Acta virologica **57**: 375 – 377, 2013 doi:10.4149/av_2013_03_375

LETTER TO THE EDITOR

Prophylaxis of human cytomegalovirus infection in renal transplant patients with valacyclovir and ganciclovir

P. ZHANG[1], W. WANG[2], L. ZHANG[3], S. F. LI[3], L. B. GUAN[4], L. Q. DONG[5], S. ZHOU[6], P. YU[4,7*]

[1]Department of Urology, West China Hospital, Sichuan University, Chengdu, P. R. China; [2]Department of Pathology, West China Second University Hospital, Sichuan University, Chengdu, P. R. China; [3]Key Laboratory of Transplant Engineering and Immunology, Ministry of Health, West China Hospital, Sichuan University, Chengdu, P. R. China; [4]Laboratory of cell and gene therapy, West China Second University Hospital, Sichuan University, Chengdu, P. R. China; [5]Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, P. R. China; [6]Department of Obstetric&Gynecologic, West China Second University Hospital, Sichuan University, Chengdu, P. R. China; [7]Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, Sichuan University, 610041, P. R. China

Received January 18, 2013; accepted July 8, 2013

Keywords: human cytomegalovirus; renal transplant; valacyclovir; ganciclovir

Human cytomegalovirus (HCMV) infection is the leading cause of morbidity and mortality among transplant recipients. HCMV infection may elicit indirect effects on allograft dysfunction, accelerating the appearance of acute rejection, inducing opportunistic infections, and causing late-onset malignancies such as Epstein-Barr virus lymphoproliferative disease. HCMV infection and disease occur in 10–60% of all renal transplant recipients, most frequently during the period of maximal immunosuppression between 6 weeks and 6 months post-transplantation (*1, 2*). Antiviral prophylaxis is recommended for high-risk patients (seronegative recipients of seropositive grafts, D+/R-; seropositive recipients of seropositive grafts, D+/R+) (*3, 4*). Ganciclovir (GCV) and valacyclovir (VCV) prophylaxis can be given either orally or intravenously and has been shown to be effective in preventing HCMV infection (*5,6*). Previous research showed a significantly improved graft survival for those high-risk recipients who received antiviral prophylaxis compared with those without treatment (*7*). Here we describe an open, prospective and randomized study designed to test the safety and efficacy of VCV and GCV for HCMV prophylaxis in renal transplant recipients.

Eightyone patients who received renal allografts between 2005 and 2010 at West China Hospital of China were retrospectively evaluated. The mean age of the recipients was 42.9 ± 9.1 years, 56 were males and 26 were females. Inclusion criteria were cold ischemia time of 3.5–16 hrs. The HCMV serological status of donors and recipients was determined by detection of HCMV IgG-specific antibodies by FACS. The immunosuppressive regimens included cyclosporine microemulsion oral formulation (CsA), mycophenolate mofetil (MMF) and corticosteroids in 56 patients, and tacrolimus (Tac), MMF and corticosteroids in 35 patients. Participants were assigned randomly to receive oral acyclovir and GCV. Oral GCV was introduced to the test groups at 3 g/day, starting 3 days post-transplantation, and VCV was introduced at 4g/day, 3 days post-transplantation, with the dose being adjusted according to the graft function and continued for 3 months. The VCV group included 17 patients (D+/R-, 9; D+/R+, 3; D-/R+, 3 and D-/R-, 2),

*Corresponding author. E-mail: yup@scu.edu.cn; phone: +8628-85502385. P. Zhang and W. Wang contributed equally to this work.

Abbreviations: CsA = cyclosporine microemulsion oral formulation; GCV = ganciclovir; HCMV = human cytomegalovirus; MMF = mycophenolate mofetil; RTx = renal transplant; Tac = tacrolimus; VCV = valacyclovir

Table 1. Efficacy of prophylaxis of HCMV infection in renal transplant patients with VCV and GCV

Patient group	No. of patients					
	VCV-treated		GCV-treated		Untreated	
	Total	HCMV-positive	Total	HCMV-positive	Total	HCMV-positive
D+/R-	9	2	20	3	8	6
D+/R+	3	1	8	2	7	4
D-/R+	3	0	6	1	5	3
D-/R-	2	0	3	1	7	3
Total	17	3	37	7	27	16

and GCV group included 37 recipients (D+/R-, 20; D+/R+, 8; D-/R+, 6 and D-/R-, 3), 27 patients did not receive any antiviral chemoprophylaxis (D+/R-, 8; D+/R+, 7; D-/R+, 5 and D-/R-, 7). Data were evaluated using the statistic packages of the SPSS program (version 12.0, SPSS Inc., Chicago, IL, USA). All values were expressed as the mean ± SD. Qualitative and quantitative variables were analyzed by chi-square test or Fisher's exact test and *t*-test, respectively. *P*-values of < 0.05 were considered to be significant. This analysis was conducted in accordance with the ethical guidelines mandated by the declaration of Helsinki. All patients gave written informed consent for scientific evaluation of their data.

