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ORIGINAL ARTICLE

Efficacy and Safety of Low-Dose Valganciclovir in the Prevention of Cytomegalovirus Disease in Adult Liver Transplant Recipients

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The efficacy and safety of valganciclovir (VGCV) for cytomegalovirus (CMV) prophylaxis in liver transplant recipients has not been established. We retrospectively compared the efficacy and safety of low-dose oral VGCV (450 mg once daily for 90 days) and standard oral ganciclovir (1 g three times a day for 90 days, GCV) in preventing CMV disease in 109 adult liver transplant recipients who survived at least 1 month between January 2001 and April 2003 (49 GCV and 60 VGCV). The incidence of CMV disease at 1 year post-transplant was similar among patients treated with VGCV and GCV (3% and 4%, respectively). Three of the four CMV disease cases occurred in high-risk recipients with CMV serotype of donor+/recipient− (D+/R−) and all cases presented after completion of CMV prophylaxis, ranging 114-152 days post-transplant. Severe neutropenia was rare, and thrombocytopenia and anemia occurred at similar frequencies with both prophylaxis regimens. In conclusion, a 90-day regimen of low-dose oral VGCV has a similar efficacy and safety profile to high-dose oral GCV in adult liver transplant recipients. D+/R− liver transplant recipients remain at risk of developing CMV disease after completion of antiviral prophylaxis. Additional prospective studies with close monitoring for CMV viremia and drug resistance are needed to further establish the optimal dose and duration of VGCV in liver transplant recipients. ***Liver Transpl 12:112–116, 2006.*** © **2005 AASLD.**

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Cytomegalovirus (CMV) infection accounts for significant morbidity and mortality in solid organ transplant recipients. It can not only cause tissue-invasive infection in immunocompromised hosts but may also be associated with allograft injury, rejection, opportunistic infections, and development of malignancy via immune-modulating effects.[1] Ganciclovir (GCV) has been widely used to prevent CMV disease post-transplant since it was introduced in 1989.[2-7] However, oral GCV has poor bioavailability and requires high-dose frequent administration and intravenous GCV is costly and inconvenient, requiring long-term intravenous access.

Valganciclovir (VGCV) is the valine ester prodrug of GCV, which has markedly improved oral bioavailability compared to GCV (60% vs. 6%).[8] Oral VGCV given as 450 mg per day offers convenient once-daily dosing while delivering systemic GCV exposure equivalent to that of oral GCV 1 g three times a day.[8] To date, the safety and efficacy of VGCV in liver transplant recipients has not been established.[9,10] The aim of this study was to compare our experience with low-dose oral VGCV (450 mg once daily) for CMV prophylaxis in consecutive adult liver transplant recipients who survived at least 1 year post-transplant to that of standard oral GCV (1 g three times a day).

METHODS

Patient Population and Study Design

We retrospectively reviewed medical records of all patients > 18 years of age who underwent orthotopic, cadaveric liver transplantation at the University of Michigan between January 2001 and April 2003. A waiver of consent was obtained from the Institutional Review Board.

Abbreviations: CMV, cytomegalovirus; GCV, ganciclovir; VGCV, valganciclovir; D, donor; R, recipient; PCR, polymerase chain reaction.

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Outcome Measures

Data retrieved from the medical records included patient demographics, CMV serotype of donor and recipient (D/R), CMV prophylactic regimen, quantitative CMV-DNA by polymerase chain reaction (PCR) results, immunosuppression regimen, biopsy results, and hematological labs during the first year post-transplant. At our transplant center, medication profiling and laboratory monitoring were routinely performed at least once a week in the first month following liver transplantation and at least once a month thereafter.

For the efficacy analysis, the primary outcome measure was the incidence of CMV disease within 1 year post-transplant. CMV disease was defined as the detection of CMV by quantitative CMV-DNA PCR (detection limit 600 copies/mL) in the blood accompanied either by "CMV syndrome" (fever, malaise, or leucopenia) or by organ dysfunction in the absence of other documented causes. At our transplant center, CMV-DNA PCR and biopsy were only performed when clinically indicated. The diagnosis of CMV infection and disease has evolved considerably in the past decade, yet significant variations exist in definitions of CMV infection and disease that have been used in both research and clinical settings.[9,11-13] The criteria we used for CMV disease are similar to that used in other published studies.[11–13]

Secondary safety outcomes in our study included the incidence of hematological side effects in the GCV and VGCV groups, including severe neutropenia (absolute neutrophil count $<500/mm^3$), thrombocytopenia (platelet $< 100{,}000/mm^3$), and anemia (hemoglobin $<$ 8.0 g/dL) during post-operative days 15-90. Hematological abnormalities from post-operative days 0-14 were excluded to avoid potential bias from end-stage liver disease and blood loss during the early post-transplant period.

