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The burden of cytomegalovirus infection remains high in high-risk kidney transplant recipients despite six-month valganciclovir prophylaxis

Juulia Räihä[1] | Fernanda Ortiz[2] | Laura Mannonen[3] | Raisa Loginov[3] | Marko Lempinen[1] | Irmeli Lautenschlager[3] | Ilkka Helanterä[1]

[1]Abdominal Center, Department of Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[2]Abdominal Center, Department of Nephrology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[3]Department of Virology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

Correspondence
Juulia Räihä, MD, Abdominal Center, Department of Transplantation and Liver Surgery, Helsinki University Hospital, PO BOX 340, 00029 HUS, Helsinki, Finland.
Email: juulia.raiha@hus.fi

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Abstract

Cytomegalovirus continues to be a concern after transplantation despite prophylaxis regimens. Our aim was to analyse post-prophylaxis primary cytomegalovirus infections among kidney transplant recipients after 6-month valganciclovir prophylaxis and to determine the usefulness of surveillance after prophylaxis. Data from all cytomegalovirus D+/R- kidney transplant recipients from January 2004 to October 2018 at our center who received 6-month prophylaxis with valganciclovir were retrospectively analysed (N = 481). Detailed analyses were performed for 136 patients who were monitored every 2-4 weeks for DNAemia after the discontinuation of prophylaxis. Post-prophylaxis primary cytomegalovirus infection occurred in 182/481 (38%) patients median 264 days after transplantation (IQR: 226-367) and median 84 days after the end of prophylaxis (IQR: 46-187). In 49% patients, cytomegalovirus infection occurred over 3 months after the end of prophylaxis. Cytomegalovirus infection was not associated with lower patient or graft survival and no independent risk factors for infection were found. From patients monitored closely, 71/136 (52%) patients developed post-prophylaxis primary cytomegalovirus infection. Altogether, 52/136 (38%) patients were diagnosed with probable post-prophylaxis cytomegalovirus disease and 19/136 (14%) patients had asymptomatic CMV infection. Recurrent infection occurred in 38/71 (39%) patients. The incidence of post-prophylaxis primary cytomegalovirus infection among D+/R- kidney transplant recipients remains high despite 6-month prophylaxis. Surveillance after prophylaxis was challenging as a considerable portion of the infections occurred late and already symptomatic.

KEYWORDS

complication, cytomegalovirus, kidney transplantation, prophylaxis

1 | INTRODUCTION

Cytomegalovirus (CMV) infection remains one of the most common viral infections after kidney transplantation despite effective antiviral prophylaxis. In addition to significant morbidity, CMV infection has been associated with indirect effects such as allograft rejection,[1] chronic scarring of the allograft,[2] allograft failure,[3-5] and mortality.[3,4,6]

CMV seronegative patients receiving an allograft from a seropositive donor (D+/R-) are at the greatest risk of post-prophylaxis CMV infection and disease.[7] The prolongation of valganciclovir prophylaxis from 3 to 6 months is shown to reduce the incidence of primary CMV infections[8-11] and 6-month prophylaxis is generally recommended.[12,13] However, after the discontinuation of antiviral medication a major concern is post-prophylaxis primary CMV infection. In a previous study done in our institution, despite prolonged 6-month prophylaxis, post-prophylaxis CMV infection developed in 37% patients and probable post-prophylaxis CMV disease in 34% patients.[14]

In effort to reduce the incidence of post-prophylaxis primary CMV infection and disease, surveillance after prophylaxis has been suggested for CMV high-risk patients. Current guidelines do not support this strategy as supporting data are limited,[12] however, it is still used by many centers occasionally. Surveillance after prophylaxis requires many resources and may not be cost-effective in initiating timely treatment with rapidly doubling viral load.[15] Furthermore, defining follow-up time for intensive monitoring is a challenge, since post-prophylaxis primary CMV infection may occur months after the cessation of prophylaxis and the frequency of routine follow-up decreases with time.

