advances in prophylaxis, cytomegalovirus (CMV) continues to be the most frequent opportunistic pathogen in patients undergoing solid-organ transplantation [30]. Acute CMV disease manifests itself in a mild form (so-called CMV syndrome) including fever and constitutional symptoms combined with laboratory abnormalities such as leukopenia, thrombocytopenia, and mild elevation of liver enzymes. However, severe

life-threatening tissue-invasive CMV disease involving various organs (e.g., pneumonitis, hepatitis, retinitis, and gastrointestinal disease) may also develop [9, 30]. Besides, CMV enhances the net state of immunosuppression, resulting in an increase in the incidence of opportunistic super-infections [11, 29]. CMV is associated with an increased risk of acute and chronic rejection [13, 26, 27, 31]. In renal transplantation (RTx) patients, CMV disease ultimately leads not only to increased morbidity and mortality rates [8, 24] but also to a marked increase in transplantation-related costs [22].

Recently, oral ganciclovir, despite its low bioavailability [7], has been shown to reduce significantly the incidence of CMV disease following RTx [1, 4]. Despite the inconsistent efficacy of acyclovir in the prophylaxis of CMV disease [2, 12, 16], a large multicenter study has demonstrated that oral valacyclovir (a valine ester of acyclovir) is effective in the prevention of post-RTx CMV disease [20]. The reason for this is the appreciably higher bioavailability of acyclovir after valacyclovir administration than can be obtained by the administration of oral acyclovir [32]. Flechner et al. have shown that oral ganciclovir is more effective than oral acyclovir [10]; however, no study comparing ganciclovir and valacyclovir has been conducted to date. Besides, use of novel, more potent immunosuppressives requires continuous re-evaluation of the current protocols of CMV-disease prevention, as their efficacy may not be sufficient [6, 15, 25]. Our study was designed to compare the efficacy, safety, and costs of oral ganciclovir versus oral valacyclovir in the prophylaxis of CMV disease in patients undergoing RTx and treated with mycophenolate mofetil. Because of high CMV seroprevalence in our country, this study mainly concerns the prophylaxis of CMV disease in RTx recipients at risk of CMV superinfection and/or re-infection.

Patients and methods

Patients and study design

The study was conducted at the Charles University Teaching Hospital, Pilsen, Czech Republic. Its protocol was approved by the local ethics committee and complied with the 1964 Declaration of Helsinki. In the period from April 1999 through December 2000, a total of 38 adult renal graft recipients with serologic donor (D) and recipient (R) D+R–, D+R+, and D–R+ status was randomized at a 1:1:1 ratio to 3-month treatment with either oral ganciclovir (Cymevene; Hoffman-La Roche, UK) at a dose of 1 g t.i.d. or oral valacyclovir (Valtrex; Glaxo Wellcome, UK) at a dose of 2 g q.i.d.; the third group of patients did not receive any CMV prophylaxis and their condition was managed by so-called deferred therapy [3]. Treatment with ganciclovir and valacyclovir was started within 3 days post-RTx, and the doses were adjusted according to renal function (Table 1). All patients signed an informed consent form. Not eligible for the study were patients with unknown or D–R– CMV serology prior to RTx, active viral infection, leukopenia of below 4.0×10^9/l, thrombocytopenia of below 150×10^9/l, known allergy to ganciclovir or acyclovir, and patients using systemic antiviral agents. Short-term treatment with low-dose acyclovir in the event of herpes simplex virus (HSV) infection was allowed.

