Very Early Cytomegalovirus Infection After Renal Transplantation: A Single-Center 20-Year Perspective

Virology: Research and Treatment
Volume 10: 1–6

DOI: 10.1177/1178122X19840371
SAGE

MR Jorgenson[1], JL Descourouez[1], BC Astor[2], JA Smith[3], F Aziz[3], RR Redfield[4] and DA Mandelbrot[3]

[1]Department of Pharmacy, University of Wisconsin Hospital and Clinics, Madison, WI, USA. [2]Department of Medicine and Population Health Sciences, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI, USA. [3]Department of Medicine, University of Wisconsin-Madison School of Medicine and Public Health, University of Wisconsin Hospital and Clinics, Madison, WI, USA. [4]Department of Surgery, University of Wisconsin-Madison School of Medicine and Public Health, University of Wisconsin Hospital and Clinics, Madison WI, USA.

ABSTRACT

BACKGROUND: Cytomegalovirus (CMV) infection risk in the first month after transplantation is felt to be minimal; however, the epidemiology has not been specifically investigated, particularly in the modern era of potent immunosuppressive regimens and universal CMV prophylaxis.

OBJECTIVE: The aim of this study was to describe the incidence of and risk factors associated with CMV occurring less than 30 days after transplant and evaluate the effect of very early CMV on outcomes.

METHODS: Retrospective, single-center study of adult renal transplant (RTX) recipients between January 1, 1994 and December 31, 2014.

RESULTS: A total of 5225 patients who received a renal transplant in the study time period were reviewed for the presence of CMV infection occurring less than 30 days after transplant. Of these, only 14 patients demonstrated this finding for an overall incidence of 0.27%. Half of these patients were considered to be at heightened risk due to being a recipient of a non-primary transplant or on chronic immunosuppression. This left seven patients without known risk factors for very early CMV to evaluate. In this group, time from transplant to CMV infection was 13.5 ± 7 days. The majority (57.1%, n = 4) were high-risk serostatus (CMV D+/R−) and occurred in the valganciclovir era (71.4%, n = 5). Lymphocyte-depleting induction predominated (57.1%, n = 4). Average cold ischemic time (CIT) was 19.7 ± 7.7 hours. Three patients had post-operative complications, two required exploratory-laparotomy for hemorrhage. When evaluating outcomes, 43% (n = 3) had subsequent episodes of CMV infection, 28.6% (n = 2) developed rejection, and 28.6% (n = 2) died. Outcomes between patients with CMV infection less than 30 days and those with CMV infection more than 30 days after transplant were not significantly different.

CONCLUSIONS: In our review of over 5000 kidney transplants, the incidence of CMV infection in the first 30 days after renal transplant is 0.2%. Notable common patient characteristics include hemorrhage requiring re-operation and prolonged CIT. Outcomes were similar to CMV occurring more than 30 days after transplant. This study should provide the clinician with some reassurance; despite potent immunosuppressive therapy, CMV infection in the first 30 days is unlikely.

KEYWORDS: transplantation, renal transplant, infectious disease, viral infections, antivirals

RECEIVED: January 10, 2019. **ACCEPTED:** February 21, 2019.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: MR Jorgenson, Department of Pharmacy, University of Wisconsin Hospital and Clinics, 600 Highland Avenue, Madison, WI 53792, USA.
Email: MJorgenson@uwhealth.org

Introduction

Cytomegalovirus (CMV), a ubiquitous herpesvirus present in 40% to 70% of the population, is common after solid organ transplantation (SOT) and is an independent risk factor for graft loss and mortality. Iatrogenic immunosuppression targeting T cells may result in uncontrolled CMV replication.[1] The risk of CMV infection in the first month after transplantation is generally felt to be minimal, despite the high-intensity immunosuppression used at the time of transplant due to a lack of prolonged immunosuppressive exposure.[1–3] Duration of immunosuppressive exposure is thought to be the most significant factor involved in the development of opportunistic infections, such as CMV.[1] Indeed, the most respected sources in the field suggest a search for unusual nosocomial exposures or preexisting iatrogenic immunosuppression in the setting of opportunistic infection, such as CMV, occurring less than 1 month after renal transplant.[1–3] However, this notion of a required sustained effect of immunosuppression on the development of CMV infection is theoretical and has not been clinically evaluated, particularly in the modern era of potent immunosuppressive regimens and universal CMV prophylaxis.

