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Delayed graft function and rejection are risk factors for cytomegalovirus breakthrough infection in kidney transplant recipients

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ABSTRACT

Breakthrough cytomegalovirus (CMV) disease during valganciclovir prophylaxis is rare but may cause significant morbidity and even mortality. In order to identify patients at increased risk the incidence of CMV disease was studied in a large population of renal transplant recipients who underwent a kidney transplantation in the Radboud University Medical Center between 2004 and 2015 (n = 1300). CMV disease occurred in 31/1300 patients. Multivariate binary linear regression analysis showed that delayed graft function (DGF) (p = 0.018) and rejection (p = 0.001) significantly and independently increased the risk of CMV disease, whereas CMV status did not. Valganciclovir prophylaxis was prescribed to 281/1300 (21.6%) high-risk patients (defined as CMV IgG-seronegative recipients receiving a kidney from a CMV IgG-seropositive donor (D+/R-)). Of these 281 patients, 51 suffered from DGF (18%). The incidence of breakthrough CMV disease in D + /R- patients with DGF was much higher than in those with immediate function (6/51 (11.8%) vs 2/230, (0.9%), p = 0.0006 Fisher's exact test), despite valganciclovir prophylaxis. This higher incidence of CMV disease could not be explained by a higher incidence of rejection (and associated anti-rejection treatment) in patients with DGF. D + /R- patients with DGF are at increased risk of developing CMV disease despite valganciclovir prophylaxis. These findings suggest that underexposure to ganciclovir occurs in patients with DGF. Prospective studies evaluating the added value of therapeutic drug monitoring to achieve target ganciclovir concentrations in patients with DGF are needed.

1. Introduction

Valganciclovir, the pro-drug of ganciclovir, is the first-choice drug for the prophylaxis of cytomegalovirus (CMV) disease after kidney transplantation. In the double-blind phase 3 trial that led to the registration of valganciclovir, solid organ transplant recipients were treated with either valganciclovir 900 mg once daily or oral ganciclovir 1000 mg t.i.d. for the first 100 days after transplantation [1]. In this trial the primary end point was the proportion of patients developing CMV disease (i.e., CMV syndrome and/or tissue-invasive CMV) during the first 6 months post-transplantation. The incidence of CMV disease in this study at 6 months was 12.1% for the valganciclovir-treated patients and 15.2% for the ganciclovir group. Only four cases of CMV disease (0.8% valganciclovir, 1.6% ganciclovir) occurred during the first 100 days post-transplant, while patients were still on prophylaxis. In an additional analysis of the data of this phase 3 trial it was found that patients with a low creatinine clearance (below 40 mL/min) at screening had a significantly increased hazard of developing CMV disease (hazard ratio 4.28, 95%-confidence interval 1.69–10.83) [2]. Based on the study of Humar et al., valganciclovir prophylaxis for 6 months is now prescribed in many centers worldwide [3]. In this study, the incidence of CMV disease at 6 months post-transplant was 11/155 (7.1%) in high-risk patients, (defined as CMV seronegative recipients of a kidney from a seropositive donor, D+/R-), who were treated with 900 mg q.d. of valganciclovir for

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200 days.

Although the number of breakthrough CMV infections during prophylaxis is low, these patients may suffer from significant morbidity and sometimes even mortality. Clinical observations in the Radboud UMC suggested that patients suffering from delayed graft function (DGF) or rejection had a higher risk of CMV breakthrough. In the present study therefore the association between both DGF and rejection and the incidence of CMV disease in kidney transplant recipients was investigated.