Immunosuppression

All patients received, from RTx onward, cyclosporine (Neoral; Novartis, Switzerland) at 10 mg/kg per day divided into two daily doses with the following adjustments to maintain 12-h whole-blood cyclosporine trough levels between 250 and 350 ng/ml (monoclonal fluorescent polarization assay, TDx; Abbott Laboratories) over the first 2 months post-RTx and between 150 and 250 ng/ml thereafter. Steroids were initiated with 250 mg intravenous methylprednisolone from days 0 to 3 post-RTx, with subsequent tapering to 30 mg of oral prednisone on day 6 and 10 mg at month 6 post-RTx. All patients but two were treated with mycophenolate mofetil (CellCept; Hoffman-La Roche, Switzerland) at a dose of 1 g b.i.d., with the remaining two patients receiving azathioprine (Imuran; Glaxo Wellcome, UK) at 1 mg/kg per day. Patients at immunologically high risk were given 7-day induction therapy with OKT3 (Orthoclone; Cilag, Switzerland). Acute rejection episodes were confirmed by biopsy and initially managed by high doses of intravenous methylprednisolone; for steroid-resistant episodes, 10-day treatment with OKT3 or 10 to 14-day treatment with rabbit anti-thymocyte globulin (ATG; Fresenius, Germany) was instituted. For recurrent steroid-resistant and/or OKT3/ATG-resistant episodes, patients were switched to rescue therapy with tacrolimus (Prograf; Fujisawa, Ireland).

Patient monitoring

Patients were prospectively monitored clinically and by laboratory tests for 6 months post-RTx or until death. Nested PCR for CMV DNA was performed from 2 ml of whole blood in EDTA tubes once a week for the first 15 weeks and then at months 5 and 6. Two sets of commercially synthesized primers complementary to DNA sequence for major immediate early gene CMV were used in each cycle of PCR. DNA was isolated from 200 µl of whole blood with a QIAamp DNA Blood Kit (Qiagen, Germany) according to the manufacturer's instructions. Isolated DNA was initially amplified in a reaction mixture with external primers 5-ATGGAGTCCTC-TGCCAAGAG-3 and 5-CAATACACTTCATCTCCTCG-3 and DNA polymerase. The second cycle was performed by use of another pair of primers: 5-GTGACCAAGGCCACGACGTT-3 and 5-TCTGCCAGGACATCTTTCTC-3 and other amplification

Table 1 Doses of antiviral agents according to renal function (C_{Cr} creatinine clearance)

C_{Cr} (ml/min)	Ganciclovir	C_{Cr} (ml/min)	Valacyclovir
> 70	1,000 mg t.i.d.	> 75	2,000 mg q.i.d.
51–70	500 mg t.i.d.	51–75	1,500 mg q.i.d.
26–50	500 mg b.i.d.	26–50	1,500 mg t.i.d.
10–25	500 mg qd	10–25	1,500 mg b.i.d.
< 10 or dialysis	500 mg t.i.w.	< 10 or dialysis	1,500 mg qd

cycle characteristics. The resultant amplification product was visualized with ethidium bromide on 2% agar gel under UV light. To minimize false-positive results, we observed predefined conditions [17]. If CMV disease was suspected, CMV pp65 antigenemia was investigated by use of isolated polymorphonuclear cells and a commercially available CINA kit (Argene BIOSOFT, France). More than five positive cells per 100,000 tested were considered a positive result. CMV cultures from bronchoalveolar lavage, biopsy samples, and urine were performed in human fibroblasts. CMV was identified by the cytopathic effect and immunofluorescence with the help of monoclonal antibody (Monofluokit CMV; Sanofi, Czech Republic). Serological determination of anti-CMV IgM and IgG was performed with ELISA (Test-Line, Czech Republic) and indirect immunofluorescence (Vidia, Czech Republic).

Study end points

The primary study end point was the incidence of CMV disease over the first 6 months post-RTx. Secondary end points included the incidence of CMV viremia, patient and graft survival, graft function and safety profile, CMV-associated costs, incidence of acute rejections, and other infections. CMV viremia was defined as positive nested PCR. CMV disease was defined as CMV viremia combined with the CMV syndrome or tissue-invasive CMV disease [19]. The CMV syndrome included the presence of at least one of the following: unexplained temperature over 38 °C for 2 or more days, constitutional symptoms (fatigue, myalgia, arthralgia), leukopenia of below 4.0×10^9/l on 2 consecutive days, thrombocytopenia of below 150×10^9/l on 2 consecutive days, and elevation of liver function tests. For fear of low nested-PCR specificity, CMV viremia before the final diagnosis of CMV disease was verified by positive CMV pp65 antigenemia. CMV disease was treated by intravenous ganciclovir (Cymevene; Hoffman-La Roche, Switzerland) at 5 mg/kg every 12 h for a minimum of 3 weeks or longer, if needed clinically. The doses were adjusted according to renal function as recommended by the manufacturer.

