Pharmacokinetics of Ganciclovir after Oral Valganciclovir versus Intravenous Ganciclovir in Allogeneic Stem Cell Transplant Patients with Graft-versus-Host Disease of the Gastrointestinal Tract

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ABSTRACT

The pharmacokinetics of ganciclovir after oral valganciclovir versus intravenous ganciclovir were compared in allogeneic stem cell transplant recipients with stable graft-versus-host disease of the gastrointestinal tract. Twenty-two evaluable adult patients were randomized to receive a single dose of open-label study drug (900 mg of oral valganciclovir or 5 mg/kg of intravenous ganciclovir). After a washout period of 2 to 7 days, patients were crossed over to receive the alternate study drug. Ganciclovir and valganciclovir concentrations in plasma were measured over 24 hours after dosing. Noninferiority of 900 mg of valganciclovir relative to intravenous ganciclovir was concluded if the lower limit of the 1-sided 95% confidence interval of the ratio of least-square means of the ganciclovir area under the curve (AUC) for the 2 study drugs was >80%. Valganciclovir was found to be rapidly absorbed and converted into ganciclovir. The ganciclovir exposure after 900 mg of valganciclovir noninferior to that of intravenous ganciclovir ($AUC_{0-\infty}$, 52.1 and 53.8 μg·h/mL, respectively; 95% confidence interval of the ratio of least square means of $AUC_{0-\infty}$, 82.48%-118.02%). Oral valganciclovir could be a useful alternative to intravenous ganciclovir in certain stable stem cell transplant patients who require prophylaxis or preemptive therapy for cytomegalovirus infection.
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KEY WORDS

Valganciclovir   •   Pharmacokinetics   •   Graft-versus-host disease

INTRODUCTION

Cytomegalovirus (CMV) disease can be effectively prevented in allogeneic hematopoietic stem cell transplant recipients by using ganciclovir. Preventive strategies that use ganciclovir include the initiation of preemptive therapy only in patients who become positive for CMV antigen or CMV DNA in the blood after transplantation and universal prophylaxis initiated in all patients at the time of engraftment and continued until day 100 after transplantation [1-4]. Because of the low bioavailability of oral ganciclovir capsules, ganciclovir is usually administered intravenously through a central venous catheter to hematopoietic stem cell transplant patients [5]. Although effective, this route of administration is limited by inconvenience, cost, and the risk of line-related infections.

Valganciclovir is a valine ester prodrug of ganciclovir. After oral administration, the vast majority of valganciclovir is converted rapidly by hydrolysis to

ganciclovir. In human immunodeficiency virus (HIV)–infected patients and solid-organ transplant recipients, the oral bioavailability of valganciclovir is approximately 60%, or 10-fold higher than the bioavailability of oral ganciclovir capsules [6,7]. Studies in HIV-infected patients and liver transplant recipients have shown that a 900-mg dose of oral valganciclovir results in an area under the plasma concentration-time curve (AUC) for ganciclovir similar to that of intravenous ganciclovir 5 mg/kg/d [7,8].

Patients who develop graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation are especially at risk for CMV disease and thus frequently require preemptive or prophylactic ganciclovir therapy. However, GVHD that involves the gastrointestinal tract can be particularly troublesome, causing severe diarrhea and decreased absorption of certain drugs such as cyclosporine [9,10]. If oral valganciclovir is to become an appropriate alternative to intravenous ganciclovir for allogeneic hematopoietic stem cell transplant recipients, then the pharmacokinetic profile of oral valganciclovir in patients with GVHD that involves the gastrointestinal tract needs to be established. For this reason, we undertook this study to compare the pharmacokinetic parameters of ganciclovir after oral valganciclovir versus intravenous ganciclovir in stem cell transplant recipients with stable GVHD of the gastrointestinal tract.

METHODS

Patients

Patients who had received an allogeneic hematopoietic stem cell transplant were eligible for the study if the following criteria were satisfied: (1) ≥16 years of age, (2) absolute neutrophil count of ≥1000 cells per microliter, (3) calculated creatinine clearance >60 mL/min, (4) no active CMV infection or disease, and (5) GVHD of the gastrointestinal tract. The diagnosis of GVHD was established by standard criteria [11,12]. GVHD of the gastrointestinal tract was defined as biopsy-proven GVHD of the gastrointestinal tract plus diarrhea (300-1500 mL/d) and/or nausea or biopsy-proven GVHD of the liver or skin plus diarrhea (300-1500 mL/d) with no other explanation. Patients who had received ganciclovir or acyclovir within 96 hours before the start of the study were excluded. Immunosuppressive agents were used as clinically indicated, but doses of cyclosporine and tacrolimus were kept stable during the duration of the study. The study was approved by the institutional review board at each transplant center. Informed consent was obtained from each patient before enrollment.