Methods

All adult patients who received a renal transplant at our institution between January 1, 1994 and December 31, 2014 were reviewed for the presence of CMV occurring less than 30 days after transplant (very early CMV). Patients were deemed to have very early CMV if they had evidence of CMV infection defined as any positive CMV detected via molecular diagnostics or biopsy-proven tissue-invasive disease less than 30 days following SOT. Data were collected from the Wisconsin Allograft Recipient Database (WisARD). This study was approved by the local institutional review board.

Our primary objective was to describe the epidemiology of and our experience with very early CMV, including evaluation of possible unknown risk factors associated with very early CMV and response to treatment. Our secondary objective was to describe the patient and graft outcomes after very early CMV and compare these outcomes to the unaffected population (never CMV), and the population with CMV more than 30 days after renal transplant.

Throughout the study period, methodology for detection and quantification of CMV viral load changed. Prior to 2006, CMV was measured via hybrid capture DNA assay at our center due to its significant improvement in sensitivity over blood culture assay. However, quantitative CMV nucleic acid amplification polymerase chain reaction (PCR) testing (CMV QNAT) is more sensitive than the capture assay, with concordance between PCR and capture reported at approximately 79%.[4] When PCR values are available, they are reported in copies/mL as the study time period is prior to the adoption of the World Health Organization (WHO) international standard and conversion to the current measurements (IU/mL).

Throughout the study period, CMV prophylaxis protocols at our center changed due to the approval and marketing of the potent antivirals ganciclovir, and its oral prodrug valganciclovir (VGC). Prior to 1996, no effective antiviral medication was available for prophylaxis. From 1996 to 2003, oral ganciclovir at a renally adjusted dose of 3 g/day was used for universal prophylaxis in high-risk patients. After 2003, VGC at a renally adjusted dose of 900 mg daily was used. After publication of a pivotal clinical trial in 2010, duration of prophylaxis was extended from 3 to 6 months in these patients.[19] Despite these changes, our CMV prophylactic protocol remained consistent. Preventive antiviral therapy was initiated within 72 hours after renal transplant, and CMV viral load monitoring was not routinely done during prophylactic antiviral therapy.[5]

Recipients were categorized by CMV status, and baseline characteristics were described by mean, median, and interquartile range (IQR). Outcomes were compared across groups using chi-square and Fisher exact tests.

Results

A total of 5225 patients who received a renal transplant in the study time period were reviewed for the presence of CMV infection occurring less than 30 days after transplant (very early CMV). Of these, only 14 patients demonstrated this finding for an overall incidence of 0.27%. Median follow-up time of the total cohort was 10 years. Half of these patients (n = 7) were considered to be at heightened baseline risk for very early CMV due to being a recipient of a non-primary transplant or on chronic immunosuppression. This left seven patients without known risk factors for very early CMV to evaluate (Figure 1). In this population, date of transplantation ranged from 1994 to 2009 with a median follow-up time of 6 years. Mean time from transplant to CMV infection was 13.5 ± 7 days. Four patients were high-risk serostatus (CMV D+/R–) and one patient was low-risk serostatus (CMV D–/R–), as defined by the International Consensus Guidelines.[5] The majority (71%, n = 5) were receiving dialysis prior to transplant, with a median duration of 27 (range = 17-237) months. Average cold ischemic time (CIT) was 19.7 ± 7.7 hours, with a median of 20 hours. Lymphocyte-depleting induction at the time of transplant predominated (57.1%, n = 4) (Table 1). All patients were on triple drug immunosuppressive therapy with a corticosteroid, antimetabolite, and calcineurin inhibitor (CNI) at the time of CMV infection; 85.7% were receiving mycophenolic acid products (MPA, mycophenolate mofetil, or mycophenolate sodium). Three patients had post-operative complications, two of whom required exploratory laparotomy and hematoma evacuation. One patient required intra-operative donor arterial reconstruction. Mean transplant length of stay was 10 ± 6 days. Almost half were receiving appropriate renal dosing of VGC prophylaxis at the time of CMV infection. Overall, when reported, CMV viral load was relatively low at detection, with the exception of the previously unexposed (CMV D–/R–) patient with new onset (primary) disease, who was above the upper limit of quantification at detection (Table 2). More than half of the patients (57.1%, n = 4) with evidence of very early CMV were symptomatic per chart review; in the others, symptoms were not specifically recorded (Table 2). CMV infection was treated in 71.4% of cases (n = 5) with immunosuppressive reduction ± a ganciclovir derivative (intravenous ganciclovir or oral VGC) for a median of 52 (range = 11-450) days.