Statistical analysis

Data were analyzed on an intention-to-treat basis. Treatment failure was defined as CMV disease, graft failure, and death and/or exclusion from the study. Fischer's exact test was used for categorical variables and Kruskal-Wallis analysis of variance was used to compare laboratory and other quantitative data among the three groups. Data are expressed as means ± SD. Calculations were made using computer software SigmaStat for Windows Version 2.03. P values of below 0.05 were considered significant.

Results

Patient characteristics

A total of 38 patients was included in the study, with 14 receiving ganciclovir (GAN group) at an average daily dose of 1.3 ± 0.6 g, 12 receiving valacyclovir (VAL group) with an average 5.5 ± 1.3 g per day, while 12 patients (C group) were given no prophylaxis. One patient of the GAN group lost his graft due to renal vein thrombosis on day 8 post-RTx and was assessed in the intention-to-treat analysis only. The groups did not differ significantly in basic demographic and immunological characteristics, donor and recipient pre-RTx CMV serology, or in immunosuppression therapy (Table 2).

Table 2 Baseline characteristics of the patients. None of the differences was significant. (*PRA* panel-reactive antibody, *MMF* mycophenolate mofetil)

Feature	GAN group $n=14$	VAL group $n=12$	C group $n=12$
Age (mean ± SD; years)	44.5 ± 11.6	47.8 ± 12.4	46.0 ± 13.1
Gender			
Male (*n*, %)	10 (71.4)	10 (83.3)	8 (66.7)
Female (*n*, %)	4 (28.6)	2 (16.7)	4 (33.3)
Donor source			
Cadaveric donor (*n*, %)	12 (85.7)	11 (91.7)	12 (100.0)
Living donor (*n*, %)	2 (14.3)	1 (8.3)	0 (0.0)
Previous transplantation (*n*, %)	3 (21.4)	1 (8.3)	2 (16.7)
Cause of renal failure			
Chronic glomerulonephritis (*n*, %)	9 (64.3)	6 (50.0)	5 (41.7)
Chronic interstitial nephritis (*n*, %)	3 (21.4)	2 (16.7)	5 (41.7)
Diabetic nephropathy (*n*, %)	0 (0.0)	2 (16.7)	0 (0.0)
Polycystic kidney disease (*n*, %)	0 (0.0)	1 (8.3)	2 (16.7)
Hypertensive nephrosclerosis (*n*, %)	2 (14.8)	0 (0.0)	0 (0.0)
Other (*n*, %)	0 (0.0)	1 (8.3)	0 (0.0)
HLA-A,B,DR mismatches (mean ± SD)	3.1 ± 1.2	3.2 ± 0.8	3.6 ± 1.3
Pre-transplant PRA (mean ± SD; %)	15.1 ± 25.6	9.5 ± 18.9	7.3 ± 11.4
Cold ischemia time (mean ± SD; h)	17.7 ± 8.0	18.9 ± 7.2	20.3 ± 3.6
CMV serologic status			
D+R− (*n*, %)	1 (7.1)	0 (0.0)	1 (8.3)
D+R+ (*n*, %)	11 (78.6)	9 (75.0)	8 (66.7)
D−R+ (*n*, %)	2 (14.3)	3 (25.0)	3 (25.0)
Immunosuppression			
Antilymphocyte antibody therapy[a] (*n*, %)	6 (42.9)	3 (25.0)	4 (33.3)
Maintenance MMF therapy (*n*, %)	13 (92.1)	11 (91.7)	12 (100.0)
Tacrolimus rescue therapy (*n*, %)	2 (14.3)	0 (0.0)	2 (16.7)