The aim of this study is to characterize the burden of CMV infections in the high-risk CMV D+/R- kidney transplant cohort and to determine whether careful monitoring after the end of prophylaxis could help identifying post-prophylaxis CMV diseases early.

2 | MATERIAL AND METHODS

Data from all CMV seronegative patients receiving a kidney from a seropositive donor between January 2004 and October 2018 in our country were retrospectively analysed.

All kidney transplantations in Finland are performed in Helsinki University Hospital. After 3-12 weeks of follow-up in the transplant unit, patients are followed in their local nephrology centers and data are sent to nationwide Finnish Kidney Transplant Registry. Data collection to the registry is obliged by law. Patients residing in the Helsinki metropolitan area and followed up at the Helsinki University Nephrology clinic are screened for CMV-DNAemia every 2-4 weeks after the end of prophylaxis or if symptoms occur. In other nephrology centers CMV-DNAemia is routinely monitored according to local protocols, and if symptoms occur.

Baseline immunosuppression comprised primarily of cyclosporine, mycophenolate mofetil (MMF) and steroid. In immunologically high-risk patients tacrolimus was the drug of choice and in selected cases induction therapy with either basiliximab or ATG was administered.

Six-month prophylaxis with valganciclovir (900 mg once daily, or dose adjusted to renal function) was intended for patients with CMV D+/R- constellation. In Finland, this 6-month prophylaxis protocol was initiated in the beginning of 2004. Compliance was not tested, but the medication was given from the hospital free of charge. CMV infections were treated with valganciclovir (900 mg twice daily or dose adjusted for renal function) or iv ganciclovir in case of severe disease (severe gastrointestinal symptoms, tissue-invasive disease, very high viral load). Infections were treated until two consecutives samples were below the level of detection. Secondary prophylaxis was given according to clinician's discretion with valganciclovir (900 mg once daily or dose adjusted for renal function).

Quantitative detection of CMV DNAemia from plasma specimens was performed at HUSLAB laboratories, Department of Virology and Immunology. Until October 2011 HUSLAB used a real time “in-house” CMV-PCR with lower limit of quantitation (LLOQ) of 250 genome copies/mL (cp/mL).[16] October 2011 HUSLAB implemented automated COBAS® AmpliPrep/COBAS® TaqMan® CMV Test (Roche Molecular Systems) with LLOQ of 150 cp/mL for quantitative detection of CMV DNA. The first World Health Organization (WHO) CMV international standard became available at 2011[17] and February 2014 HUSLAB started to use COBAS® AmpliPrep/COBAS® TaqMan® CMV Test version calibrated against this standard with LLOQ of 137 IU/mL. A conversion factor from cp/mL to IU/mL was also determined for the “in-house” PCR.[18] From June 2018 HUSLAB has used Cobas® CMV Test (Roche Molecular Systems) with LLOQ of 35 IU/mL on fully automated Cobas6800® platform. Quantitative PCR-methods used in this study have shown good viral load correlation between real-time “in-house” test and COBAS® AmpliPrep/COBAS® TaqMan® CMV Test.[18] Also, COBAS® AmpliPrep/COBAS® TaqMan® CMV Test and Cobas® CMV for use on COBAS® 6800 has been shown to produce comparable viral loads, although Cobas® CMV test produces slightly higher viral loads with an average of 0,29 log10 IU/mL than COBAS® AmpliPrep/COBAS® TaqMan® CMV Test.[19]

The following definitions were used which are consistent with the American Society of Transplantation Infectious Diseases Community of Practice and CMV Drug Development Forum recommendations for use in clinical trials.[13,20] Patients with a positive CMV-DNAemia were defined as suffering from CMV infection regardless of symptoms. Probable post-prophylaxis CMV disease was defined as CMV DNAemia accompanied by clinical signs or symptoms. Probable CMV syndrome was defined as presence of CMV-DNAemia combined with at least two of the following: manifestation of fever, malaise, leukopenia, thrombocytopenia, or elevation of hepatic aminotransferases. Recurrent CMV infection was defined as new CMV DNAemia after initially achieving clearance of viremia with at least 4-week period of undetectable DNAemia in between viremias during active surveillance. According to a proposal to standardize the terminology of “late-onset” CMV infection and disease, the term post-prophylaxis CMV infection and disease was used.[21]

Baseline data and follow-up data from all risk patients were collected from The Finnish Kidney Transplant Registry. Data from patients followed in Helsinki University Nephrology clinic were reviewed from patient charts and laboratory database. This study was approved by the Helsinki University Hospital Institutional Review Board (HUS/269/2017).