Immunosuppression and CMV Prophylaxis

Most patients received triple immunosuppression with tacrolimus, mycophenolate mofetil, and corticosteroids. Tacrolimus was started as 0.05 mg/kg orally twice a day and the dose was adjusted to maintain trough concentrations 12-15 ng/mL for the first month, 8-12 ng/mL for the second month, and 4-8 ng/mL thereafter. Mycophenolate mofetil was given 1 g orally twice a day and reduced for myelotoxicity and withdrawn after 6 months in selected patients with hepatitis C. Corticosteroids were initiated intraoperatively with 500 mg of intravenous methylprednisolone, followed by intravenous methylprednisolone or equivalent oral prednisone taper to 30 mg/day by post-operative day 6 and gradually decrease to stop by 3 to 6 months. Corticosteroid use was completely avoided in 5 patients who were enrolled in a steroid-free protocol in the VGCV arm, while using the same tacrolimus and mycophenolate mofetil regimen. Episodes of biopsy proven acute cellular rejection were treated with 500 mg of intravenous methylprednisolone for three days along with a steroid taper. Steroid-resistant or severe rejection was treated with intravenous muromonab-CD3 5 mg/dose or rabbit anti-thymocyte globulin 1.5 mg/kg/dose for 7-14 days.

All patients except for D−/R− patients received CMV prophylaxis for 90 days post-transplant and after the antibody therapy for rejection. Oral GCV 1 g three times a day was used until March 15, 2002. Thereafter, our prophylaxis protocol was changed to oral VGCV 450 mg once daily. Doses of both drugs were reduced for impaired renal function per manufacturers guidelines. D−/R−; patients received oral acyclovir 400 mg twice a day for herpes prophylaxis for 30 days post-transplant and were not included in this analysis.

Statistical Analysis

Two-sample t-test for continuous variables and Fisher's exact test for binomial proportions were used to compare differences between GCV and VGCV groups. In all tests, two-sided p-values less than 0.05 were considered to be significant.

RESULTS

Patient Characteristics

Between January 2001 and April 2003, 148 adult liver transplants were performed in 145 patients at the University of Michigan. Thirty-nine transplants in 37 patients were excluded for the following reasons: 13 died or had re-transplant <1 month post-transplant; 20 received acyclovir for D−/R− status; five received an investigational antiviral agent for CMV prophylaxis; and one had a prior kidney transplant. None of the 13 patients (three GCV treated and 10 VGCV treated patients) who were excluded for death or re-transplant < 1 month post-transplant experienced CMV disease during their follow-up. The remaining 109 liver transplants were used for the final data analysis. One-year follow-up data were available for 96% of GCV patients (85-365 days) and 88% of VGCV patients (31-365 days).

The characteristics of patients in the two study groups are summarized in Table 1. Of note, the distribution of CMV D/R serotypes was similar in the two groups as well as the duration of CMV prophylaxis. The rates and treatment for acute cellular rejection were also similar in the two groups.

CMV Disease

The overall incidence of CMV disease within 1 year post-transplant was low (3.7%) in high to moderate risk liver transplant recipients (D+ or R+) when either oral GCV or low-dose VGCV prophylaxis was used. The incidence of CMV disease was similar between the GCV and the low-dose VGCV groups (4% and 3%, respectively) (Table 2). All but one case occurred in patients with high risk CMV serotype (D+/R−; 7% with VGCV and 22% with GCV, $p = 0.533$) and all cases developed after completion of the 90 day CMV prophylaxis, at a median of 133 days post-transplant (range, 114-152 days). One patient in the VGCV group (V-2) received

TABLE 1. Patient Characteristics of Ganciclovir and Valganciclovir Groups*

	Ganciclovir (n = 49)	Valganciclovir (n = 60)
Age, mean ± SD (years)	50 ± 10	49 ± 10
Gender, no. (%) of patients		
Male	27 (55%)	42 (70%)
Female	22 (45%)	18 (30%)
Race, noumber (%) of patients		
Caucasian	44 (90%)	53 (88%)
Black	1 (2%)	3 (5%)
Other	4 (8%)	4 (7%)
Primary liver disease†		
Hepatitis C	15 (31%)	29 (48%)
Alcoholic liver disease	8 (16%)	11 (18%)
Hepatitis B	7 (14%)	1 (2%)
Cryptogenic cirrhosis	3 (6%)	4 (7%)
Primary biliary cirrhosis	4 (8%)	2 (3%)
Autoimmune hepatitis	3 (6%)	2 (3%)
Primary sclerosing cholangitis	2 (4%)	7 (12%)
Other	7 (14%)	4 (7%)
CMV serotype, number (%) of patients		
D+/R−	9 (18%)	15 (25%)
D+/R+	24 (49%)	25 (42%)
D−/R+	16 (33%)	20 (33%)
Duration of CMV prophylaxis, mean ± SD (days)	90 ± 26	81 ± 20
Re-transplant, number of patients	0	1
Deaths from 1 to 12 months	2	7
Steroid-free immunosuppression, number of patients	0	5
Biopsy-proven rejection, no. (%) of patients	15 (31%)	13 (22%)
Steroid treated	13	12
r-ATG treated	2	1

Abbreviations: SD, standard deviation; CMV, cytomegalovirus; D, donor; R, recipient; r-ATG, rabbit anti-thymocyte globulin.
*P-values for all items > 0.05
†Owing to rounding, percentages do not total 100.