[a]Included induction or antirejection treatment with OKT3 or rabbit ATG

CMV viremia and disease

CMV viremia occurred within the first 3 months post-RTx in only one (7.7%) patient of the GAN group and in no patient of the VAL group, compared with ten (83.3%) patients of the C group ($P=0.0002$, GAN vs C; $P=0.00007$, VAL vs C). After the end of prophylaxis at month 6 post-RTx, a significant decrease in CMV viremia persisted in the GAN group (4/13, 30.8%) compared with the C group (11/12, 91.7%, $P=0.001$), while in the VAL group there was only a trend towards a decrease in CMV viremia versus the C group (6/12, 50.0%, $P=0.07$). The differences between the GAN and VAL groups were not significant ($P=0.43$) (Fig. 1). The C group experienced, over the period of 6 months post-RTx, a total of 13 episodes of CMV disease in 8/12 (66.7%) patients. No case of CMV disease was seen in either the GAN or the VAL group ($P=0.0005$ GAN vs C; $P=0.001$ VAL vs C). Of the total of 13 episodes, 11 cases involved the CMV syndrome, with tissue-invasive CMV disease occurring in only two (16.7%) patients (gastrointestinal disease in each case). In no case was life-threatening CMV disease involved. Fever was present in 12 (92.3%), constitutional symptoms in 12 (92.3%), leukopenia in six (46.1%), thrombocytopenia in seven (53.8%), and elevation of liver enzymes in eight (61.5%) of the 13 episodes of CMV disease. Apart from CMV viremia, at least two criteria of the CMV syndrome were always met. The first episode of CMV disease occurred in all patients within 3 months (mean 43 ± 22 days) post-RTx. Of the eight patients with CMV disease, four experienced recurrence.

In both prophylactic groups, CMV viremia tended to increase after the end of prophylaxis. Therefore, patients were further followed up to 12 months post-RTx to undergo checks for the occurrence of late CMV disease. CMV disease was observed in two (15.4%) patients in the GAN group (pneumonitis + hepatitis in one patient and CMV syndrome in the second one) and in one (8.3%) patient in the VAL group (pneumonitis). No late CMV disease occurred in the C group. However, over the period of 12 months post-RTx, the incidence of CMV disease remained significantly lower in both prophylactic groups compared with the C group ($P=0.015$, GAN vs C; $P=0.009$, VAL vs C) (Fig. 2). The onset of CMV disease was delayed in the GAN and VAL groups compared with the C group (mean 286 ± 31 days vs 43 ± 22 days post-RTx, $P=0.000001$). All first and recurrent episodes of CMV disease showed a good response to intravenous ganciclovir. No resistance to ganciclovir was noted.

Clinical outcome

Patient and graft survival did not differ significantly among the groups. One patient died suddenly from pulmonary embolism at month 2 post-RTx and another one lost his graft on day 8 because of renal vein thrombosis. Both were in the GAN group. The cumulative rates of treatment failure at month 6 were 2/14 (14.3%), 0/12 (0.0%), and 8/12 (66.7%) in the GAN, VAL, and C groups ($P=0.014$, GAN vs C; $P=0.001$, VAL vs C; $P=0.48$, GAN vs VAL), respectively. The C group showed a higher, yet not statistically significant, number of patients with biopsy-confirmed acute rejection (6/12, 50.0%) than did the other two groups (GAN group 5/13, 38.4%; VAL group 4/12, 33.3%). No significant differences were observed in the incidence of vascular and steroid-resistant acute rejection episodes.

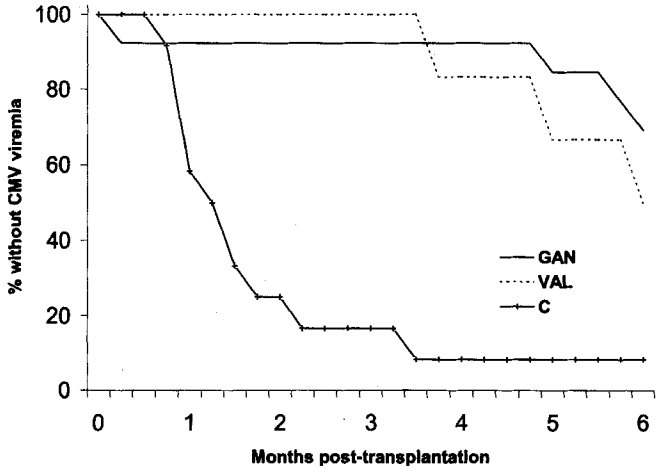

Fig. 1 Cumulative incidence of CMV viremia. The *y axis* represents the percentage of patients free of CMV viremia. $P=0.004$, GAN vs C; $P=0.07$, VAL vs C; $P=0.43$, GAN vs C

