Letters to the Editor

Pharmacokinetics of Oral Valganciclovir and Intravenous Ganciclovir Administered to Prevent Cytomegalovirus Disease in an Adult Patient Receiving Small-Intestine Transplantation

Cytomegalovirus (CMV) is the most common viral pathogen following intestine transplantation, with an overall incidence of 30 to 40% (2).

Current prophylactic strategies are center specific and usually include intravenous (i.v.) ganciclovir (GCV) for 6 months. Administration of i.v. GCV is problematic because of the risk of infection associated with the use of a long term-catheter. Oral GCV capsules have a low bioavailability (6%) and limit the drug concentration in serum, which is especially important in these patients.

Valganciclovir (VGCV) is a prodrug of GCV. Following oral intake, the great majority of VGCV is rapidly converted to GCV by intestinal and hepatic esterases; no other metabolites have been detected. The absolute bioavailability of GCV from VGCV tablets following oral administration is approximately 60% (3).

No data about safety and bioavailability have been reported for the use of VGCV in small-intestine transplant recipients for CMV infection prophylaxis.

We report the pharmacokinetic profile of VGCV in an adult patient with a small-intestine transplant performed because of an intestinal desmoid tumor. The patient was a 23-year-old female. She weighted 50 kg. She was seropositive for CMV and had received an organ from a donor seropositive for CMV. She had a long history on total parenteral nutrition (TPN) requirements. After transplantation, she had an episode of acute cel-

lular rejection resolved by an increase in the doses of the immunosuppressors and a bolus of corticosteroids. She started to eat on day 12 after transplantation, although she received concomitant support by parenteral nutrition until week 8. The immunosuppression regimen was azathioprine, tacrolimus, corticosteroids, and basiliximab. Tacrolimus was changed from the i.v. to the oral route on day 17. The patient received i.v. GCV as CMV prophylaxis while waiting for the approval of VGCV for compassionate use. On month 2 after transplantation, CMV prophylaxis was changed from i.v. GCV to oral VGCV. At the time, she was receiving a diet of 2,600 cal/day, containing 15 to 20% protein, 30 to 35% fat, and 50 to 60% carbohydrate. We obtained scheduled serum samples to measure GCV levels on the last day she received i.v. GCV (5 mg/kg once a day [q.d.]) and also during the first day she received oral VGCV (900 mg q.d.). Before obtaining the samples for GCV levels of i.v. GCV and also for oral VGCV, the patient had a 3-day washout period. The GCV levels were determined by high-performance liquid chromatography as described previously (4). Bioavailability was calculated as follows: $[AUC \text{ of oral VGCV} \times \text{i.v. GCV dose (milligrams)}] / [AUC \text{ of i.v. GCV} \times \text{oral VGCV dose (milligrams)}]$.

The results are shown in Fig. 1. The area under the concentration-time curve over 24 h ($AUC_{0-24 \text{ h}}$) for i.v. GCV was $35.27 \mu\text{g} \cdot \text{h/ml}$, and that for oral VGCV was $85.67 \mu\text{g} \cdot \text{h/ml}$. The maximal drug concentration achieved with i.v. GCV was

FIG. 1. Concentrations of GCV over the 24-h dosing interval after administration of a single dose of i.v. GCV (5 mg/kg) and oral VGCV (900 mg q.d.) determined in serum samples by high-performance liquid chromatography.

14.36 $\mu\text{g/ml}$, and that obtained with oral VGCV was 9.82 $\mu\text{g/ml}$. The time to the maximum observed drug concentration was 1 h with i.v. GCV and 6 h with oral VGCV. The absolute bioavailability of GCV derived from 900 mg of oral VGCV administered once daily was 64.7%.

The patient continued receiving oral VGCV, adjusted to renal function, until month 6 after transplantation. She was monitored monthly by pp65 antigenemia and by scheduled viral culture of small-intestine biopsies, and she did not develop a CMV infection during the first year after transplantation.

Oral VGCV has been studied in different populations as prophylaxis and treatment of CMV infection. The bioavailability of oral VGCV is 60%. In liver transplant recipients, the mean AUC of GCV following a single dose of 900 mg of VGCV was greater (41.7 $\mu\text{g} \cdot \text{h/ml}$) (3) than that observed in human immunodeficiency virus-infected patients (24.8 $\mu\text{g} \cdot \text{h/ml}$) (1). Greater AUCs in transplant recipients are probable due to the longer terminal elimination resulting from the use of nephrotoxic immunosuppressive drugs (e.g., tacrolimus). Too large a GCV AUC could lead to an increase in the frequency of hematological and renal toxicity.

Preliminary studies have shown that oral VGCV is effective for the prevention of CMV disease, including donor-positive, recipient-negative solid-organ transplant recipients (C. Paya, 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. LB-4, 2002).

In a study analyzing the pharmacokinetic profile of GCV in a population of solid-organ transplant patients after 100 days of oral administration of VGCV, the average daily systemic exposure ($\text{AUC}_{0-24 \text{ h}}$) was 40.2 $\mu\text{g} \cdot \text{h/ml} \pm 41$. Viremia was totally suppressed during prophylaxis when the GCV $\text{AUC}_{0-24 \text{ h}}$ was $>50 \mu\text{g} \cdot \text{h/ml}$. The development of CMV disease 1 month after prophylaxis ended was reduced with a greater AUC. The development of CMV disease within 1 year of transplantation was 17.6% and was independent of exposure to GCV during prophylaxis. The greater systemic exposure to GCV delivered by VGCV was associated with delayed development of viremia (H. Wiltshire, S. Hirankarn, C. Farrell, and K. Zuideveld, 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1794, 2003).

However, there are concerns about the absorption of oral VGCV in recipients of small-intestine transplants. Patients with functional grafts are able to be completely weaned from TPN within 4 to 6 weeks postoperatively, although patients may require partial TPN during episodes of rejection and infection. Most patients are started on enteral feeding via a jejunostomy tube within 2 weeks posttransplantation. Adequate absorption is a good indicator of satisfactory function of the transplanted intestine and is determined by serial monitoring of carbohydrate and fat absorption. The ability to maintain a stable and satisfactory tacrolimus (FK-506) level can also be an indicator of adequate absorption. An appropriate tacroli-

mus level is usually achieved within 1 month posttransplantation (5).

Oral VGCV was an effective approach for CMV infection prophylaxis in this patient with an intestinal transplant. This situation represents a challenge for oral therapy because of the difficult absorption and the risk of CMV infection. The levels of GCV while the patients was receiving oral VGCV were in the GCV AUC range for efficient suppression of viremia, providing effective prophylaxis of CMV infection. Adjusting the dosing of oral VGCV to creatinine clearance is the best way to avoid renal and hematological toxicity.

VGCV may be preferable to GCV for long-term prophylaxis given the ease of administration and the good drug levels in plasma achieved after its administration. The optimal duration of the prophylaxis remains unknown.

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