Data are expressed as mean ± standard deviation (SD) for normally distributed continuous variables and the median and interquartile range (IQR) for non-normally distributed continuous variables. Differences between groups were compared with the independent-samples *t* test or Mann-Whitney U-test for continuous variables and Fisher's exact test for categorical variables. Univariable and multivariable logistic regression was used to estimate risk factors for CMV infection and results are expressed as odds ratio (OR) and 95% confidence interval (CI). Variables significant in univariable analyses ($P < .1$) were selected to the multivariable models. Graft survival (defined as patient death or return to dialysis treatment) and patient survival probabilities were estimated by the Kaplan-Meier method. The calculations were performed with SPSS statistical software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp), *P*-values of < 0.05 were considered significant.

3 | RESULTS

From January 2004 to October 2018, altogether 2848 adult kidney transplantations were performed in our institution. A total of 534 CMV seronegative patients received a kidney from a seropositive donor (D+/R-) and by protocol received 6-month valganciclovir prophylaxis. Altogether 28 patients who had CMV infection within 3 months after transplantation were excluded with confirmed failure to start prophylaxis according to protocol. Additionally, 19 patients who died or lost their graft within 3 months after transplantation were excluded from analysis. Six patients with inadequate follow-up data were also removed from the analysis, resulting in 481 patients included in this study (Figure 1.). Of these high-risk patients, 27 received a simultaneous pancreas-kidney transplantation, 3 patients combined heart-kidney transplantation, and 1 patient had previous heart transplantation prior to kidney transplantation.

Detailed analysis was performed for 136 patients, who were followed up at the Helsinki University Hospital and monitored closely every 2-4 weeks after the end of prophylaxis for CMV-DNAemia.

3.1 | CMV infections in whole study population

Of all patients included in this study, post-prophylaxis primary CMV infection occurred in 182/481 (38%) patients median 264 days after transplantation (IQR: 226-367) and 84 days after the end of prophylaxis (IQR: 46-187). In 89/182 (49%) patients CMV infection occurred over 3 months and in 49/182 (27%) patients over 6 months after the end of prophylaxis. As our PCR platforms changed during follow-up time, subgroup analysis of the incidence of CMV infection were done also according to different periods. During January 2004-October 2011, altogether 85/223 (38,1%) post-prophylaxis CMV infections occurred. Whereas, from November 2011 until June 2018, altogether 97/252 (38,4%) post-prophylaxis CMV infections were detected. During the last period from July 2018 to October 2018, only 6 CMV high-risk patients received a kidney transplantation and none of the patients had primary CMV viremia during follow-up. In patients who completed the 6-month prophylaxis, no CMV infections occurred during prophylaxis. However, 8 patients developed CMV infection within 6 months after transplantation because prophylaxis was terminated prematurely because of side effects. Baseline characteristics of patients with or without post-prophylaxis primary CMV infection are compared in Table 1.