Study Design

Eligible patients were randomized to receive a single dose of open-label study drug (900 mg of oral valganciclovir or intravenous ganciclovir at a dosage of 5 mg/kg of actual body weight). After a washout period of 2 to 7 days, patients were crossed over to receive the alternate study drug. Each dose of study drug was administered in the morning after an overnight fast and then a standardized breakfast (cereal with milk, toast with butter and jam, juice, and coffee or tea). All patients also received a light lunch and evening meal.

Laboratory Studies and Clinical Assessments

Complete blood counts, serum creatinine and blood urea determinations, urinalyses, and liver function studies (total serum bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and alkaline phosphatase) were performed before and after each treatment period. Creatinine clearance was calculated before each dose of study drug by using the Cockcroft-Gault equation. A serum pregnancy test for female patients and a test for CMV antigen or DNA in the blood were performed before the study started.

Blood for plasma levels of ganciclovir and valganciclovir was drawn before administration of the study drug and then at 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours, 3 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, and 24 hours after study drug administration. When a patient had received intravenous ganciclovir, blood was drawn from the arm opposite the injection site of intravenous ganciclovir. Blood samples were centrifuged immediately. Plasma was extracted and stored at −70°C until analysis. Plasma levels of ganciclovir and valganciclovir were determined by a specific high-pressure liquid chromatography column-switching method and mass spectrometry [13,14].

A complete medical history, physical examination, and list of medications were recorded before the study. Patients were assessed for adverse events after each dose of study medication.

Pharmacokinetic Parameters

Pharmacokinetic parameters were derived by noncompartmental methods by using the WinNonlin Professional Version 4.1 software package, NCA model 202 (Pharsight Corporation, Mountain View, CA). Samples below the limit of quantification at the beginning or end of the profiles were considered to have a value of 0 μg/mL, whereas values below the limit of quantification that occurred during the profile were assumed to be missing. The primary pharmacokinetic parameter was the plasma ganciclovir AUC from time 0 to infinity ($AUC_{0-\infty}$) after either 900 mg of oral valganciclovir or 5 mg/kg of intravenous ganciclovir

administered over 1 hour. The $AUC_{0-\infty}$ was calculated by using the linear-trapezoidal method up to the maximum observed plasma ganciclovir concentration taken directly from the concentration-time data for each patient (C_{max}) and by using the log-linear-trapezoidal method after C_{max} ($AUC_{0-\infty} = AUC_{0-t} + C_{last}/\lambda_z$). C_{last} is the last measurable plasma concentration, and λ_z is the first-order rate constant associated with the terminal (log-linear) portion of the plasma concentration curve. Other pharmacokinetic parameters used for comparison were AUC_{0-t} (plasma ganciclovir AUC from 0 to t hours using the linear trapezoidal method), C_{max}, time to C_{max}, λ_z (terminal elimination rate constant), and terminal elimination half-life, calculated as the $Ln(2)/\lambda_z$.

Statistics

On the basis of a previous pharmacokinetic study that compared intravenous or oral ganciclovir with valganciclovir in liver transplant patients [7], the within-subject coefficient of variation for the $AUC_{0-\infty}$ was estimated to be 16.9%. A 20% increase in the coefficient of variation was used to account for additional variability that may occur in stem cell transplant recipients. When this estimate of variability is used, a total sample size of 20 evaluable patients (10 per sequence group) is needed to establish the noninferiority of the ganciclovir $AUC_{0-\infty}$ after oral valganciclovir versus intravenous ganciclovir on the basis of a Δ of 20% and a 1-sided α of .05 with 80% power. To account for possible dropouts, a total of 24 patients were enrolled in the study.

The pharmacokinetic analysis was based on data only from patients who completed both treatment periods of the study. An analysis of variance model for the 2-way crossover design was used to assess the ratio of the means of $AUC_{0-\infty}$ for ganciclovir after oral valganciclovir versus intravenous ganciclovir. Noninferiority was concluded if the lower limit of the 1-sided 95% confidence interval of the ratio of least square means of the ganciclovir $AUC_{0-\infty}$ after valganciclovir versus intravenous ganciclovir was >80%. Other pharmacokinetic parameters were summarized by treatment group by using descriptive statistics.

