The incidence and risk factors associated with varicella zoster virus infection in kidney transplant recipients after 1-month acyclovir prophylaxis in a CMV preemptive therapy era

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Background

- Varicella zoster virus (VZV) infection is a well-known opportunistic infection in solid organ transplant recipients (SOT).
- Since the various strategies of the use of anti-herpetic drugs including ganciclovir or acyclovir have evolved, the epidemiology of VZV infection is changing. However, there are limited data on the recent incidence and risk factors of post-transplant VZV infection in popular preemptive ganciclovir era for CMV infection.
- We evaluated the incidence, risk factors and clinical characteristic of patients with development of post-transplant VZV infection in kidney transplant (KT) recipients after 1-month acyclovir prophylaxis in the hospital that adopted preemptive ganciclovir therapy for CMV infection.

Methods

- ***Study population***

  All patients admitted for KT in a kidney transplant unit between January 2014 and December 2017 at a 2,700 bed, tertiary-care hospital in Seoul, South Korea, were retrospectively reviewed. The resulting cohort was observed until November 2019 with a focus on VZV infection development after KT.

- ***Study design and VZV, CMV and BKV prevention strategies***

  The objective of this study was to evaluate the incidence, risk factors and clinical characteristics of patients with development of post-transplant VZV infection in KT recipients. We administered a 1-month course of acyclovir prophylaxis therapy immediately after KT to all CMV seropositive recipients. In addition, our hospital adopted preemptive ganciclovir therapy for CMV infection in CMV seropositive KT recipients.

- ***Induction Immunosuppressive regimens***

  Anti-interleukin (IL)-2 receptor antibody (basiliximab, Simulect, Novartis, East Hanover, New Jersey, USA) or anti-thymocyte globulin (ATG) (Thymoglobulin, Genzyme/Sanofi, Cambridge, Massachusetts, USA) were administered for induction therapy after KT. In simultaneous pancreas-kidney transplantation (SPK), ATG was administered for induction therapy. In addition, the KT recipients with ABO incompatible were administered rituximab (500 mg, 7-10 days before transplantation, Mabthera, Roche, Basel, Switzerland). Furthermore, the KT recipients with HLA cross-matching positivity underwent plasmapheresis until the anti-A or anti-B titer was < 1:8.

- ***Assessment of outcomes***

  The primary outcome was development of VZV infection after KT. The development of VZV infection after transplantation was observed between January 2014 and November 2019. Secondary outcomes were mortality and rejection. Recipients were evaluated every month during the first 6 months after transplantation and every 3 months after that.

Results

- ***Patients' characteristics***

  During study period, a total of 1339 patients underwent KT in our hospital between January 2014 and December 2017. Of these 1339 patients, 51 patients were excluded from the final analysis. The resulting study cohort of 1288 KT recipients was followed up for 4541.9 person-years; median duration of follow-up was 42.8 months (interquartile range [IQR], 31.2 to 55.3).

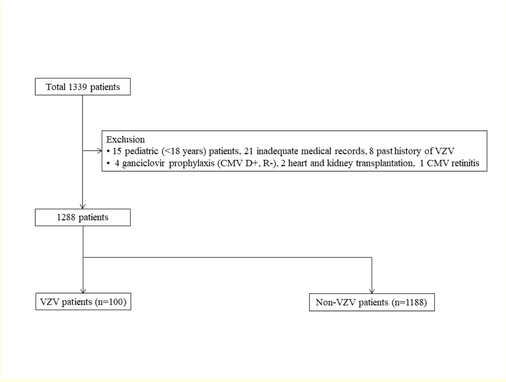

Figure 1. Schematic flow chart of the study

- ***Development of VZV infection***

  Of 1288 KT recipients with 1-month acyclovir prophylaxis, 107 VZV infection episodes identified in 100 VZV patients of 1288 KT recipients (8.3%, 2.36 per 100 person-years, 95% CI 1.93 to 2.85).

  In a subgroup analysis, 31 episodes (31 of 277, 11.2%) of 29 patients in 277 deceased-donor KT recipients developed VZV infection, whereas 72 (72 of 936, 7.7%) of 67 patients in 936 living-donor KT recipients (rate difference 0.95 per 100 person-years, 95% CI -0.15 to 2.06, P = 0.09). And 4 (5.3%) of 75 pancreas-kidney transplantation patients developed VZV infection (rate difference 1.67 per 100 person-years, 95% CI – 0.57 to 3.91, P = 0.14).

Table 1. Incidence of VZV infection in KT recipients

Variable	VZV incidence rates				
	No. of patients	No. of VZV episodes	No. of person-years	VZV rate per 100 person-years	95% CI
Total patients with 1-month acyclovir prophylaxis	1288	107	4,541.90	2.36	1.93-2.85
Living donor kidney transplantation	936	72	3,284.52	2.19[a]	1.72-2.76
Deceased donor kidney transplantation	277	31	985.50	3.15[a,b]	2.14-4.47
Pancreas-kidney transplantation	75	4	271.89	1.47[b]	0.40-3.77