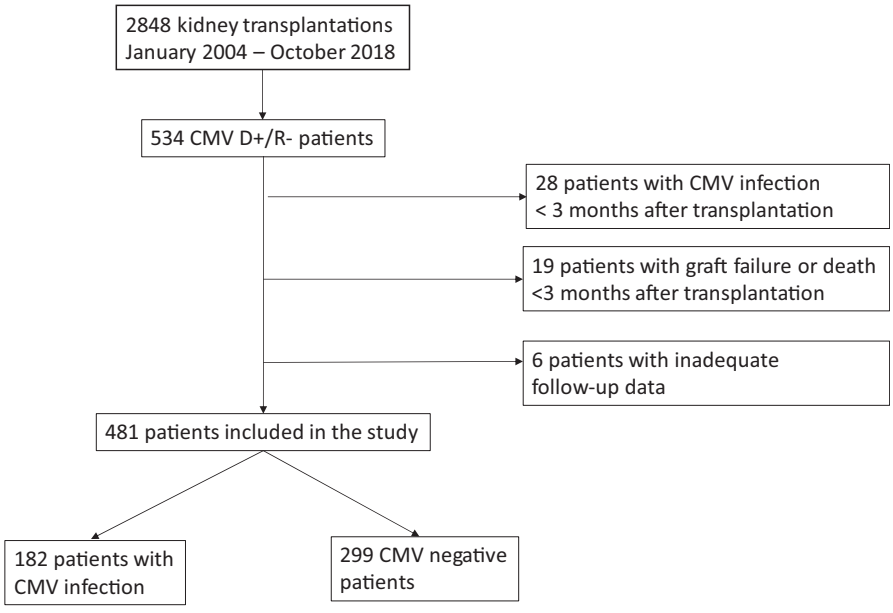


FIGURE 1 Flow-chart of all the patients included in the study: Description of patients included in the study and the number and reasons for exclusions of patients from the study population

TABLE 1 Baseline characteristics of patients with or without post-prophylaxis primary CMV infection in the whole study population (n = 481)

	No CMV infection (n = 299)	Post-prophylaxis CMV infection (n = 182)	*P*-value
Recipient age, y, mean ± SD	47 ± 14	49 ± 13	0.08
Donor age, y, mean ± SD	50 ± 15	53 ± 12	0.06
HLA A, B- and DR-mismatch, mean ± SD	2.7 ± 1.1	2.4 ± 1.2	0.03
HLA AB-mismatch, mean ± SD	1.9 ± 0.8	1.7 ± 0.9	0.01
HLA DR-mismatch, mean ± SD	0.8 ± 0.5	0.8 ± 0.6	0.58
Female gender, n (%)	97 (32)	52 (29)	0.42
Diabetes, n (%)	91 (30)	61 (34)	0.42
Cold ischemia time (h), mean ± SD	18.9 ± 6.5	18.7 ± 7.0	0.72
Delayed graft function, n (%)	83 (28)	50 (28)	1.00
Patients with induction therapy, n (%)	40 (13)	23 (13)	0.89
Patients on tacrolimus, n (%)	101 (34)	47 (26)	0.07
Patients with acute rejection, n (%)	54 (18)	21 (12)	0.07
Plasma creatine at last follow-up, mg/dL, mean ± SD	2.0 ± 1.8	2.0 ± 1.8	0.67

Patient or graft survival did not differ in patients with or without CMV infection in Kaplan-Meier estimates (Figure 2, Figure 3). In univariable analysis or multivariable analysis adjusted for recipient and donor age, recipient gender, diabetes, cold ischemia time, HLA-AB and HLA-DR mismatch, induction therapy, rejection, and the type of calcineurin inhibitor used, CMV infection was not associated with these outcomes (data not shown).

When analysing risk factors for post-prophylaxis CMV infection, univariable analyses showed lower number of HLA A/B-mismatch in patients who developed CMV infection. In multivariable analyses, on the other hand, no independent risk factors for post-prophylaxis CMV infection could be characterized (Table 2).

3.2 | CMV infections in Helsinki University Hospital

From patients followed up at our institution who were monitored closely after the end of prophylaxis, 71/136 (52%) patients developed post-prophylaxis primary CMV infection and 52/136 (38%) patients probable post-prophylaxis CMV disease. Median interval was 260 days after transplantation (IQR: 225-364) and 72 days after the end of prophylaxis (IQR: 44-177). The median duration of viremia was 24 days (IQR: 18-33) and median peak viral load 4617 IU/mL (IQR: 1677-24813).