When evaluating outcomes, 43% of patients with very early CMV had a subsequent episode of CMV infection and 28.6% developed rejection, although 85.7% had functional renal allografts at last evaluation, with a mean estimated glomerular filtration rate (eGFR) of 53.7 ± 20.3 at last follow-up (Table 2). The low-risk serotype (D–/R–) patient with de novo infection developed ganciclovir-resistant disease which failed treatment with cidofovir and required prolonged foscarnet administration. Two patients died (n = 28.6%), one of which was due to CMV infection (the patient with drug-resistant CMV). When comparing these outcomes to our entire population of primary renal transplant recipients without early CMV (n = 3404), 15.6% developed CMV infection. The median time to CMV

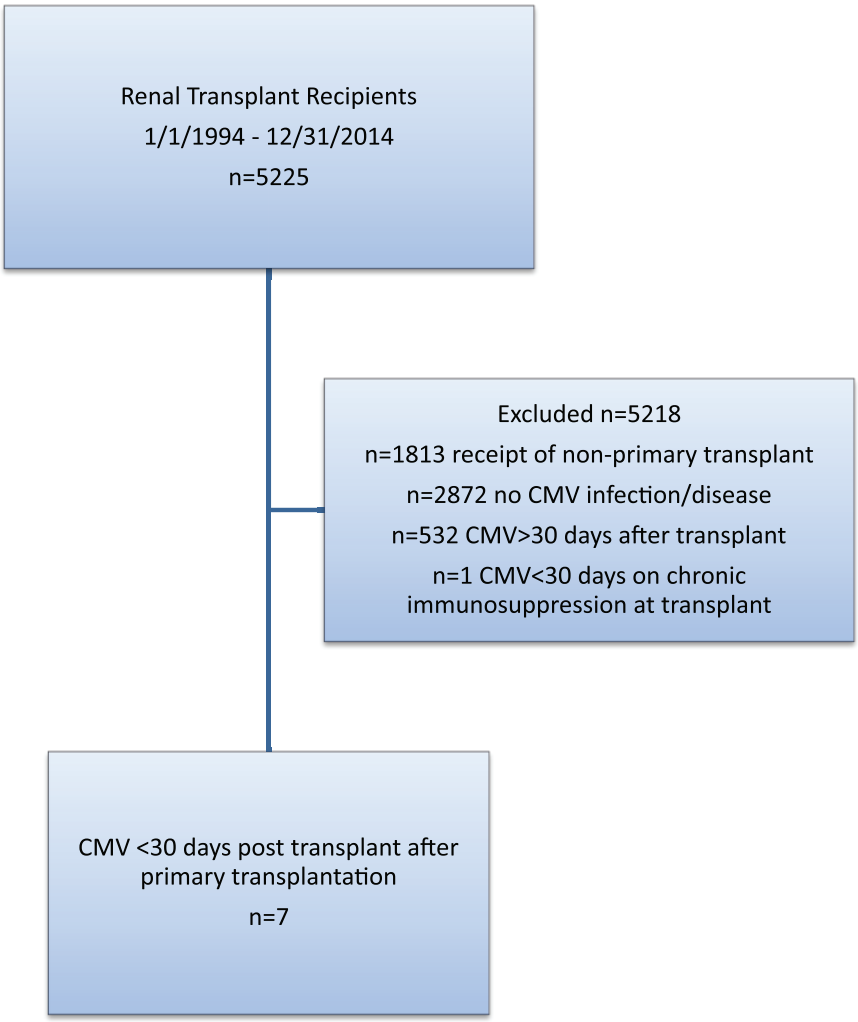

Figure 1. Process to identify the incidence of very early CMV.

was 163 (IQR = 258) days. In the entire cohort, 27.4% developed rejection, 14% experienced graft failure, and 36.9% died. In the subset with CMV occurring more than 30 days after transplant (n = 532), 39.3% developed rejection, 16% experience graft failure, and 47.6% died (Table 3). Outcomes between the CMV less than 30 day group and the CMV more than 30 day group were not significantly different. However, when comparing the presence of CMV at any time after transplant to those without CMV, rejection and mortality outcomes were less favorable in those with CMV (Table 3).

