ELSEVIER

Cytomegalovirus Infection after Prophylactic Valganciclovir Therapy Post–Kidney Transplantation: Case Reports

K. Nose, T. Oki, E. Banno, M. Nakagawa, K. Sugimoto, T. Nishioka, and T. Akiyama

ABSTRACT

This report describes three patients who developed cytomegalovirus infection 4 months after high-risk donor+/recipient−(D+/R−) kidney transplantation, despite treatment with valgancyclovir (VGCV) for 3 months at low dose (450 mg/d).

THE OUTCOME OF kidney transplantation has greatly improved along with the development of new immunosuppressants, but the occurrence of infectious disease after the operation is still a big concern. Cytomegalovirus (CMV) infection is the most prevalent and serious viral infection in kidney transplant recipients. Regarding prophylactic anti-CMV therapy, current reports have shown that prophylactic therapy for 3 to 6 months results in a reduced occurrence of CMV infection and its complications among high-risk donor +/recipient− (D+/R−) kidney transplantations.[1–3]

CASE REPORTS

We performed living kidney transplantation in 12 patients from January 2010 to December 2010 including three high-risk (D+/R−) subjects who were administered valganciclovir (VGCV) as prophylactic therapy. In our hospital, VGCV is prescribed for 3 months when CMV antibody is detected before the operation in the donor by a CMV antibody test. However, all three patients developed CMV infections shortly after completion of the prophylactic therapy. The detailed clinical courses of these three patients are shown in Table 1.

Case 1

This 26-year-old man who underwent ABO-compatible living kidney transplantation received immunotherapy with tracolimus (Tac) + mycophenolate mofetil (MMF) + prednisolone (Pred) + basiliximab (Bx). Good renal graft function was maintained without a postoperative rejection episode. Prophylactic therapy with VGCV (450 mg/d orally) was prescribed for 3 months after the operation. One month after therapy was completed, general fatigue and diarrhea appeared along with neutrophils positive for CMV antigenemia cell (185 positive 50,000 cells). The diagnosis was CMV colitis. MMF was promptly replaced with mizoribine (Miz); in addition, ganciclovir (GCV) was administered intravenously for 12 days and replaced with VGCV (900 mg/d). The symptoms disappeared but the patient continued on VGCV for about 5 months after the onset of CMV infection. Currently, the patient is not under treatment.

Case 2

This 34-year-old woman underwent preemptive ABO-incompatible living kidney transplantation due to chronic renal failure caused by hemolytic-uremic syndrome. Induction immunotherapy consisted of Tac + MMF + Pred + Bx, Good renal graft function was attained without a postoperative rejection episode. Prophylactic therapy with VGCV (450 mg/d) was prescribed for 3 months after the operation. One month after therapy was completed, the patient visited our hospital complaining mainly of diarrhea and fever. CMV neutrophil antigenemia test detected positive cells (411 positive/50,000 cells). The patient was diagnosed with CMV colitis and viremia. MMF was promptly changed to Miz, GCV intravenously administered for 14 days was subsequently replaced with one course of VGCV (900 mg/d), followed by two courses of high anti-CMV antigen globulin (10 g). Her condition improved, allowing the dose of VGCV to be reduced to 450 mg/d at about 3 months after the onset of CMV infection, It was administered for 2 months. Currently, the patient is under treatment.

Case 3

This 37-year-old woman underwent preemptive ABO-compatible living kidney transplantation due to chronic renal failure caused by IgA nephropathy. Immunotherapy consisted of cyclosporine (CsA) + Miz + Pred + Bx. Good renal graft function was attained without a postoperative rejection episode. Prophylactic therapy with VGCV (450 mg/d) was prescribed for 3 months after the operation; however, 2 months after therapy was completed, the patient visited our hospital complaining mainly of general fatigue and fever. A CMV neutrophil antigenemia test detected positive cells (586 positive/50,000 cells). The patient was diagnosed with CMV viremia. GCV was immediately administered after hospitalization. Because her condition was improving at 1 week after GCV therapy, we changed to VGCV (450 mg/d). The symptoms disappeared but she contin-

From the Department of Urology, Sakai Hospital Kinki University Faculty of Medicine, Sakai City, Japan.