When comparing tacrolimus and cyclosporine trough levels in patients with or without post-prophylaxis CMV infection 6 months after transplantation, no difference was detected. Mean tacrolimus trough levels were 7.4 μg/L (± SD 0.8) in patients with post-prophylaxis CMV infection compared to 6.5 μg/L (± 1.2) in patients without post-prophylaxis CMV infection (*P* =.15). In patients on cyclosporine, mean 6-month trough levels were 133 μg/L (± 35.9) in patients with post-prophylaxis CMV infection compared to 131 μg/L (± 23.3) in patients without post-prophylaxis CMV infection (*P* =.86).

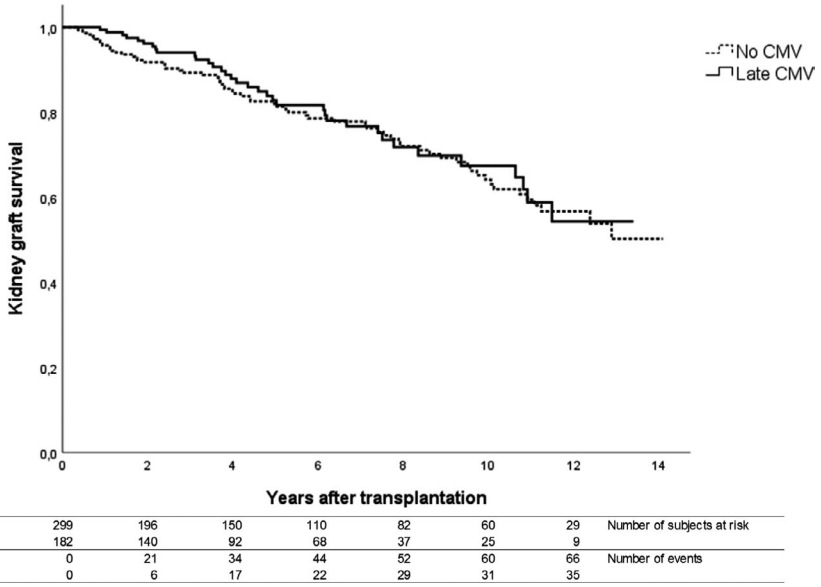
CMV infection was asymptomatic among 19 patients. Symptoms occurred among 52 patients and most common symptoms included fever (n = 35) and gastrointestinal symptoms (n = 19). None of the patients underwent biopsy to diagnose tissue invasive disease as clinical presentation fitted probable post-prophylaxis CMV disease and symptoms resolved with treatment and declining viral load. In 22 patients the criteria of probable post-prophylaxis CMV syndrome were fulfilled. Of the 71 primary CMV infections, 13 patients were treated with iv ganciclovir followed by oral valganciclovir. For 49 patients treatment was initiated with only oral valganciclovir (900 mg twice daily, adjusted for renal function). In 7 patients who were asymptomatic or with mild symptoms and low viral load, infection was treated only with MMF dose reduction. In 2 asymptomatic patients the infection was unnoticed and no intervention was applied. A total of 21/71 (30%) patients were hospitalized, mostly because of frail condition, high fever, or unclear onset situation, but also because of iv ganciclovir administration. Symptoms and treatments are summarized in Table S1.

After the primary CMV infection, 47/71 (66%) received secondary prophylaxis for 1- to 3 months. Recurrent CMV infection occurred for 28/71 (39%) patients. From patients who had received secondary prophylaxis, 17/47 (36%) patients developed recurrent CMV infection, whereas among patients without secondary prophylaxis, 11/24 (46%) patients developed CMV infection (*P* =.45). When analyzing risk factors for recurrent CMV infection, univariable and multivariable analyses failed to detect any risk factors (Table S2).