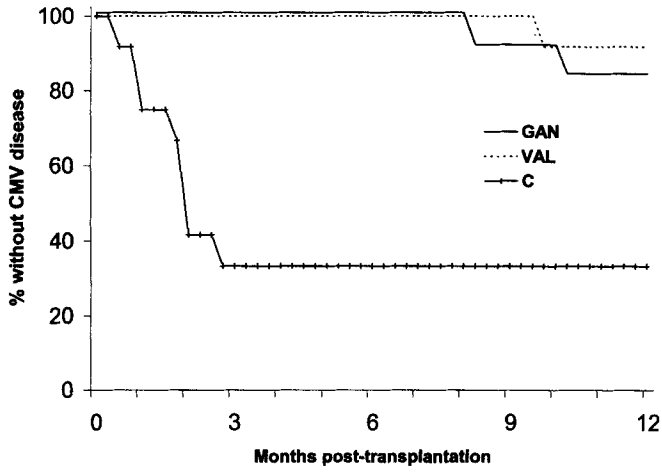

Fig. 2 Cumulative incidence of CMV disease. The *y axis* represents the percentage of patients free of CMV disease. $P=0.015$, GAN vs C; $P=0.009$, VAL vs C

Table 3 Patient outcomes in control and prophylactic groups

Feature	GAN group	*P*	C group	*P*	VAL group
CMV viremia at 3 months (*n*, %)	1/13 (7.7)	0.0002	10/12 (83.3)	0.00007	0/12 (0.0)
CMV viremia at 6 months (*n*, %)	4/13 (30.8)	0.001	11/12 (91.7)	0.07	6/12 (50.0)
CMV disease at 6 months (*n*, %)	0/13 (0.0)	0.0005	8/12 (66.7)	0.001	0/12 (0.0)
CMV disease at 12 months (*n*, %)	2/13 (15.4)	0.015	8/12 (66.7)	0.009	1/12 (8.3)
Treatment failure at 6 months (*n*, %)	2/14 (14.3)	0.014	8/12 (66.7)	0.001	0/12 (0.0)
Acute rejection at 6 months (*n*, %)	5/13 (38.4)	NS	6/12 (50.0)	NS	4/12 (33.3)
Creatinine at 6 months (μmol/l)	171 ± 75	NS	169 ± 42	NS	155 ± 44

Graft function was similar in all groups throughout the study. The mean serum creatinine levels at month 6 post-RTx were 171 ± 75, 155 ± 44, and 169 ± 42 μmol/l in the GAN, VAL, and C groups (P = NS), respectively (Table 3).

Other infections

No statistically significant difference was seen among the groups in the incidence of other bacterial, fungal, parasitic, and viral infections, apart from a decrease in the incidence of clinical HSV infection in the GAN and VAL groups, with no case of HSV infection compared with 5/12 (41.7%) patients in the C group (P = 0.015, GAN vs C; P = 0.037, VAL vs C) (Table 4).

Safety

The incidence of side effects was similar among the groups. Both study drugs were well tolerated. Ganciclovir had to be reduced because of leukopenia and/or thrombocytopenia in three (23.1%) patients, with one of them even requiring short-term discontinuation. Valacyclovir had to be reduced because of leukopenia in one (8.3%) patient (P = NS). The cumulative rates of incidence of leukopenia ($< 3.0 \times 10^9$/l), thrombocytopenia ($< 100 \times 10^9$/l), and anemia (hemoglobin < 80 g/l) did not differ significantly among the groups (Table 5). There was no case of thrombotic microangiopathy. GAN-group patients showed higher levels of uric acid at months 1 and 3 post-RTx ($P < 0.05$) than did patients in the VAL group; the differences were no longer evident at month 6. Hallucinations and/or confusion were more frequent, but not significantly so, in the VAL group (3/12, 25.0%) than in the GAN (1/13, 7.7%) and C (0/12, 0.0%) groups. They invariably occurred within 1 week post-RTx, subsiding quickly without the need for valacyclovir reduction.