Discussion

Studies exist outlining the incidence and risks associated with early CMV, or CMV occurring less than 100 days after transplant.[6,7] However, ours is the first to describe very early CMV infection, occurring less than 30 days after transplant. This clinical scenario is postulated to be incredibly uncommon due to a lack of prolonged immunosuppressive exposure, making the population relatively immunocompetent compared with their counterparts with more than 30 days of immunosuppressive exposure.[1–3] Still it is possible in the modern era of potent immunosuppression that duration of exposure has less of a profound effect and concern regarding CMV breakthrough despite potent antiviral therapy exists.[8] Indeed, clinically, in the setting of fever and leukopenia, the transplant clinician will test for CMV infection regardless of time from transplant. This 20-year analysis, which spans the pre- and post-VGC eras and incorporates a population that would have uniformly received potent immunosuppression with CNIs and MPA as of 2000, suggests that the theoretical historical adage is accurate. In a population exceeding 5000 renal transplants, only 0.27% had CMV infection in the first 30 days.

Many of the widely recognized CMV risk factors were present in our population including high-risk serostatus and lymphocyte-depleting induction.[5,8] Interestingly, there was no representation of antithymocyte globulin in our small cohort, with alemtuzumab accounting for most lymphocyte-depleting induction. This may reflect the historical practice of a two-dose induction regimen that was the standard of care in the early 2000s at our center and the resultant potent immunosuppressive effect. Indeed, in a previously published retrospective analysis from our center, alemtuzumab induction was associated

Table 1. Demographic data.

PT NO.	TXP YEAR	AGE AT TXP	CMV SEROSTATUS	DONOR TYPE	CIT (HOURS)	INDUCTION IMMUNOSUPPRESSION	MAINTENANCE IMMUNOSUPPRESSION	SGF/ DGF	SIGNIFICANT POST-OP COMPLICATION	TXP LENGTH OF STAY (DAYS)	REJECTION PRIOR TO CMV
1	1994	33	D+/R–	DBD	33	OKT3	CsA, AZA, pred 30/d	NA	Pneumothorax	12	NA
2	1999	49	D+/R–	DBD	25	Basiliximab	CsA, MPA, pred 30/d	NA	NA	7	NA
3	2004	49	D+/R–	DBD	16	Alemtuzumab	CsA, MPA, pred 10/d	NA	NA	5	NA
4	2005	54	D+/R+	DCD	13	Alemtuzumab	CsA, MPA, pred 10/d	NA	NA	5	NA
5	2006	50	D–/R–	DCD	21	Alemtuzumab	CsA, MPA, pred 10/d	NA	Re-operation: RP hematoma	6	NA
6	2008	51	D+/R–	DBD	20	Basiliximab	FK, MPA, pred 30/d	Yes	Donor IVC interposition with OR reconstruction	14	Yes
7	2009	34	D–/R+	DBD	10	Basiliximab	FK, MPA, pred 30/d	Yes	Re-operation: RP hematoma	20	NA

Abbreviations: AZA, azathioprine; CIT, cold ischemic time; CMV, cytomegalovirus; CsA, cyclosporine; D, donor; DBD, donation after brain death; DCD, donation after cardiac death; DGF, delayed graft function; MPA, mycophenolic acid; NA, not applicable; pred, prednisone; Pt, patient; R, recipient; SGF, slow graft function; TXP, transplant.

Table 2. Infection-specific variables.

PT NO.	TXP YEAR	DAYS TO CMV FROM TXP	CMV VL AT DETECTION	CMV PPX	SYMPTOMS	INITIAL CMV TREATMENT	ANTI-CMV DOT (DAYS)	CMV RECURRENCE AFTER VERY EARLY CMV (DAYS FROM TXP)	REJECTION AFTER VERY EARLY CMV (DAYS FROM TXP)	ALIVE AT LAST FOLLOW-UP	EGFR AT LAST FOLLOW-UP
1	1994	14	NR	Acyclovir	Fever	GCV	14	690	No	Yes	37
2	1999	17	1.7[a]	PO GCV	Fever	GCV + CMVIg	11	NA	No	Yes	70
3	2004	20	1.7[a]	VGC	GI	Not treated	NA	NA	67	No	83
4	2005	2	2.8[a]	VGC	NR	Not treated	NA	NA	No	Yes	55
5	2006	21	>100000 copies/mL	Acyclovir	Fever	GCV	450	171	78	No	21
6	2008	14	NR	VGC	NR	Not treated	NA	180	No	Yes	NA
7	2009	6	207 copies/mL	Acyclovir	NR	VGC	90	NA	No	Yes	56

Abbreviations: CMV, cytomegalovirus; DOT, duration of therapy; GCV, ganciclovir; GI, gastrointestinal symptoms; NA, not applicable; NR, not reported; Pt, patient; VGC, valganciclovir; VL, viral load.
[a]CMV DNA capture: measured in genomes per milliliter. According to the manufacturer's instructions, a ratio of sample to control value of less than 1.0 was considered positive for CMV DNA.