4 | DISCUSSION

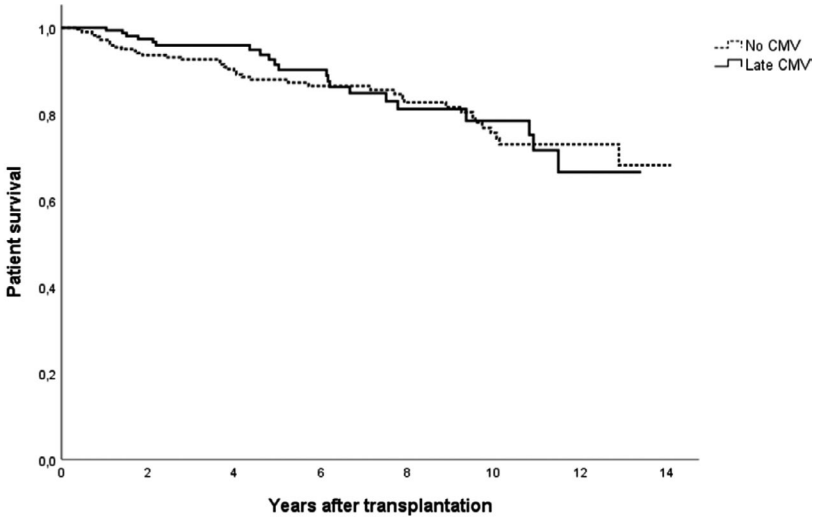
Our results show that the post-prophylaxis primary CMV infection and probable post-prophylaxis CMV disease among CMV D+/R- kidney transplant recipients is still a significant problem even though the recommended 6-month prophylaxis is administered. Also, this study suggests that surveillance after prophylaxis may not be a useful strategy in preventing CMV disease as almost half of the post-prophylaxis primary infections occurred more than 3 months after the end of prophylaxis.

Previously, the IMPACT-study demonstrated the significant reduction of primary CMV viremia and disease in high-risk kidney



No CMV	299	196	150	110	82	60	29	Number of subjects at risk
Late CMV	182	140	92	68	37	25	9	
No CMV	0	21	34	44	52	60	66	Number of events
Late CMV	0	6	17	22	29	31	35	

FIGURE 2 Kidney graft survival among the whole study population: The death-censored Kaplan-Meier kidney graft survival curves for patients with post-prophylaxis CMV primary infection compared to patients without post-prophylaxis CMV infection among the whole study population



No CMV	299	198	152	110	81	61	29	Number of subjects at risk
Late CMV	182	139	94	69	38	26	9	
No CMV	0	16	23	28	32	38	40	Number of events
Late CMV	0	4	6	11	17	18	21	

FIGURE 3 Patient survival among the whole study population: The Kaplan-Meier patient survival curves for patients with post-prophylaxis CMV primary infection compared to patients without post-prophylaxis CMV infection among the whole study population

allograft recipients receiving 200 days vs 100 days valganciclovir prophylaxis without adding safety concerns associated with the extended prophylaxis.[8,9] Similar results were shown also in previous retrospective studies comparing 3- to 6-month prophylaxis.[10,11] Nonetheless, the incidence of post-prophylaxis CMV infection after 6-month valganciclovir prophylaxis in long-term is not well-described. The previous follow-up done by our institution suggested that CMV primary infections were delayed but not efficiently prevented with 6 month-prophylaxis[14,22] and this study shows similar results. In the 2-year follow-up of the IMPACT-study, the incidence of CMV disease was 21.3% in the 200 day group,[9] which compared to our results is lower. However, in the IMPACT-study CMV disease was defined as either CMV syndrome or biopsy-proven tissue-invasive disease, whereas we counted all symptomatic CMV infections as probable post-prophylaxis CMV disease.

Despite the reasonably high occurrence of post-prophylaxis infections reported in our study, one benefit of extending the prophylaxis from 3- to 6-months is the delayed presentation of the primary infections to a later period after transplantation, during which immunosuppression is already reduced and the overall status of the patient is more stable. This approach is supported also by our current study, in which no serious or life-threatening primary infections were recorded. On the other hand, delaying the onset of primary infections to a later period after transplantation may lead to more symptomatic infections, as also the diagnosis of CMV infection may be delayed because of the less frequent monitoring of transplant recipients at this point after transplantation.