2. Patients and methods

2.1. Study design

From the database of the Radboud university medical center (UMC) data were collected from all patients who underwent a kidney transplantation (both deceased and living donor transplantation) between January 1, 2004 and December 31, 2015. Patients were excluded if information on graft function was unknown or in case of a never functioning graft (primary non-function) as these patients typically lose their graft due to technical complications within the first few days after transplantation. Patients under the age of 18 years were excluded. Standard immunosuppressive therapy consisted of tacrolimus, mycophenolate mofetil, and prednisolone. In case of a kidney transplantation between HLA identical siblings, mycophenolate mofetil was omitted. From December 2007 to June 2012 patients could participate in a randomized clinical trial comparing one dose of rituximab (375 mg/m^2) with placebo as induction therapy [4]. From August 2014 onwards basiliximab was added to the standard immunosuppressive therapy.

During the study period, only CMV-seronegative patients receiving a kidney from a seropositive donor (D+/R-) were treated with prophylactic valganciclovir during the first 3 months after transplantation. In addition, prophylactic valganciclovir was prescribed for a duration of 2 months after the start of T cell-depleting antibody therapy in CMV-seropositive patients. Dose adjustments for renal impairment were based on the drug label, leading to a dosage of 450 mg valganciclovir twice weekly in patients with DGF, defined as the requirement for dialysis within the first week after transplantation. Ganciclovir levels were not measured in this population. The incidence of CMV disease within the first three months after transplantation, defined as clinical signs of CMV infection confirmed with a positive CMV PCR (> 100 copies/mL), was studied. Furthermore, the incidence of CMV disease in patients with DGF was compared to the incidence in patients with immediate kidney function.

The variables which were studied in multivariate analysis were CMV status (D+/R- vs all other combinations), DGF (no vs the requirement for dialysis in the first week after transplantation), rejection (no treatment vs methylprednisolone and/or anti-T cell therapy) and duration of DGF (one week vs longer duration).

2.2. Statistical analysis

The Chi–Square and Fisher's Exact tests were used to test the difference in prevalence between categorical variables, for larger and smaller numbers respectively (expected values more or less than 5). Binary logistic regression analysis was used to study the influence of DGF, rejection, CMV status (D+/R- vs other combinations) and the duration of DGF on the risk of CMV disease. Backward elimination was used to select each final model. To determine the number of covariates in the initial multivariable model, the square root of the number of events (CMV disease) was calculated. The outcome reflected the maximum total number of degrees of freedom in the model. Three variables were allowed. First, covariates with the lowest p values in univariable analysis were included. In the multivariable model, covariates that did not contribute significantly were removed using backward elimination. Subsequently, the covariates with higher p values were included followed by backward elimination. This procedure was repeated until all covariates had been included in the model.

All analyses were performed using Statistical Package for the Social Sciences 21.0.0.1 (IBM Corporation, Armonk, NY). P values below 0.05 were considered statistically significant.

3. Results

There were 1441 incident kidney transplant patients in the Radboud UMC between January 1, 2004 and December 31, 2015. After excluding patients under the age of 18 years (n = 106) and patients with a never functioning graft (n = 28) or missing information on graft function (n = 7), 1300 patients remained for analysis. Prophylactic valganciclovir was prescribed to 281 patients who were D + /R- and to 96 patients after they received anti-rejection treatment with T cell-depleting antibodies within the first three months after transplantation (17 D+/R- patients were also treated with T cell-depleting antibodies). There were no patients who received induction therapy with T-cell depleting antibodies.

Baseline characteristics of the study population are shown in Table 1. Delayed graft function occurred in 274/1300 (21.1%) patients. In the overall population of 1300 patients, 31 patients (2.4%) developed CMV disease within the first three months after transplantation. The incidence of CMV disease within the first 3 months after transplantation was higher in patients with DGF (15/274 = 5.5%), compared to patients with immediate graft function (16/1026 = 1.6%). This difference was statistically significant (X^2 (1, n = 1300) = 14.2391, p = 0.0002; Table 2). However, not all these patients were treated with valganciclovir prophylaxis.