Address reprint requests to Kazuhiro Nose, MD, Department of Urology, Sakai Hospital Kinki University Faculty of Medicine, 2-7-1 Harayamadai Minami-ku, Sakai City, Japan. E-mail: kams.nose@sakai.med.kindai.ac.jp

0041-1345/12/$–see front matter
doi:10.1016/j.transproceed.2011.11.036

Table 1. Details of Renal Transplant Recipients Who Had Prophylactic Therapy for CMV

	Case 1	Case 2	Case 3
Recipient age/sex	26 y/male	34 y/female	37 y/female
Original disease	CGN	HUS	IgA nephropathy
HD period	PET	2 mo	PET
Donor age/relation	64 y/father	60 y/mother	71 y/mother
ABO type	Incom (A+ → O+)	Incom (AB+ → B+)	com (A+ → A+)
LCT/FCXM	B(−)T(−)/B(−)T(−)	B(−)T(−)/B(−)T(−)	B(−)T(−)/B(−)T(−)
Induction immunosuppression	Tac + MMF + Pred	Tac + MMF + Pred	CyA + Miz + Pred
Rituximab/basiliximab	+/+	+/+	−/+
BPAR time	0	0	1
S-Cr of post-Tx (mg/dL)	1.2	0.9	1.8
Drug/dose (mg/d)	VGCV/450	VGCV/450	VGCV/450
Medication period	3M	3M	3M
Time to onset of CMV	4M	4M	4M
Therapy	GCV 200 mg/d × 14 d VGCV 900 mg/d	GCV 250 mg/d × 10 d IVIG (10 g/3 d) VGCV 900 mg/d	GCV 250 mg/d × 10 d VGCV 900 mg/d
CMV-ab IgG/IgM (pre-tx)*	NT	<2.0/0.42	<2.0/0.27
CMV-ab IgG/IgM (post-tx)*	NT/3.2	3.7/4.34	4.2/5.09
Convert of Immunosuppression	MMF → Miz	MMF → Miz	—
S-Cr of post therapy (mg/dL)	1.4	0.9	1.7

CMV, cytomegalovirus; HD, hemodialysis; CGN, chronic glomerulonephritis; HUS, hemolytic uremic syndrome; PET, preemptive kidney transplantation; Incom, incompatible; com, compatible; LCT, lymphocyte cross-match test; FCXM, flow cytometry; T, tacrolimus; MMF, mycophenolate moefetil; Pred, predonisolone; BPAR, biopsy-proven acute rejection; Tx, transplantation; VGCV, valganciclovir; GCV, granciclovir, IVIG, intravenous immunoglobuline; NT, not test; Tx, anti-CMV therapy.
*4.0 < positive.

ued on VGCV for about 3 months after the onset of CMV infection. Currently, she is not under treatment.

DISCUSSION

Because prophylactic therapy against CMV infection is not covered by the insurance system in Japan, many institutions treat using a preemptive strategy.[4] In addition, in the present condition of monitoring CMV, we measure CMV antigenemia only twice a month. We emphasize the importance of prophylactic therapy because (D+/R−) kidney transplant recipients are at high risk of developing CMV infections. CMV DNAemia was monitored at least weekly in all patients. Subjects who tested positive were treated preemptively with VGCV (900 mg once daily).[5]

At present, there is no agreement whether preemptive therapy is better than prophylaxis. Kliem et al[6] randomized 148 renal transplant patients to preemptive therapy (intravenous GCV) versus prophylaxis (oral GCV for 3 months). Long-term graft survival at 4 years posttransplant significantly improved among the prophylaxis group. Other authors have reported oral VGCV to provide good prophylaxis. In a recent study, VGCV was similar to GCV regarding therapy for CMV infection among solid organ transplant recipients.[7,8]

In addition, Miura[9] reported prophylactic anti-CMV therapay provided for (D+/R−) kidney transplant recipients showed a significantly more delayed onset although there were no difference in the onset rate of CMV infection. Reischig et al[10] reported prophylactic VGCV therapy to be equivalent to preemptive VGCV administered to kidney transplant recipients to prevent CMV infection, but they observed a significantly higher rate of biopsy-proven acute rejection (BPAR) during the first 12 months after surgery among the preemptive group (36% vs 15%; $P = .034$). In addition, patients subjected to prophylactic therapy experienced an increased incidence of psychiatric side effects in the early posttransplant period as well as leukopenia and neutropenia. Our patients did not experience adverse effects of prophylactic therapy with VGC. In addition, BPAR occurred in only one patient, and after the end of prophylactic therapy.