Determining the optimal frequency and duration of surveillance after prophylaxis is challenging and the data about this strategy are limited. One study implied that weekly viral load monitoring after

TABLE 2 Univariable and multivariable logistic regression of the risk factors of post-prophylaxis CMV infection in the whole study population (n = 481). Bold variables (*P* <.1) were selected to the multivariable models.

	Univariable OR (95% CI)	Multivariable OR (95% CI)
Recipient age	**1.012 (0.998-1.026), *P* =.08**	1.007 (0.992-1.023), *P* =.37
Donor age	**1.013 (0.999-1.027), *P* =.06**	1.009 (0.993-1.025), *P* =.28
Cold ischemia time	1.000 (0.999-1.000), *P* =.72	
HLA AB-mismatch	**0.758 (0.610-0.942), *P* =.01**	0.760 (0.492-1.175), *P* =.22
HLA DR-mismatch	0.911 (0.658-1.261), *P* =.58	
HLA A, B and DR-mismatch	**0.825 (0.696-0.977), *P* =.03**	1.054 (0.747-1.486), *P* =.77
Female gender	0.863 (0.575-1.296), *P* =.48	
Diabetes	1.152 (0.777-1.709), *P* =.48	
Delayed graft function	0.986 (0.653-1.489), *P* =.95	
Patients with induction therapy	0.937 (0.541-1.623), *P* =.82	
Patients with ATG	1.437 (0.649-3.179), *P* =.371	
Patients on tacrolimus	**0.683 (0.453-1.028), *P* =.07**	0.840 (0.541-1.305), *P* =.44
Patients with acute rejection	**0.592 (0.344-1.017), *P* =.06**	0.651 (0.372-1.142), *P* =.13

prophylaxis was not useful since CMV disease developed in 40.8% solid organ transplant (SOT) recipients during the first year after transplantation and a significant proportion occurred after the 8-week surveillance period.[23] Another study in which SOT recipients were monitored every 15 days up to 3 months after the discontinuation of prophylaxis, the clinical impact in the high-risk group was also modest.[24] Our results are consistent with these studies as this strategy failed to detect the post-prophylaxis CMV infections early among patients followed in our institution. However, the very rapid increase in viral loads of CMV D+/R- SOT recipients has previously raised concerns about pre-emptive strategy in these high-risk patients.[25,26] Therefore, also our 2-4-week surveillance protocol may be insufficient to detect viremia prior to the onset of symptoms.

At diagnosis, most of the CMV infections were already symptomatic and most common symptoms were fever and gastrointestinal symptoms. The domination of these symptoms were also described in a previous large two-center cohort study, including our center, focusing on the characteristics of CMV infections.[27] None of the patients in our material were diagnosed with CMV retinitis. This entity seem to be quite rare, since in a review article covering 12 653 liver transplant recipients, only 0,1% were diagnosed with chorioretinitis.[28] In our study, symptoms showed no correlation with the viral load. In contrast, a previous study comparing prophylactic and preemptive approaches including also CMV seropositive recipients, indicated the association of symptomatic CMV infections with higher peak levels of CMV DNAemia.[29] Literature also suggests that viral load in the initial phase of active CMV infection and the rate of increase are associated with CMV disease development in transplant recipients.[30]

Previous studies have associated CMV infection with increased mortality[4,6] and lower renal graft survival.[4,5] The negative influence of CMV has been suggested to be delayed, but not prevented by prophylactic treatment,[3,31] even though prophylactic treatment has also been shown to improve long-term renal graft survival compared to preemptive therapy in a randomized clinical trial.[32] Interestingly, in our cohort patient or graft survival did not differ between patients with or without CMV infection, not even after adjustment for multiple variables. The reasons for this difference between our findings and earlier studies remain to be explored. When assessing clinical features that could be predisposing to post-prophylaxis CMV infection we failed to find any risk factors. Unfortunately, T cell counts or IgG levels during or after prophylaxis were not routinely monitored. In a study by Razonable et al,[33] allograft rejection was found as a predictor for CMV disease among CMV D+/R − SOT recipients. Also, other studies have reported bacterial and fungal infections,[3] delayed graft function,[10] and induction therapy with thymoglobulin[11] as risk factors for the development of CMV infection.