A subpopulation total of 281 CMV seronegative patients with a seropositive donor (D+/R-) did receive prophylaxis with valganciclovir. Of these 281 patients, 51 (18.1%) patients suffered from DGF and 230 (81.9%) had immediate graft function. As shown in Table 3, the incidence of CMV disease was significantly higher in patients with DGF (11.8%) than in patients without DGF (0.9%; p = 0.0006). In the subpopulation of patients with R + /D-, R + /D+ and R-/D- in whom no prophylaxis was started after transplantation (n = 1019) the incidence of CMV disease in patients with DGF was not significantly higher compared to those without DGF (4.0% vs 1.8%; p > 0.05). In a subpopulation of 96 patients treated with T cell-depleting antibodies, the incidence of CMV disease was also significantly higher in the DGF group than in the group with immediate graft function (12.5% vs. 2.1% (X^2 (1, n = 62) = 3.8523, p = 0.0497; Table 4). To exclude the possibility that the higher risk of CMV disease in high-risk patients with DGF was mediated by a higher rate of anti-T cell treatment in this population, the analysis was repeated after exclusion of 17 patients who received T-cell depleting therapy. Again, the incidence of CMV disease was higher in patients with DGF than in patients with immediate graft function (11.4% vs. 0.9%; X_2 (1, n = 264) = 15.526, p < 0.0001; Table 5).

In the complete population of 1300 patients, a multivariate analysis

Table 1
Baseline characteristics.

Patient characteristics	n = 1300
Recipient age, mean (SD), years	49,7 (13,3)
CMV D + /R-, n (%)	281 (21,6)
Patients with DGF, n(%)	274 (21,1)
Patients with CMV disease, n (%)	31 (2,4)
Patients with rejection, n(%)	366 (28,2)
T-cell depleting therapy, n(%)	96 (7,4%)
rATG, n	69
OKT3, n	12
Other	16
Duration of DGF[a], n(%)	
>1 week	174 (63,5)
<1 week	100 (36,5)

[a] Based on duration of dialysis from the moment of transplantation. n = 274

Table 2
DGF and incidence of CMV disease.

		CMV disease[a]		Total
		Absent	Present	
DGF	Absent	1010 (98.4%)	16 (1.6%)	1026
	Present	259 (94.5%)	15 (5.5%)	274
Total		1269	31	1300

CMV = Cytomegalovirus; DGF = Delayed Graft Function
X_2 (1,n = 1300) = 14.2391 p = 0.0002
[a] Defined as clinical signs of CMV infection confirmed with a positive CMV PCR in the first three months after transplantation

Table 3
DGF and incidence of CMVdisease in D+ /R- patients on valganciclovir prophylaxis.

		CMV disease[a]		Total
		Absent	Present	
DGF[b]	Absent	228 (99.1%)	2 (0.9%)	230
	Present	45 (88.2%)	6 (11.8%)	51
Total		273	8	281

CMV = Cytomegalovirus; DGF = Delayed Graft Function
[a] Defined as clinical signs of CMV infection confirmed with a positive CMV PCR in the first three months after transplantation
[b] Significantly more CMV infections in patients with DGF versus without DGF. (p = 0.0006 Fisher's exact test)

Table 4
DGF and incidence of CMV disease in patients on valganciclovir prophylaxis after T cell-depleting anti-rejection therapy.

		CMV disease[a]		Total
		Absent	Present	
DGF[b]	Absent	47 (97.9%)	1 (2.1%)	48
	Present	42 (87.5%)	6 (12.5%)	48
Total		89	7	96

[a] Defined as clinical signs of CMV infection confirmed with a positive CMV PCR in the first three months after transplantation CMV = Cytomegalovirus; DGF = Delayed Graft Function
[b] Significant difference in CMV infection in DGF or no DGF (X_2 (1,n = 62) = 3.85, p = 0.0497

Table 5
CMV disease in D + /R- patients with DGF and valganciclovir prophylaxis without T-cell depleting anti- rejection therapy.