Concerning the dosage of prophylactic therapy with VGCV, Paya et al[11] reported no significant clinical differences between low- and high-dose groups. Kalil et al[12] reported the risk of CMV infection to be 1.06 (95% confidence interval, 0.64–1.76; $P = .81$) for VGCV 900 mg versus controls and 0.77 (0.49–1.18; $P = .23$) for VGC 450 mg versus controls. The risk of leukopenia was 5.24 (2.09–13.15; $P = .0004$) for VGCV 900 mg versus controls and 1.58 (0.96–2.61; $P = .07$) for VGCV 450 mg versus controls. The risk for an acute allograft rejection episode was 1.71 (0.45–6.50; $P = .43$) for VGC 900 mg and 0.80 (0.50–1.28; $P = .34$) for VGCV 450 mg. Humar et al[3] showed that the incidence of confirmed CMV infection was 36.8% in the 100-day group versus 16.1% in the 200-day group ($P < .001$) at 1 year posttransplant. The incidence of CMV viremia was 50.9% versus 37.4%, respectively ($P < .015$). Extending prophylaxis to 200 days significantly reduced the incidence of CMV infection up to 2 years posttransplantation among the high risk (D+/R−) kidney transplant recipients compared with 100 days of prophylaxis. As for the present patients, VGCV was prescribed at a 450 mg/d dose for 3

months, which were considered adequate based on present data.

CMV IgG antibody titer at the end of the dosage period was negative in all of out patients. Nevertheless, as CMV infection developed within 1 month after the end of the course, we must carefully reconsider about when we should finish the medication.

Prophylactic therapy seems to be more beneficial, but late-onset CMV infection is still a major problem. Late-onset CMV infection is observed particularly after prophylactic therapy with VGCV, especially among D+/R− transplant patients, but not in cases of preemptive therapy.[13] In liver transplant recipients, late-onset infections contribute to morbidity. They are associated with higher overall mortality.[14] It is necessary to consider all the potential options to deal with late-onset CMV infection. Humar and Syndman[1] have suggested (1) careful clinical follow-up post-transplantation together with treatment of an infection as soon as symptoms appear; (2) virological monitoring after completion of prophylaxis with periodic check of antigenemia or viral load for 8 to 12 weeks after completion of prophylaxis;, and (3) prolonged prohylaxis from 3 to 6 months for (D+/R−) kidney transplantation.

In conclusion, preemptive or prophylactic therapy has pros and cons. Prophylactic therapy reduced the acute rejections, however, there was no significant difference in long-term survival rate. In addition, late onset of CMV infection in the prophylactic therapy was treated efficiently. VGCV administration period for 3 months at our facility should be extended to 6 months. We consider that 450 mg/d VGCV is effective.

REFERENCES

1. Humar A, Syndman D: Cytomegalovirus in solid organ transplant recipients. Am J Transplant 9:9, S78, 2009

2. Kotton CN, Kumar D, Caliendo AM, et al: International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation 89:779, 2010

3. Humar A, Ajit P. Emily A, et al: Extended valganciclovir prophylaxis in D+/−R kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: two year results of the IMPACT study. Transplantation 90:1427, 2010

4. Watarai Y: Impact of late-onset cytomegalovirus infection and BK virus infection on patient's survival and renal allograft survival. Transplantation New 23:90, 2010

5. Myhre HA, Dorenberg DH, Kristiansea KI, et al: Incidence and outcomes of ganciclovir-resistant cytomegalovirus infections in 1244 kidney transplant recipients. Transplantation 92:217, 2011

6. Kliem V, Fricke L, Wollbrink T, et al: Improvement in long-term renal graft survival due to CMV prophylaxis with oral ganciclovir: results of a randomized clinical trial. Am J Transplant 8:975, 2008

7. Asberg A, Humar A, Rollag H, et al: Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 7:2106, 2007

8. Asberg A, Humar A, Jardine AG, et al: Long-term outcomes of CMV disease treatment with valganciclovir versus IV ganciclovir in solid organ transplant recipients. Am J Transplant 9:1205, 2009

9. Miura M: Strategies for cytomergalovirus infection after kidney transplantation; prospects of prophylactic therapy for high risk recipients. Transplantation Now 21:109, 2008

10. Reischig T, Jindra P, Hes O, et al: Valacyclovir prophylaxis versus preemptive valganciclovir therapy to prevent cytomegalovirus disease after renal transplantation. Am J Transplant 8:69, 2008

11. Paya C, Humar A, Dominguez E, et al: Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 4:611, 2004

12. Kalil Ac, Mindru C, Florescu DF: Effectiveness of valganciclovir 900 mg versus 450 mg for cytomegalovirus prophylaxis in transplantation: direct and indirect treatment comparison meta-analysis. Clin Infect Dis 28:313, 2010

13. Sun Hy, Wagener MM, Singh N: Prevention of posttransplant cytomegalovirus disease and related outcomes with valganciclovir: a systematic review. Am J Transplant 9:2110, 2008

14. Limaye AP, Bakthavatsalam R, Kim HW, et al: Late-onset cytomegalovirus disease in liver transplant recipients despite antiviral prophylaxis. Transplantation 78:1390, 2004