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Risk Factors for Failure of Primary (Val)ganciclovir Prophylaxis Against Cytomegalovirus Infection and Disease in Solid Organ Transplant Recipients

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Background. Rates and risk factors for cytomegalovirus (CMV) prophylaxis breakthrough and discontinuation were investigated, given uncertainty regarding optimal dosing for CMV primary (val)ganciclovir prophylaxis after solid organ transplantation (SOT).

Methods. Recipients transplanted from 2012 to 2016 and initiated on primary prophylaxis were followed until 90 days post-transplantation. A (val)ganciclovir prophylaxis score for each patient per day was calculated during the follow-up time (FUT; score of 100 corresponding to manufacturers' recommended dose for a given estimated glomerular filtration rate [eGFR]). Cox models were used to estimate hazard ratios (HRs), adjusted for relevant risk factors.

Results. Of 585 SOTs (311 kidney, 117 liver, 106 lung, 51 heart) included, 38/585 (6.5%) experienced prophylaxis breakthrough and 35/585 (6.0%) discontinued prophylaxis for other reasons. CMV IgG donor+/receipient- mismatch (adjusted HR [aHR], 5.37; 95% confidence interval [CI], 2.63 to 10.98; $P < 0.001$) and increasing % FUT with a prophylaxis score <90 (aHR, 1.16; 95% CI, 1.04 to 1.29; $P = .01$ per 10% longer FUT w/ score <90) were associated with an increased risk of breakthrough. Lung recipients were at a significantly increased risk of premature prophylaxis discontinuation (aHR, 20.2 vs kidney; 95% CI, 3.34 to 121.9; $P = .001$), mainly due to liver or myelotoxicity.

Conclusions. Recipients of eGFR-adjusted prophylaxis doses below those recommended by manufacturers were at an increased risk of prophylaxis breakthrough, emphasizing the importance of accurate dose adjustment according to the latest eGFR and the need for novel, less toxic agents.

Keywords. CMV; cytomegalovirus; ganciclovir; prophylaxis; valganciclovir; SOT; transplantation.

Infection with cytomegalovirus (CMV) frequently complicates the course after solid organ transplantation (SOT), and if left untreated, asymptomatic CMV DNAemia can in some cases progress to CMV disease with poorer clinical outcomes [1, 2]. To prevent progression to CMV disease in SOT recipients, most transplantation centers administer universal prophylaxis with valganciclovir or ganciclovir after transplantation [3]. However, the optimal dosage and duration of universal prophylaxis are currently debated [4, 5]. Despite being considerably less nephrotoxic than the second-line drugs with activity against CMV, namely foscarnet and cidofovir, (val)ganciclovir may still induce other treatment-limiting side effects such as myelosuppression, leading to early cessation of prophylaxis [2, 3, 6–8]. In such patients, it could potentially be beneficial to administer lower dosages of prophylaxis [4]. On the other hand, some patients may experience CMV DNAemia breakthrough during active administration of prophylaxis, especially if the recipient is at risk of primary CMV infection from the donor (CMV IgG donor [D]+/recipient [R]-) [9, 10]. Although current guidelines recommend valganciclovir 900 mg daily (adjusted for renal function) for universal prophylaxis [8, 10], some studies have demonstrated an equivalent efficacy of a dose reduction to 450 mg/d [2, 3, 6, 11, 12]. At present, the optimal dose still remains unclear, particularly with regards to type of SOT [3]. The aim of the current study was to investigate if, and to what extent, different dosages of (val)ganciclovir prophylaxis affect the risk of experiencing prophylactic breakthrough during active administration of prophylaxis. Furthermore, we aimed to identify reasons and risk factors for premature prophylaxis discontinuation.

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METHODS

Patients

The Management of Post-Transplant Infections in Collaborating Hospitals (MATCH) program was initiated in 2011 with the goal of serving as a collaborative platform between individual transplant units and the Infectious Disease Department at Rigshospitalet, University Hospital Copenhagen; 3000 consecutive transplant patients are currently registered, with transplantations performed back to 2004 [13].

Recipients ≥18 years of age who were registered in MATCH and who received a heart, lung, liver, or kidney transplantation between January 1, 2012, and September 1, 2016, were evaluated for inclusion. Combined SOTs were excluded. Only recipients who were anticipated to receive prophylaxis for at least 90 days were included, corresponding to CMV IgG seroconstellations of D+/R+, D+/R- and D-/R+ for kidney, heart, and lung recipients. Only D+/R+ and D+/R- were included from the liver recipients; other seroconstellations are managed solely preemptively. Patients with incomplete medical records and patients not starting prophylaxis within the first 14 days post-transplantation were also excluded (Figure 1). Approval from the regional ethics committee, Danish Data Protection Agency, and Danish Patient Safety Authority was acquired before the study.

Data on Prophylaxis Administration

At our center, recipients of liver, heart, and lung transplantation generally receive 90 days of valganciclovir prophylaxis after transplantation with the standard dose of 900 mg daily (adjusted for their renal function), whereas the dose is set at 450 mg every other day irrespective of estimated glomerular filtration rate (eGFR) for the recipients of kidney transplants.