RESULTS

A total of 24 patients were enrolled in the study. Twelve patients were randomized to each treatment sequence (valganciclovir followed by intravenous ganciclovir or intravenous ganciclovir followed by valganciclovir). Two patients assigned to the sequence of intravenous ganciclovir followed by valganciclovir were excluded from analysis. One patient withdrew from the study before receiving any study drug, and a second patient withdrew after receiving only intravenous ganciclovir.

Table 1. *Patient Demographics*

Variable	Data
No. patients	22
Mean age, y (range)	45 (23-63)
Sex (n)	
Male	16
Female	6
Mean weight, kg (range)	76 (52-107)
Underlying disease (n)	
Lymphoma	7
Acute leukemia	5
Chronic leukemia	5
Multiple myeloma	2
Aplastic anemia	2
Myelodysplastic syndrome	1
GVHD (n)	
Chronic	14
Acute (grade II or III)	8
Biopsy-proven GVHD (n)	
Gastrointestinal	19
Liver	2
None	1
Immunosuppressive drugs (n)	
Tacrolimus, corticosteroids	9
Tacrolimus, corticosteroids, mycophenolate	1
Tacrolimus	2
Cyclosporine, corticosteroids	6
Cyclosporine, corticosteroids, mycophenolate	1
Sirolimus, corticosteroids	3
Median time (range) after transplantation for entry onto study (d)	227 (61-988)
Mean creatinine clearance, mL/min (range)	92 (45-182)

The demographics of the 22 evaluable patients are summarized in Table 1. All patients were adults with a mean weight of 76 kg. Eight patients had acute GVHD, and 14 patients had chronic GVHD. Nineteen patients had GVHD of the gastrointestinal tract documented by a biopsy. Two patients with chronic GVHD had diarrhea (which had no other explanation) and biopsy-proven GVHD of the liver. Their diarrhea stabilized on increased immunosuppressive therapy. One patient with clinical evidence of acute GVHD of the liver and gastrointestinal tract responded to corticosteroids but had an inconclusive gastrointestinal biopsy. All patients were taking immunosuppressive drugs at the time of study. Twenty of the 22 patients were receiving corticosteroids in combination with tacrolimus, cyclosporine, or sirolimus. The median time after transplantation for entering the study was 227 days. Nine patients were studied <6 months after transplantation, whereas 13 patients were studied >6 months after transplantation. The mean interval between administration of the 2 study drugs was 5.2 days.

Mean plasma ganciclovir concentrations over time are shown in Figure 1. The mean ganciclovir concentration in plasma after intravenous ganciclovir reached a maximum of approximately 13 μg/mL in approximately 1 hour, which was approximately 2.5 hours
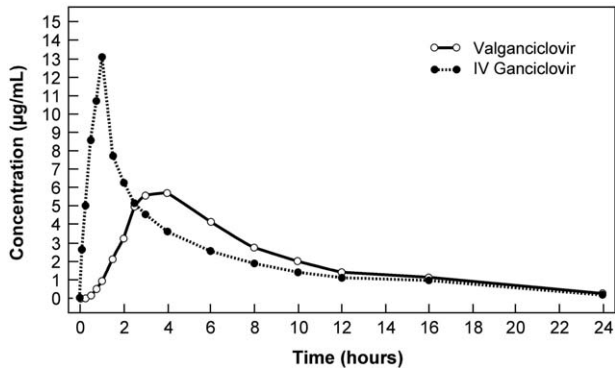
Figure 1. Mean plasma ganciclovir concentration over time after dosing with 900 mg of oral valganciclovir or 5 mg/kg of intravenous ganciclovir.

Table 2. *Mean Ganciclovir Pharmacokinetic Parameters after Dosing with Oral Valganciclovir or Intravenous Ganciclovir*

Parameter	900 mg of Oral Valganciclovir (n = 22)	5 mg/kg of Intravenous Ganciclovir (n = 22)
$AUC_{0-\infty}$ (µg·h/mL)	52.1 (41)	53.8 (40)
AUC_{0-t} (µg·h/mL)	49.0 (37)	51.3 (37)
C_{max} (µg/mL)	6.7 (27)	13.3 (30)
T_{max} (h)	3.5 (26)	0.9 (14)
λ_z (1/h)	0.1 (38)	0.1 (28)
$t_{1/2}$ (h)	5.1 (28)	5.2 (29)

Values in parentheses are coefficients of variation (%).