TABLE 2. Incidence of Cytomegalovirus Disease within 1 Year Post-Transplant

	Ganciclovir	Valganciclovir	P-value
Overall	2/49 (4%)	2/60 (3%)	NS
D+/R−	2/9 (22%)	1/15 (7%)	NS
D+/R+	0/24 (0%)	1/25 (4%)	NS
D−/R+	0/16 (0%)	0/20 (0%)	NS

Abbreviations: D, donor; R, recipient; NS, not significant.

steroid pulse treatment for rejection 4 months prior to the onset of CMV disease. Patient G-1 was treated with intravenous GCV 5 mg/kg twice daily for two months followed by oral VGCV 450 mg daily for another month. Three patients (G-2, V-1, and V-2) were treated for their CMV disease with VGCV 900 mg twice daily for three weeks. Patients G-1, G-2, and V-2 cleared viremia on repeat CMV-PCR testing during the antiviral treatment. Follow-up virological testing was not available for patient V-1. None of the CMV disease cases experienced recurrent CMV disease during the first year post-transplant (Table 3). An additional patient receiving VGCV developed CMV viremia (73,100 copies/mL) at 261 days post-transplant without documented CMV syndrome or organ dysfunction. This patient did not require antiviral therapy or experience further viral infectious complications throughout the 1 year follow-up period.

Hematological Side Effects

The hematological side effect profile of VGCV was similar to that of GCV. Severe neutropenia was uncommon with both low-dose VGCV and GCV (2% and 0%, respectively). There was a trend toward higher incidences of thrombocytopenia and anemia in the low-dose VGCV group compared to the GCV group, but the differences were not statistically significant (Table 4).

DISCUSSION

Although the efficacy and safety of VGCV in CMV prophylaxis is well documented in other types of solid organ transplantation, it has not been established in liver transplant recipients.[9-12] In a randomized double-blind controlled study of high-risk solid organ transplant recipients (D+/R−), oral VGCV 900 mg once daily for 100 days was as effective as oral GCV 1 g three times a day

TABLE 3. Summary of Cytomegalovirus Disease Cases

Case	Prophylaxis	CMV serotype	Time of onset (POD)	CMV-DNA PCR (copies/mL)	Symptoms or organ dysfunction	Treatment
G-1	GCV	D+/R−	133	95,900	Hepatitis	GCV IV followed by VGCV
G-2	GCV	D+/R−	152	37,100	Fever	VGCV
V-1	VGCV	D+/R−	114	Not available	Gastritis	VGCV
V-2	VGCV	D+/R+	132	64,300	Malaise	VGCV

Abbreviations: CMV, cytomegalovirus; POD, post-operative day; GCV, ganciclovir; VGCV, valganciclovir; D, donor; R, recipient; IV, intravenous.

TABLE 4. Incidence of Hematological Side Effects during 15-90 Days Post-Transplant

	Ganciclovir (n = 49)	Valganciclovir (n = 60)
Neutropenia (Absolute neutrophil count < 500/mm^2)	1 (2%)	0 (0%)
Thrombocytopenia (Platelet < 100,000/mm^2)	8 (16%)	13 (22%)
Anemia (hemoglobin < 8.0 g/mL)	1 (2%)	4 (7%)

during the first year post-transplant.[9] When data from the liver transplant subgroup were analyzed, there was no statistical difference in the overall incidence of CMV disease at 6-month post-transplant between the GCV group and the VGCV group (12% vs. 19%). However, significantly more patients in the VGCV group developed tissue-invasive disease compared to the GCV group (14% vs. 3%, $P = 0.037$).[10] Based on these findings, VGCV was approved by the U.S. Food and Drug Administration for use as CMV prophylaxis in high-risk kidney, heart, and kidney-pancreas transplant recipients but not in liver transplant recipients.

Because oral VGCV 450 mg once daily yields a similar area under the GCV concentration-time curve as oral GCV 1 g three times a day, it was proposed that low-dose VGCV (450 mg once daily) may be as efficacious as the standard oral GCV (1 g three times a day) in CMV prophylaxis while offering convenient once daily dosing and improved patient compliance.[8] Promising clinical outcomes of low-dose VGCV prophylaxis have been documented in kidney transplant recipients including high-risk patients (D+/R−).[11–13] Based on these data, we felt it would be reasonable to offer low-dose oral VGCV to our adult liver transplant recipients and then compare the rates of CMV disease to a historic control group of GCV treated patients.