		CMV disease[a]		Total
		Absent	Present	
DGF[2]	Absent	218 (99.1%)	2 (0.9%)	220
	Present	39 (88.6%)	5 (11.4%)	44
Total		257	7	264

[a] Defined as clinical signs of CMV infection confirmed with a positive CMV PCR in the first three months after transplantation.CMV = Cytomegalovirus; DGF = Delayed Graft Function (X_2 (1,N = 264) = 15.526, p < 0.000081).

on the risk of CMV disease was performed. There were 31 events. Multivariate binary regression analysis showed that DGF and treatment of acute rejection (treatment with methylprednisolone and/or anti-T cell therapy) were both significantly associated with the occurrence of CMV disease (Table 6). This influence was independent as there was no interaction between the two variables. The analysis also showed no significant influence of CMV status (D+/R- vs other combinations). Although DGF was significantly associated with the occurrence of CMV, the duration of DGF was not. The subgroup of patients who received valganciclovir prophylaxis was too small to perform a multivariable regression analysis. In the patients without valganciclovir prophylaxis, the incidence of CMV disease was not significantly increased in patients with DGF.

Table 6
Results of the multivariate binary logistic regression analysis Events = *31*.

Variable	Exp (B)	95% CI		P
		Lower	Upper	
DGF (none)	2520	1168	5437	0018
Rejection (no rejection)	4067	1813	9126	0001

Event is CMV disease defined as clinical signs of CMV infection confirmed with a positive CMV PCR in the first three months after transplantation.DGF = Delayed Graft Function Final model after backward elimination of the following covariates: CMV status (D + /R- versus others), duration of DGF (≤1 week versus > 1 week dialysis).
Missing cases n = 3. Missing data of CMV disease (n = 7) defined as not having CMV.

4. Discussion

Valganciclovir is the preferred drug for the prophylaxis of CMV infection after solid organ transplantation. Breakthrough CMV infections during valganciclovir prophylaxis are rare. Prophylaxis is so effective, even in high risk (D+/R-) patients, that in the analysis of this large cohort of 1300 patients CMV status did not turn out to be a significant risk factor for CMV disease. Without doubt, if prophylaxis would not have been given, CMV status would have been a strong predictor for CMV disease [5]. The present study did demonstrate that DGF and anti-rejection therapy are independent risk factors for developing CMV disease during the first three months after transplantation, in patients on valganciclovir prophylaxis.

Since only the patients with D+ /R- CMV status and patients after T cell-depleting antibody therapy received valganciclovir prophylaxis, these specific groups were selected for further analysis. In this group the incidence of CMV disease in D + /R- patients receiving valganciclovir prophylaxis who suffered from DGF was higher. DGF is known to be associated with innate immune activation, with complement activation and release of damage-associated molecular patterns, and with a higher incidence of rejection [6]. One might think that the higher incidence of CMV disease could be due to the higher incidence of rejection, and associated anti-rejection therapy in patients with DGF. However, the higher risk of CMV disease in patients with DGF persisted after exclusion of patients who received T cell-depleting antibody therapy, indicating that T cell-depleting antibody therapy is not the main cause of the higher risk of CMV disease in these patients.

The higher incidence of CMV disease in patients with DGF is possibly explained by underexposure to ganciclovir, resulting from dose adjustments because of impaired renal function and by clearance of ganciclovir during the intermittent dialysis sessions for the duration of DGF. Ganciclovir is not metabolized and is eliminated by both glomerular filtration and tubular secretion. As ganciclovir may accumulate in patients with reduced renal function, the dose is adjusted for renal function. Patients with a creatinine clearance below 25 mL/min typically receive as little as 450 mg valganciclovir twice weekly. The data on which the dose adjustments for patients with poor renal function is based are limited. There is a potential risk that in renal transplant patients with DGF, in whom the dose is most strongly reduced, prolonged periods of low to sub-therapeutic exposure occur.