Recurrent CMV infections were common in our material as 39% of patients were diagnosed with a new episode of DNAemia. In a recent study including all SOT recipients, the incidence of virologic recurrence was 29,5% but this study included a cut-off level of 1000 IU/mL,[34] whereas in our study all patients with recurrent DNAemia were included. In this study by Natori et al,[34] D+/R- serostatus, recent acute rejection, lung transplant and treatment phase viral kinetics were risk factors for recurrence. The long-term follow-up of the VICTOR study (a randomized trial comparing intravenous ganciclovir vs oral valganciclovir for treatment of CMV) showed 30% virologic recurrence rate and this study indicated persistent DNAemia at day 21 to be a predictor for recurrence.[35] In contrary with these studies, we found no specific risk factors for recurrent infections, whereas a previous study from our institution including also seropositive patients, found high viral load at diagnosis and delayed graft function to be associated with CMV recurrence.[36]

The role of secondary prophylaxis in the prevention of CMV recurrence is unclear as no prospective randomized trials exist. In retrospective studies, the benefit of secondary prophylaxis has not been demonstrated[27,37] and in current guidelines secondary prophylaxis is not routinely recommended.[12] Our results are consistent with the previous literature as secondary prophylaxis failed to prevent recurrent CMV infections.

The current situation of CMV prevention strategies after transplantation is summarized in a review article.[38] In the future, the use of CMV-specific cell-mediated immunity assays will probably have clinical utility in predicting CMV disease in high-risk SOT

recipients.[39] For now, an alternative to surveillance after prophylaxis is clinical follow-up and careful patient guidance combined with early treatment of CMV disease, as maintaining a sufficient surveillance frequency for months is difficult. In our opinion, some CMV D+/R- patients with multiple risk factors or low CMV-specific cell-mediated immunity could perhaps benefit from prolonged prophylaxis.

The strength of this study is our long experience with 6-month valganciclovir prophylaxis in CMV high-risk patients. Also, the systematic monitoring for CMV DNAemia in patients followed in our institution since 2004 enables the evaluation of the benefit of surveillance after prophylaxis in long-term. Our study had some limitations to note. First, this was a single center study as our center is the only transplant center in Finland and results may not be comparable to other populations. The data of this retrospective study were collected from a long time period, during which our diagnostic CMV assay changed. It has been suggested, that CMV sequence variability, amplicon size, and unprotected CMV DNA fragments may affect the comparability of viral load of different assays.[40] The different PCR-methods used in this study have been shown good viral load correlation.[18,19] However, different detection thresholds may have affected the diagnosis of CMV DNAemia in patients with mild viremia. In addition, CMV DNAemia in other nephrology centers was monitored according to local protocols. These data were not available for the purposes of this study, and we rely only on the information of confirmed CMV infections, as reported to The Finnish Kidney Transplant Registry. Therefore, some asymptomatic CMV infections may have been missed. Similarly, as only part of the study population was monitored closely after the end of prophylaxis, the results of these analyses may be limited by a relatively small sample size.

In conclusion, our results showed that the burden of primary CMV infections remains high in D+/R- kidney transplant recipients despite 6 months of valganciclovir prophylaxis. The majority of post-prophylaxis primary CMV infections occurred delayed, making surveillance after prophylaxis challenging.

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CONFLICTS OF INTEREST

The authors of this manuscript have no conflicts of interest to declare.

AUTHOR CONTRIBUTION

JR, IH, ML, IL designed research. JR, IH performed research. JR, IH analysed data. JR, FO, LM, RL, ML, IL, IH participated in the writing of the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request because of privacy/ethical restrictions.

ORCID

Juulia Räihä https://orcid.org/0000-0002-2681-3742

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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