HCMV infection/antigenemia was defined as positive when pp65-immunofluorescence-testing became positive, defined as >20 of 200,000 leukocyte nuclei being positive, as previously reported (*8*). Overall, in the high risk group (D+/R-), HCMV infection developed in 22% (2/9) and 15% (3/20) of patients in VCV and GCV treatment, respectively, which was lower than that in the no- treatment group (75%, 6/8) (P <0.05). In another high risk group D+/R+, the HCMV infection was also lower in VCV (33%, 1/3) group and GCV group (25%, 2/8) than that in the no-treatment group (57% (4/7) (P <0.05). In these two high-risk groups, no statistical difference was noted in HCMV-infection rates between VCV and GCV groups (P>0.05). In the lower risk group D-/R+, no HCMV infection was detected in VCV-treated patients, 17% (1/6) and 60% (3/5) experienced active HCMV infection in the GCV and no-treatment group, respectively. In D-/R- group, HCMV infection was also not detected after VCV treatment, 1 of 3 patients (33%) was found HCMV-positive compared with 3 of 7 patients (43%) in the no-treatment group (Table 1).

Our study clearly indicated that renal transplant patients receiving triple immunosuppressive therapy, but no anti-HCMV prophylaxis, have a 59% (16/27) incidence of HCMV infection, compared with an incidence of less 20% in patients receiving VCV (18%, 3/17) or GCV (19%, 7/37) treatment (Table 1). The results also showed that both VCV and GCV conduce equally in preventing HCMV infection in renal transplant recipients, which was in agreement with another study of renal transplant recipients (*9*). Recently published guidelines of the Canadian Society of Transplantation emphasize the role of antiviral prophylaxis in high-risk recipients (D+/R-) and recommend preventive therapy for low-risk patients (*10*). Our study provides some important information about HCMV infection and the dose of antiviral prophylaxis drugs in renal transplant patients in China, but we need to take its limitations into consideration. It is a small-sized, retrospective study; unrecognized biases might affect the results. Further investigation is needed to define the optimal prophylactic regimen for patients. The choice of prophylactic regimen provided to renal transplant patients is complex and should take into consideration the efficacy, toxicity, cost and the possibility of emergence of resistant strains.

Acknowledgements. This work was supported by the grants No. 81070499 and 81101261 from National Natural Science Foundation, grant No. 2009CB522401 from National Basic Research Program of China, and the grant No. IRT0935 from Program for Changjiang Scholars and Innovative Research Team in University.

References

1. Couzi L, Helou S, Bachelet T, Moreau K, Martin S, Morel D, Lafon ME, Boyer B, Alain S, Garrigue I, Merville P, Am. J. Transplant. 12, 202–209, 2012. http://dx.doi.org/10.1111/j.1600-6143.2011.03766.x

2. Linares L, Sanclemente G, Cervera C, Hoyo I, Cofán F, Ricart MJ, Pérez-Villa F, Navasa M, Marcos MA, Antón A, Pumarola T, Moreno A, Transplant. Proc. 43, 2145–2148, 2011. http://dx.doi.org/10.1016/j.transproceed.2011.05.007

3. Villacian JS, Paya CV, Transplant. Infect. Dis. 1, 50–64, 1999. http://dx.doi.org/10.1034/j.1399-3062.1999.10106.x

4. McGee J, Mave V, Yau CL, Killackey M, Paramesh A, Buell J, Slakey DP, Hamm LL, Zhang R, Transpl. Infect. Dis. 14, 604–610, 2012. http://dx.doi.org/10.1111/j.1399-3062.2012.00759.x
5. Ginevri F, Losurdo G, Fontana I, Rabagliati AM, Bonatto L, Valente R, Venzano P, Nocera A, Basile GC, Valente U, Gusmano R, Transpl. Int. 11, S130–S134, 1998.
6. Witzke O, Hauser IA, Bartels M, Wolf G, Wolters H, Nitschke M, VIPP Study Group, Transplantation 93, 61–68, 2012. http://dx.doi.org/10.1097/TP.0b013e318238dab3
7. Gutiérrez CA, Chaparro C, Krajden M, Winton T, Kesten S, Chest 113, 924–932, 1998. Lopau K, Greser A, Wanner C, Clin. Transplant. 21, 80–85, 2007.
8. Flechner SM, Avery RK, Fisher R, Mastroianni BA, Papajcik DA, O´Malley KJ, Goormastic M, Goldfarb DA, Modlin CS, Novick AC, Transplantation 66, 1682–1688, 1998. http://dx.doi.org/10.1097/00007890-199812270-00019
9. Preiksaitis JK, Brennan DC, Fishman J, Allen U, Am. J. Transplant. 5, 218, 2005. http://dx.doi.org/10.1111/j.1600-6143.2004.00692.x