Based on previous studies with intravenous ganciclovir treatment of acute CMV infection in HIV-infected patients, ganciclovir concentrations below 0.6 mg/L were defined as sub-therapeutic [7]. The median pre-dose concentration of ganciclovir in a small group of adult kidney transplant recipients, treated with oral valganciclovir 450 mg qd, was below this cut-off of 0.6 mg/L. The authors of this study concluded that it may be necessary to use higher doses of valganciclovir, mainly during

periods of high-intensity immunosuppression or anti-rejection therapy [8].

Trevillyan et al. found sub-therapeutic ganciclovir concentrations (<0.6 mg/L) in 10/22 liver or kidney transplant recipients (45.4%) and very low ganciclovir concentrations (<0.3 mg/L) in 7 of them [9]. They also stressed that the low ganciclovir exposure was in part due to the fact that the estimation of the glomerular filtration rate (with the MDRD formula) underestimated the 24-hour urine creatinine clearance. More reliable assessment of renal function might help to prevent under-dosing of valganciclovir. Wiltshire et al. showed that the target area under the concentration vs time curve (AUC) of 40–50 mg*h/L for ganciclovir was often not achieved in patients who received a reduced valganciclovir dose because of renal impairment, especially if the creatinine clearance was below 50 mL/min. A similar conclusion was reached in a more recent population pharmacokinetic study [10,11]. The data in this article are in line with a study by Khurana et al. who found that transplant recipients receiving prophylaxis in dosages adjusted for eGFR are at an increased hazard of subsequent CMV prophylaxis breakthrough infections [12]. Freedman et al. found 15/138 (11%) breakthrough CMV infections, of which more than half (11/15) were related to underdosing of valganciclovir [13]. In this study DGF was not identified as a risk factor for CMV breakthrough.

A potential solution to reduce the risk of CMV disease in D + /R- renal transplant patients with DGF would be to monitor ganciclovir plasma concentrations and adjust the valganciclovir dose to reach target concentrations. The advantage of a TDM-based approach is that both under- and over-exposure can be prevented. Over-exposure would put the patient at risk for side effects in general, and neutropenia in particular. In the Netherlands such a dosing strategy has not been used so far, and probably only very few centers routinely perform TDM for ganciclovir. The aim of this article is not to recommend TDM for all patients on valganciclovir. In patients with normal renal function, monitoring ganciclovir levels is unlikely to be useful, since an additional value of routine TDM for ganciclovir in solid organ transplant recipients could not be demonstrated [14]. However, the observation that DGF is a risk factor for CMV disease independent of anti-T cell therapy, suggests that TDM may be of added value in this specific population. Another factor to consider is the timely escalation of the valganciclovir dose in patients in whom renal function gradually improves. Although no exact numbers are available, maybe in some patients the very low dose valganciclovir prophylaxis should have been increased earlier when renal function improved.

A limitation of this study is the relatively small size of the cohort and the low incidence of CMV disease. This did not allow for multivariable regression analysis in the subgroup of patients who received valganciclovir prophylaxis. Another important limitation is the lack of information of ganciclovir levels in this population and the lack of confirmation that the dosage changes were in line with the guidelines when improvement of kidney function was seen. This study shows that an increased awareness of CMV breakthrough in patients with DGF is indicated. It does not provide evidence for the added value of TDM for valganciclovir in patients with DGF but prospective trials are needed to study the impact of novel dosing strategies on drug exposure and clinical outcome.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: WK reports no conflicts of interest. TvG has received lecture fees from Chiesi and Astellas Pharma, and consulting fees from Roche Diagnostics, Aurinia, Vitaeris, Astellas and Novartis. LH has received consulting fees from Chiesi and Novartis. DAH has received lecture and consulting fees from Astellas Pharma and Chiesi, as well as grant support from Astellas Pharma, Bristol Myers-Squibb and Chiesi. MB reports no conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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