Cost analysis

Over the 6-month post-RTx period, the mean CMV-associated costs per patient (expressed in 2001 euros) were 2,449 ± 1,178 in the GAN group, 2,485 ± 581 in the VAL group, and 4,259 ± 4,616 in the C group (including patients both with and without CMV disease), which means savings of 42.5% and 41.7% of costs in the GAN and VAL groups compared with untreated patients. The mean CMV-associated costs were lower in both prophylactic groups even within the 12-month post-RTx period (3,565 ± 2,785, 3,710 ± 4,096, and 4,997 ± 5,792 euros in the GAN, VAL, and C groups, respectively). The average cost per patient who developed CMV disease in all groups was 8,323 ± 5,865 euros.

Table 4 Cumulative incidence of other infections over the first 6 months after transplantation

Feature	GAN group $n = 13$	VAL group $n = 12$	C group $n = 12$
HSV (*n*, %)	0 (0.0)	0 (0.0)	5 (41.7)*
Fungal infections			
Mucocutaneous (*n*, %)	4 (30.8)	5 (41.7)	6 (50.0)
Invasive (*n*, %)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis (*n*, %)	1 (7.7)	1 (8.3)	3 (25.0)
Urinary tract infections (*n*, %)	3 (23.1)	3 (25.0)	6 (50.0)
Pneumonia (*n*, %)	2 (15.4)	2 (16.7)	0 (0.0)
Pneumocystis (*n*, %)	0 (0.0)	0 (0.0)	0 (0.0)

*P = 0.015, GAN vs C; P = 0.037, VAL vs C

Table 5 Hematological adverse events. None of the differences was significant

Feature	GAN group $n = 13$	VAL group $n = 12$	C group $n = 12$
Leukopenia (*n*, %)	3 (23.1)	4 (33.3)	4 (33.3)
Thrombocytopenia (*n*, %)	5 (38.5)	3 (25.0)	4 (33.3)
Anemia (*n*, %)	3 (23.1)	3 (25.0)	5 (41.7)

Discussion

CMV infection and disease is reported in 20%–70% of renal graft recipients depending on D/R CMV serology and the type of immunosuppression administered [28, 29]. While current prophylactic protocols have improved CMV control, CMV infection continues to pose a serious problem. The advent of new, more effective immunosuppressives such as mycophenolate mofetil, sirolimus, or tacrolimus may make the results of previous prophylactic regimens unsatisfactory. This applies primarily, but not exclusively, to patients with D+R– CMV serology prior to transplantation at risk of developing primary CMV infection [5, 6, 15]. The authors of a retrospective study, in which RTx patients were treated with cyclosporine-based triple combination immunosuppression including mycophenolate mofetil and received no anti-CMV prophylaxis, reported a 67% incidence of primary CMV disease compared with 30% ($P < 0.05$) of patients not given mycophenolate mofetil [23].

Our study demonstrated a high efficacy of 3-month therapy with both oral ganciclovir and valacyclovir in the prophylaxis of CMV disease in patients after RTx who were treated with mycophenolate mofetil, with a significant proportion of these patients receiving induction or anti-rejection therapy with anti-lymphocyte antibody. Moreover, both regimens were cost-effective and were associated with savings of approximately 1,800 euros per patient compared with the control group. Both ganciclovir and valacyclovir prophylactic regimens remained cost-effective, even at the 12-month evaluation, in spite of the occurrence of late CMV disease in 3/25 (12%) patients receiving prophylaxis. However, it should be noted that our results cannot be automatically extrapolated to D+R– patients, as there were only 2/38 (5%) in our series (one from the GAN group did not develop CMV disease and one from the C group suffered from recurrent CMV disease). This was due to the naturally low proportion of CMV serology-negative patients in our population. The profile of our patients represents the typical situation in continental Europe, in which most renal transplant recipients are CMV-seropositive at risk of CMV superinfection and/or re-infection. Similarly to our study, other trials proved the effectiveness of oral ganciclovir and/or valacyclovir prophylaxis in R+ patients [4, 20].