Table 3. Primary transplant comparative outcomes.

	CMV < 30 DAYS (N = 7)	CMV > 30 DAYS (N = 532)	*P*-VALUE	NO CMV (N = 3404)	*P*-VALUE
Rejection	28.6% (2)	39.3% (209)	.71	27.4% (932)	< .00001
Graft failure	14.3% (1)	16% (85)	> .99	14% (477)	.23
Mortality	28.6% (2)	47.6% (253)	.45	36.9% (1256)	.000004

with a significantly increased risk of CMV infection.[9] Unique risk factors that stand out in the very early CMV cohort are early post-operative complications and bleeding. Although the population is too small to evaluate this statistically, the literature-reported rate of post-operative bleeding after renal transplant is less than 5%; here, in our study population, 25% required return to the operating room for control of post-operative hemorrhage.[10] Both of these patients were donor seronegative for CMV, one of which went on to develop de novo CMV infection in the setting of low serologic risk (D−/R−), ganciclovir resistance, and the associated negative sequelae of resistant virus infection.[8] While transfusion records were not available, it is possible the receipt of blood products introduced primary CMV in the setting of allograft seronegativity via reactivation of latent virus in donor white blood cells.[11] It has been shown that even in CMV seropositive recipients, strain variability can result in a pseudoprimary infection in the setting of donor seropositivity for CMV (D+/R+) and is associated with poorer outcomes than their donor seronegative counterparts (D−/R+).[12,13] Another interesting trend in this small population was that of prolonged CIT. A median CIT of 17 hours has been associated with primary CMV infection in D+/R− patients.[14] The mean and median CIT of our population exceeded this by 3 hours. It may be prudent for the clinician to watch for signs/symptoms of CMV infection in the first 30 days in patients with prolonged CIT or those receiving blood products who are CMV donor seronegative.

A surprising finding was the incidence of very early CMV infection in the setting of robust CMV prophylaxis. All patients received some form of antiviral prophylaxis, although the majority received less potent suppression with acyclovir or oral ganciclovir. However, three patients were receiving VGC at the time of early CMV infection. It has been postulated that early CMV, and therefore very early CMV, is highly unlikely in the modern era of potent antiviral prophylaxis with VGC; however, this study demonstrates breakthrough in an already low-incidence time period of less than 30 days post transplantation. It is important to note that all patients were receiving renally adjusted doses of VGC that were appropriate per the manufacturer suggestions, but less than the full 900 mg daily.[15] There is literature associating CMV breakthrough and viral resistance with low-dose VGC.[8,16] This finding of very early CMV despite VGC suggests more aggressive dosing in the setting of early post transplant renal dysfunction and fluctuating renal laboratory markers may be warranted, as this may underestimate true drug clearance capacity.

It is reassuring that comparative outcomes after very early CMV, and CMV occurring more than 30 days after transplant were not different. While literature exist describing increased risk of negative patient and allograft outcomes when CMV infection or disease occurs in the first 3 months after transplant, it does not appear that less than 30 days is an important clinical breakpoint, although our sample size is small.[6,7] However, when comparing those patients with CMV to the unaffected cohort (never CMV), our study again demonstrates the well-published finding that the presence of CMV infection or disease at any time point after transplant is associated with less favorable patient and allograft outcomes after solid organ transplant.[17,18]

This study has all the limitations of being a small series from a single center. However, data on all our transplant patients are collected prospectively, we analyzed matched controls, and our database is one of the few in the country that would be large enough to provide this series. The results of this study are striking as they demonstrate clinically the concept of the "net immunosuppressive state" and the importance of the duration of immunosuppressive exposure.[1–3] Despite advances in the potency of drug products and the intensification of immunosuppressive regimens after renal transplant, it seems the duration of immunosuppressive exposure is still the most significant risk factor for CMV infection, and it appears that exposure more than 30 days is necessary to create the environment conducive to this clinical scenario.

Conclusions

In conclusions, in our review of over 5000 kidney transplants, the occurrence of CMV infection in the first 30 days is very uncommon. However, when it occurred, it appeared to be accompanied by the typical symptomatology of fever in most cases. Notable common patient characteristics include hemorrhage requiring re-operation and prolonged CIT. Half of the patients in this series had subsequent episodes of CMV infection more than 30 days after transplant. De novo disease in low-risk serostatus was associated with the worst outcomes, highlighting the importance of leukocyte-reduced irradiated blood products in the CMV unexposed, immunocompromised patient. This study should provide the clinician with some reassurance that the overall risk of CMV infection in the first 30 days is very low.