T_{max} indicates time to C_{max}; λ_z, terminal elimination rate constant; $t_{1/2}$, terminal elimination half-life.

earlier than the mean maximum ganciclovir concentration of approximately 6.0 µg/mL after oral valganciclovir. After reaching maximum concentrations, the mean plasma ganciclovir concentrations after both intravenous ganciclovir and oral valganciclovir declined and decreased to <1.0 µg/mL at 16 hours after administration. In contrast, the mean peak concentration of valganciclovir was only 0.22 µg/mL at 2.5 hours after dosing and declined rapidly, decreasing below the limit of quantification within 6 hours of dosing (Figure 2).

Mean ganciclovir pharmacokinetic parameters with coefficients of variation are summarized in Table 2. Because there were no significant statistical differences in the pharmacokinetic parameters by treatment sequence, results are presented by treatment (oral valganciclovir versus intravenous ganciclovir). The mean ganciclovir $AUC_{0-\infty}$ and AUC_{0-t} values associated with oral valganciclovir and intravenous ganciclovir were similar. Because the lower limit of the 1-sided 95% confidence interval (82.48%-118.02%) of the ratio of least square means of the $AUC_{0-\infty}$ for ganciclovir after valganciclovir versus intravenous ganciclovir was >80%, the noninferiority of valganciclovir compared with intravenous ganciclovir was established. Simi-
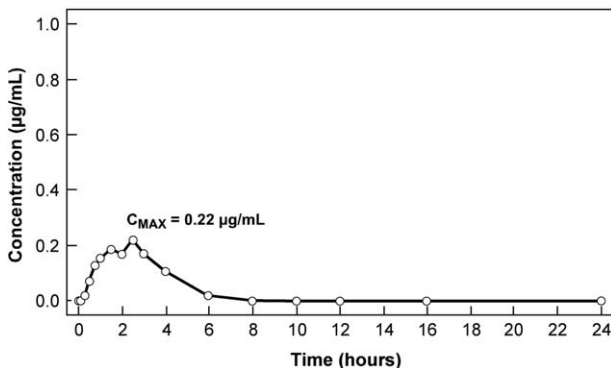
larly, the lower limit of the 1-sided 95% confidence interval (81.58%-116.77%) of the ratio of least square means of the AUC_{0-t} for ganciclovir after valganciclovir versus intravenous ganciclovir was >80%. The mean C_{max} value (6.7 µg/mL) after oral administration of valganciclovir was lower than the mean C_{max} value (13.3 µg/mL) after intravenous administration of ganciclovir. The mean time to C_{max} for ganciclovir was also longer (3.5 versus 0.9 hours) after oral valganciclovir. The mean terminal elimination ganciclovir rate constant, or λ_z (0.1 1/h versus 0.1 1/h), and the mean terminal elimination ganciclovir half-life (5.1 versus 5.2 hours) were similar after valganciclovir and intravenous ganciclovir. There were no significant differences in the ganciclovir pharmacokinetic parameters after valganciclovir versus intravenous ganciclovir when patients with acute GVHD were compared with patients with chronic GVHD. Similarly, no association could be made between pharmacokinetic parameters and the amount of diarrhea.

Adverse events related to study drug administration occurred in only 1 (4.3%) of the 23 patients who received a study drug. One patient experienced dizziness and a visual field defect during administration of intravenous ganciclovir. Both adverse events resolved without sequelae. There were no laboratory abnormalities related to the study drugs.

DISCUSSION

Although higher and earlier maximum plasma ganciclovir concentrations were achieved after intravenous ganciclovir compared with oral valganciclovir, we found that the mean $AUC_{0-\infty}$ and AUC_{0-t} values for ganciclovir after these 2 drugs were similar in patients with stable GVHD of the gastrointestinal tract. These results are consistent with those of a pharmacokinetic study in liver transplant patients which compared oral valganciclovir with intravenous ganciclovir [7]. The mean values for the $AUC_{0-\infty}$ and AUC_{0-t} of ganciclovir after dosing with 900 mg of oral

Figure 2. Mean plasma valganciclovir concentration over time after dosing with 900 mg of oral valganciclovir.

valganciclovir were 52.1 and 49.0 μg·h/mL, respectively, in our study compared with 43.9 and 41.7 μg·h/mL, respectively, in liver transplant recipients who received 900 mg of valganciclovir. These values in stem cell and liver transplant recipients are higher than the mean AUC_{0-t} value of 24.8 μg·h/mL observed in HIV-infected patients after 875 mg of oral valganciclovir [8]. The terminal elimination ganciclovir half-life after oral valganciclovir is also longer in both stem cell (5.1 hours) and liver (5.1 hours) transplant recipients compared with HIV-infected patients (4.08 hours) [7,8]. The use of immunosuppressive agents and other drugs with potential nephrotoxicity in transplant patients may decrease the renal clearance of ganciclovir.