Our retrospective analysis suggests that low-dose VGCV (450 mg once daily for 90 days) is as effective as the standard oral GCV (1 g three times a day) in preventing CMV disease in adult liver transplant recipients who survive > 1 month post-transplant. The overall incidence of CMV disease with both prophylactic regimens was low (4% with the GCV and 3% with the VGCV) and comparable to what was previously reported with the standard oral GCV (4.8%).[3] During our study period, most patients received tacrolimus, mycophenolate mofetil, and prednisone and 5 patients in the low-dose VGCV group received a steroid-free regimen. Regarding safety, the incidence of severe neutropenia, anemia, and thrombocytopenia was similar with GCV and VGCV in our study.

Potential limitations of our study include its retrospective nature, the lack of standardized monitoring for CMV viremia, and the small sample size. Although our study has a historic control group of GCV-treated patients, the clinical and disease characteristics of the patients were similar to the VGCV treated patients (Table 1). The immunosuppressive protocol was consistent over time as well. More importantly, the CMV D/R serotype distributions and duration of CMV prophylaxis were similar in the two treatment groups. In our center, CMV viremia is not prospectively monitored due to the low rate of CMV disease we have encountered in the past. In addition, recent studies demonstrate a poor correlation between CMV viremia and development of CMV disease.[14] Although we could not determine if the rates of CMV viremia were substantially different between the two prophylaxis regimens, it should be noted that our results of identifying CMV disease primarily amongst high-risk individuals (D+/R−) and the overall low 1 year incidence of CMV disease is similar to other published studies.[3–7] Only a prospective, randomized controlled study with serial monitoring of CMV viremia, symptoms and signs of organ dysfunction would be able to compare the rates of CMV infection and disease.

Our data show that CMV disease continues to be prevalent in D+/R− liver transplant recipients despite prophylaxis as reported in prior studies.[3–7] As noted in prior studies of kidney transplant recipients, most CMV disease cases occurred after completion of CMV prophylaxis with either VGCV or GCV.[11-13] Proposed strategies to decrease the incidence of CMV disease in the

high-risk group include high-dose VGCV (e.g., 900 mg/day) and a longer duration of therapy (e.g., 6 months).[9,13,15] Paya et al. reported that CMV disease developed within 6 months post-transplant in 19% of the high-risk liver transplant recipients who received 100 days of VGCV 900 mg/day.[9] In our study, CMV disease developed in 7% of the same risk group at 1-year post-transplant when 90 days of VGCV 450 mg/day was used. Because Paya et al. used more strict criteria to define CMV disease (positive CMV-DNA PCR, fever on two occasions at least 24 hours apart, and one or more signs or symptoms of CMV infection), the incidence could have been even higher if the criteria used in our study had been applied. However, the reported incidence rates cannot be compared directly because of different CMV disease criteria, follow-up periods, and study designs. In kidney transplant recipients, low-dose VGCV prophylaxis for 6 months has been used with success in high risk groups (D+/R or rabbit antithymocyte globulin treated patients).[13,15] Currently, there are no data to support using VGCV 450 mg/day for more than 3 months in liver transplant recipients, which may be associated with greater hematological toxicity, cost, and potential resistance.

With the increased use of GCV or VGCV for CMV prophylaxis in solid organ transplant recipients, concerns for emergence of GCV-resistant CMV have been raised. It has been proposed that the relatively low GCV serum concentrations achieved with oral GCV and low-dose VGCV for prolonged periods may lead to the selection of GCV-resistant CMV mutants.[16] However, GCV-resistant CMV mutants were better documented in patients receiving GCV.[16,17] Although there is no evidence thus far that demonstrates an increased risk of drug-resistant CMV with using low-dose or full-dose VGCV, this should be clarified in a larger population.[11,13,18] Although we did not perform GCV susceptiblity tests in patients with CMV disease, all of our patients responded clinically to GCV or VGCV therapy without recurrence of CMV disease during follow-up.

In summary, our retrospective study suggests that low-dose VGCV appears as efficacious and safe in the prevention of CMV disease in adult liver transplant recipients, as standard oral GCV. Our findings also demonstrate the high risk of D+/R− patients developing symptomatic CMV disease within the first year post-transplant after antiviral prophylaxis has been discontinued. To better define the optimal CMV prophylaxis regimen in adult liver transplantation, a large clinical trial of VGCV compared to oral GCV with stratified randomization for duration of therapy based on CMV D/R serotype is recommended with prospective assessment of CMV DNA levels and potential drug resistance.

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