For the sake of maximum safety in the case of our control group not receiving any anti-CMV prophylaxis, we opted for the so-called deferred therapy approach with frequent monitoring by highly sensitive nested PCR for CMV DNA from whole blood and early therapy of symptomatic CMV infections. Some authors suggest that this therapy can be employed to control CMV infection and be ever less costly than pre-emptive therapy [3]. In our study, while this policy was effective in preventing the development of serious CMV disease, the overall incidence of CMV disease (66.7%) was high. To avoid misdiagnosis when using nested PCR, which may occasionally detect even latent CMV in leukocytes [30], we invariably confirmed active CMV infection, in cases of suspected CMV disease, by pp65 antigenemia. Moreover, all diagnosed episodes of CMV disease responded well to intravenous ganciclovir. However, the incidence and early recurrence of CMV disease are comparable with those reported by other authors [4, 14]. Brennan et al. [4] observed a 61% incidence of CMV disease in patients with a proportion of D/R CMV serology similar to that seen in the group treated with low-dose acyclovir. In another study, also excluding patients with D–R– CMV serology, the incidence of CMV disease was 28%, despite 12-week prophylaxis with ganciclovir. However, more patients had acute rejection and more patients were treated with anti-lymphocyte antibody in that study than in our series [15]. A recently published model of the cost-efficacy of various strategies of CMV management supports the economic superiority of prophylaxis of CMV disease, a concept consistent with our findings [21]. However, in a multicenter trial with economic evaluation of valacyclovir prophylaxis after RTx, prophylaxis was cost-effective in the high-risk D+R– group only. In the R+ patients, prophylaxis resulted in a modest incremental cost [18]. Nevertheless, the incidence of CMV disease in the R+ patients not receiving prophylaxis was very low (6%) in that study. Furthermore, the investigators included total costs per patient in the first 6 months post-RTx. In our study, we calculated the real CMV-associated costs in each patient studied, which included the costs of prophylaxis, CMV monitoring, diagnostic procedures in cases of asymptomatic CMV viremia, and the costs of diagnosis and treatment of CMV disease.

In our study, ganciclovir was also effective in preventing asymptomatic CMV viremia while, with valacyclovir, viremia occurred in 50% of the patients after prophylaxis discontinuation. This was less than in the C group (91.7%); however, the difference did not reach statistical significance. Although an adverse indirect effect of CMV may also be present with asymptomatic active CMV infection [30], we did not demonstrate an adverse clinical impact over a period of 6 months post-RTx. In addition to the expected reduction in the incidence of HSV infection in both treated groups, we did not observe a higher incidence of other infections in the C group than in patients receiving anti-CMV prophylaxis. This may be due not only to the size of our group but also to the absence of serious episodes of CMV disease and routine prophylaxis with low-dose trimethoprim-sulfamethoxazole against *Pneumocystis carinii* infection and natamycin against oral and gastrointestinal fungal infections. Despite better results of oral

ganciclovir than high-dose oral acyclovir in the prevention of CMV disease [10], the efficacy of ganciclovir and valacyclovir was comparable in our study. This is presumably due to the bioavailability of acyclovir, which is increased several times when administered in its oral form [32]. The ability of valacyclovir to reduce the incidence of CMV disease after RTx even in patients with D+R− CMV serology has been demonstrated previously, although mycophenolate mofetil was given to only a very small number of patients [20]. Another finding was the lower incidence of acute rejection episodes in valacyclovir-treated patients [20]. The incidence of acute rejection episodes in our patients treated with ganciclovir and valacyclovir was non-significantly lower than in those in the C group. However, the study was not powered to demonstrate differences in this criterion. The safety profiles of both drugs were acceptable. As expected, hematological side effects requiring dosage adjustment were more frequent with ganciclovir, while hallucinations and confusion were seen more often with valacyclovir [7, 20].

In summary; oral ganciclovir and valacyclovir are equally effective in the prophylaxis of CMV disease in patients undergoing RTx. Both prophylactic regimens not only decrease the incidence but also delayed the onset of CMV disease. Both drugs are safe and cost-effective in saving over 40% of CMV-associated costs over the first 6 months post-RTx.

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