The amount and extent of exposure to valganciclovir in this study were low. The mean peak concentration of valganciclovir was 0.22 μg/mL at 2.5 hours after dosing. Valganciclovir levels became undetectable 6 hours after dosing. In liver transplant recipients and HIV-infected patients, similar low C_{max} values for valganciclovir (0.172 and 0.264 μg/mL, respectively) were noted after 900- or 875-mg doses of oral valganciclovir [7,8]. These results are consistent with the rapid and almost complete metabolism of valganciclovir to ganciclovir [6].

In a previous pharmacokinetic study in stem cell transplant recipients, oral ganciclovir was evaluated in 14 patients without gastrointestinal GVHD and in 7 patients with gastrointestinal GVHD [5]. The absolute bioavailability of oral ganciclovir was low but similar in patients with or without gastrointestinal GVHD (7.2% versus 6.9%, respectively). The mean $AUC_{0-\infty}$ values for ganciclovir were also comparable in patients with or without gastrointestinal GVHD (13.5 and 10.2 μg·h/mL, respectively). However, these $AUC_{0-\infty}$ values are considerably lower than the mean $AUC_{0-\infty}$ value for ganciclovir (52.1 μg·h/mL) after oral valganciclovir in our study. The lower $AUC_{0-\infty}$ values after oral ganciclovir were associated with a 38% incidence of breakthrough CMV viremia among patients taking prophylactic oral ganciclovir (1000 mg 3 times per day) from day 35 to day 100 after transplantation [5]. Oral valganciclovir also provides greater systemic exposure to ganciclovir than oral ganciclovir in solid-organ transplant recipients [15]. In a preliminary report of a multiple-dose pharmacokinetic study of valganciclovir in allogeneic stem cell transplant recipients, exposure to ganciclovir after preemptive therapy with valganciclovir for CMV viremia was comparable to that with intravenous ganciclovir in patients with and without gastrointestinal GVHD [16].

A limitation of this study is that patients were evaluated when their gastrointestinal GVHD and diarrhea (300-1500 mL/d) were relatively stable. In addition, many patients had chronic GVHD. Patients with more severe diarrhea that complicated unstable acute GVHD were excluded. However, these more ill patients frequently need hospitalization for treatment of GVHD and require intravenous therapy not only with ganciclovir, but also with other medications. After their GVHD improves and stabilizes, they may become candidates for oral valganciclovir. Although patients with chronic GVHD are generally at lower risk for CMV disease compared with patients with acute GVHD, late-onset CMV infection and disease have been associated with increased mortality [17]. Consequently, both prophylaxis and preemptive therapy with oral valganciclovir are being considered in patients with chronic GVHD, who often no longer have an intravenous line.

The single doses of valganciclovir in this study were generally well tolerated. However, the complete safety profile of valganciclovir in stem cell transplant patients can be determined only in larger studies that use multiple doses over a longer time. Neutropenia has been the primary dose-limiting toxicity of intravenous ganciclovir in stem cell transplant recipients [1-4]. In controlled trials that evaluated the efficacy and safety of oral valganciclovir in HIV-infected patients and liver transplant recipients, the incidence of neutropenia associated with valganciclovir was 8.2% to 14% and was similar to the incidence with intravenous or oral ganciclovir [18,19].

Although the results of this study suggest that oral valganciclovir could be a useful alternative to intravenous ganciclovir in certain stable stem cell transplant recipients who require prophylaxis or preemptive therapy for CMV, this study was not designed to evaluate efficacy. Currently, valganciclovir is approved for treatment of CMV retinitis in patients with acquired immunodeficiency syndrome and for prevention of CMV disease in CMV-seronegative kidney, heart, and kidney-pancreas transplant patients with CMV-seropositive donors [18,19]. In uncontrolled studies, preemptive therapy with valganciclovir appeared to prevent CMV disease in both liver and stem cell transplant patients [20,21]. Additional randomized studies are needed to fully define the efficacy and safety of valganciclovir as preemptive therapy or as long-term prophylaxis of CMV disease in stem cell transplant recipients.

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