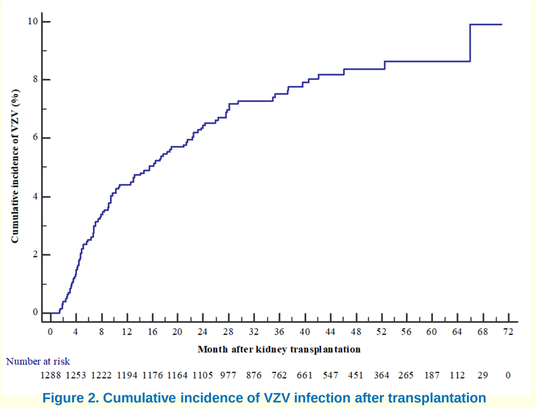

Figure 2. Cumulative incidence of VZV infection after transplantation

- ***Incident VZV cases***

  Of 1288 KT recipients who treated 1-month acyclovir prophylaxis, a total of 100 (7.7%, 2.34 per 100 person-years, 95% CI 1.90-2.84) patients developed VZV infection. The VZV infection development time ranged from 1.4 to 66.0 months after KT; median time of VZV infection development was 9.5 months (IQR 4.7 to 22.1). All patients had VZV-associated skin lesion, 9 postherpetic neuralgia, 2 visceral involvement and 3 disseminated infection. Of 100 patients, 16 patients need hospitalization due to VZV infection. Most common antiviral therapy was famciclovir (61%), followed by valacyclovir (27%) and acyclovir (15%). Seven of 100 VZV infection recipients recurred after first VZV infection episodes.

Table 2. Clinical manifestation and outcomes of VZV infection after kidney transplantation

Variable	VZV infection (n=100)
Time to onset of VZV (days) after transplantation, median (IQR)	9.5 (4.7-22.1)
Skin lesion	100 (100)
Postherpetic neuralgia (> 90 days)	9 (9)
Visceral involvement[a]	2 (2)
Disseminated VZV infection	3 (3)
Hospitalization due to VZV	16 (16)
Antiviral therapy	
Acyclovir	15 (15)
Famciclovir	61 (61)
Valacyclovir	27 (27)
Recur of VZV infection	7 (7)

- ***Risk factors of VZV infection***

  In a multivariate analysis, Age over 60 to 2.92, P = 0.03) and deceased donor kidney transplantation (HR 1.73, 95% CI 1.12 to 2.67, P = 0.01) were independent significant risk factors associated with development of VZV infection after KT. Re-transplantation (HR 0.35, 95% CI 0.11 to 1.09, P = 0.07), ganciclovir or valganciclovir treatment (HR 0.06, 95% CI 0.01 to 0.46, P = 0.01) and BK viremia episodes (HR 0.69, 95% CI 0.45 to 1.08, P = 0.11) showed a trend towards lower development of VZV infection in KT.

Table 3. Univariate and multivariate analyses of risk factors for development of VZV infection

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Median age, years				
< 60 years	Reference			
≥ 60 years	1.64 (0.99-2.70)	0.05	1.77 (1.07-2.92)	0.03
Gender				
Male	Reference			
Female	1.10 (0.74-1.64)	0.63		
Primary reason for transplantation				
Glomerulonephritis	0.79 (0.51-1.22)	0.29		
Hypertension	1.00 (0.60-1.69)	0.99		
Diabetes mellitus	0.86 (0.54-1.38)	0.53		
Unknown	1.27 (0.81-1.98)	0.30		
Polycystic kidney disease	2.08 (0.96-4.48)	0.06		
Others	0.05 (0-NA)	0.81		
Transplantation type				
Living donor kidney	0.76 (0.50-1.15)	0.19		
Deceased donor kidney	1.51 (0.98-2.33)	0.06	1.73 (1.12-2.67)	0.01
Pancreas and kidney	0.67 (0.25-1.81)	0.42		
Re-transplantation	0.36 (0.12-1.14)	0.08	0.35 (0.11-1.09)	0.07
ABO-mismatch transplantation	0.66 (0.38-1.14)	0.13		
HLA mismatch				
0	Reference			
1	0.64 (0.18-2.24)	0.48		
2	0.99 (0.49-2.02)	0.995		
3	0.71 (0.35-1.41)	0.33		
4	0.85 (0.40-1.79)	0.67		
5	0.78 (0.37-1.62)	0.50		
6	0.84 (0.39-1.80)	0.65		
Induction therapy at transplantation				
Anti-IL-2 receptor antibodies	0.82 (0.48-1.38)	0.45		
Anti-thymocyte antibodies	1.09 (0.61-1.95)	0.77		
Rituximab	0.68 (0.41-1.12)	0.13		
Rejection before VZV	0.66 (0.36-1.20)	0.17		
Within 3 months	1.35 (0.63-2.91)	0.44		
From 3 to 6 months	1.83 (0.58-5.77)	0.30		
From 6 to 12 months	1.26 (0.40-4.02)	0.68		
After 12 months	0.60 (0.24-1.47)	0.26		
Rejection treatment				
Steroid pulse therapy	1.10 (0.65-1.86)	0.71		
Therapeutic plasma exchange	1.54 (0.84-2.82)	0.16		
Rituximab	1.02 (0.45-2.32)	0.97		
Intravenous immunoglobulin	1.69 (0.74-3.85)	0.21		
Bortezomib	1.97 (0.62-6.20)	0.25		
Anti-thymocyte globulin	1.78 (0.44-7.22)	0.42		
CMV infection before VZV	0.77 (0.52-1.34)	0.19		
CMV disease before VZV	1.07 (0.40-2.92)	0.89		
Ganciclovir or Valganciclovir treatment before VZV	0.07 (0.01-0.49)	0.01	0.06 (0.01-0.46)	0.01
BK viremia before VZV	0.63 (0.41-0.99)	0.04	0.69 (0.45-1.08)	0.11

Conclusions

- About one tenth of CMV seropositive KT recipients developed zoster after 1-month ACV prophylaxis during CMV preemptive strategy, especially in those who was over 60 years or received deceased donor KT.