Author Contributions

MJ and BA developed the study protocol, procured the study data and performed the statistical analysis. All authors contributed to the drafting, review, and final approval of this manuscript.

ORCID iD

MR Jorgenson https://orcid.org/0000-0001-6088-9727

REFERENCES

1. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med*. 1998;338:1741–1751.
2. Rubin RH, Wolfson JS, Cosimi AB, Tolkoff-Rubin NE. Infection in the renal transplant patient. *Am J Med*. 1981;70:405–411.
3. Rubin RH. Infection in the organ transplant recipient. In: Rubin RH, Young LS, eds. *Clinical Approach to Infection in the Compromised Host*. 3rd ed. New York: Plenum Publishing; 1994:629–705.
4. Hebart H, Gamer D, Loeffler J, et al. Evaluation of Murex CMV DNA hybrid capture assay for detection and quantitation of cytomegalovirus infection in patients following allogeneic stem cell transplantation. *J Clin Microbiol*. 1998;36:1333–1337.
5. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation*. 2018;102:900–931.
6. Sagedal S, Hartmann A, Nordal KP, et al. Impact of early cytomegalovirus infection and disease on long-term recipient and kidney graft survival. *Kidney Int*. 2004;66:329–337.
7. Smedbraten YV, Sagedal S, Leivestad T, et al. The impact of early cytomegalovirus infection after kidney transplantation on long-term graft and patient survival. *Clin Transplant*. 2014;28:120–126. doi:10.1111/ctr.12288.
8. Rolling KE, Jorgenson MR, Descourouez JL, Mandelbrot DA, Redfield RR, Smith JA. Ganciclovir-resistant cytomegalovirus infection in abdominal solid organ transplant recipients: case series and review of the literature. *Pharmacotherapy*. 2017;37:1258–1271. doi:10.1002/phar.1987.
9. LaMattina JC, Mezrich JD, Hofmann RM, et al. Alemtuzumab as compared to alternative contemporary induction regimens. *Transpl Int*. 2012;25:518–526. doi:10.1111/j.1432-2277.2012.01448.x.
10. Hachem LD, Ghanekar A, Selzner M, Famure O, Li Y, Kim SJ. Postoperative surgical-site hemorrhage after kidney transplantation: incidence, risk factors, and outcomes. *Transpl Int*. 2017;30:474–483. doi:10.1111/tri.12926.
11. Adler SP. Transfusion-associated cytomegalovirus infections. *Rev Infect Dis*. 1983;5:977–993.
12. Stratta R, Thacker L, Sunderberg A, et al. Multivariate analysis of the influence of donor and recipient cytomegalovirus sero-pairing on outcomes in simultaneous kidney-pancreas transplantation: the South-Eastern Organ Procurement Foundation Experience. *Transplant Proc*. 2005;37:1271–1273.
13. Hughes D, Hafferty J, Fulton L, et al. Donor and recipient CMV serostatus and antigenemia after renal transplantation: an analysis of 486 patients. *J Clin Virol*. 2008;41:92–95.
14. Schlott F, Steubl D, Hoffmann D, et al. Primary cytomegalovirus infection in seronegative kidney transplant patients is associated with protracted cold ischemic time of seropositive donor organs. *PLoS ONE*. 2017;12:e0171035. doi:10.1371/journal.pone.0171035.
15. Valcyte Prescribing Information. South San Francisco, CA: Hoffmann-La Roche Inc, distributed by Genentech; A Member of the Roche Group.
16. Stevens DR, Sawinski D, Blumberg E, Galanakis N, Bloom RD, Trofe-Clark J. Increased risk of breakthrough infection among cytomegalovirus donor-positive /recipient-negative kidney transplant recipients receiving lower-dose valganci clovir prophylaxis. *Transpl Infect Dis*. 2015;17:163–173. doi:10.1111/tid.12349.
17. Kanter J, Pallardó L, Gavela E, et al. Cytomegalovirus infection renal transplant recipients: risk factors and outcomes. *Transplant Proc*. 2009;41:2156–2158.
18. López-Oliva MO, Flores J, Madero R, et al. Cytomegalovirus infection after kidney transplantation and long-term graft loss. *Nefrología (English Edition)*. 2017;37:515–525.
19. Humar A, Lebranchu Y, Vincenti F, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Am J Transplant*. 2010;10:1228–1237.