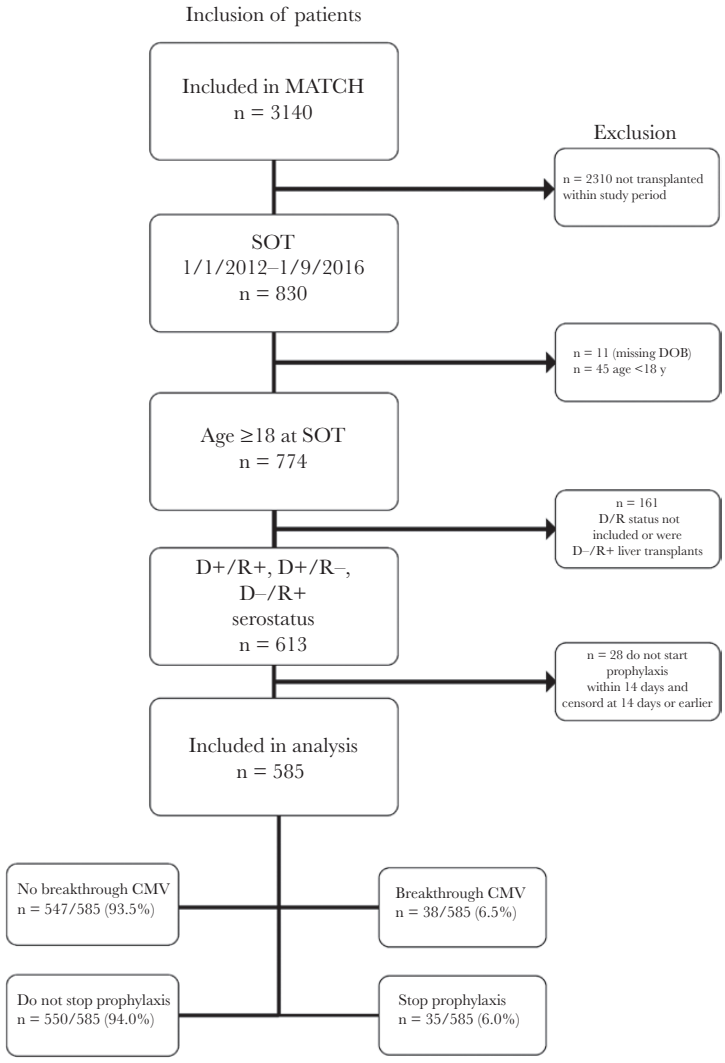

Figure 1. Flowchart describing patient inclusion and exclusion in the study population (n = 585), as well as the number of people experiencing each study outcome. Thirty-eight (6.5%) experienced prophylaxis breakthrough, and 35 (6.0%) stopped prophylaxis early. Abbreviations: BT, breakthrough; CMV, cytomegalovirus; DOB, date of birth; D/R, donor/recipient CMV IgG; MATCH, Management of Post-Transplant Infections in Collaborating Hospitals transplantation database; SOT, solid organ transplantation.

Recipients were screened once a month with quantitative CMV polymerase chain reaction (PCR) or more frequently at the treating physician's discretion. Data on CMV prophylaxis medication were collected from the date of transplantation and 90 (±7) days forward; other biochemical and clinical data were collected up to a year post-tx. Data on valganciclovir and ganciclovir dosage were recorded from a medical prescription database and were cross-referenced with clinical journals.

Prophylaxis Score Calculation

To compare prophylactic dosages between patients, a prophylaxis score for each patient was developed and calculated for each day within the prophylactic period (90±7 days) (Figure 2). Scores were calculated by dividing the actual dosage received by the manufacturers' recommended doses (adjusted for eGFR) (Supplementary Figure 1), which will be referred to as the "optimal" dosage for the sake of simplicity: score = actual dose (mg)/optimal dose (mg) ×100. We used the dose recommended by the manufacturers to maintain a universal standard as opposed to using local protocols. Optimal prophylaxis is thus a score of 100; a score of 200 would imply double the optimal dose and a score of 50 half the optimal dose. Optimal dosage was based on the patient's recorded eGFR value (mL/min/1.73 m^2; Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) and weight (kg); eGFR values were used to determine the optimal dosage for both valganciclovir and ganciclovir; weight was only used to determine the optimal dosage for ganciclovir. Weight and eGFR were carried forward until the next available value so that a longitudinal data set was created for each day in the prophylaxis period. A sample score calculation can be found in Supplementary Figure 2.

For patients for whom records on body weight were missing, median weights were used; median weights were stratified by gender, age (<50 or ≥50 years), and transplant type (kidney, lung, heart, liver).

Outcome Measures and Definitions

The primary outcome in this study was CMV breakthrough during administration of prophylaxis. This event was defined as CMV infection during a period within the first 90 (±7) days post-transplantation, while the recipient was actively receiving CMV prophylaxis. The prevalence of CMV breakthrough during prophylaxis was stratified for D/R CMV IgG serostatus, age, and type of transplantation and was compared based on the various strata of prophylaxis scores.

We also investigated the prevalence of premature discontinuation of prophylaxis and reasons for discontinuation. Premature prophylaxis discontinuation was defined as experiencing a discontinuation of prophylaxis for >7 days (prophylaxis score = 0 for ≥7 consecutive days) after an active period of prophylaxis (having a score not equal to 0 for ≥1 day post-transplantation). Reasons for prophylaxis discontinuation were defined by those noted in medical records by attending physicians. Baseline (start of follow-up) was defined as the first day a patient receives prophylaxis (score ≠ 0) or day 14 post-transplantation.

CMV PCR

CMV was monitored through quantitative PCR assays using the COBAS AmpliPrep/COBAS TaqMan instrument. The conversion factor for the instrument is 1 copy/mL to 0.91 IU/mL, with the lower quantification limit being 273 IU/mL. CMV infection

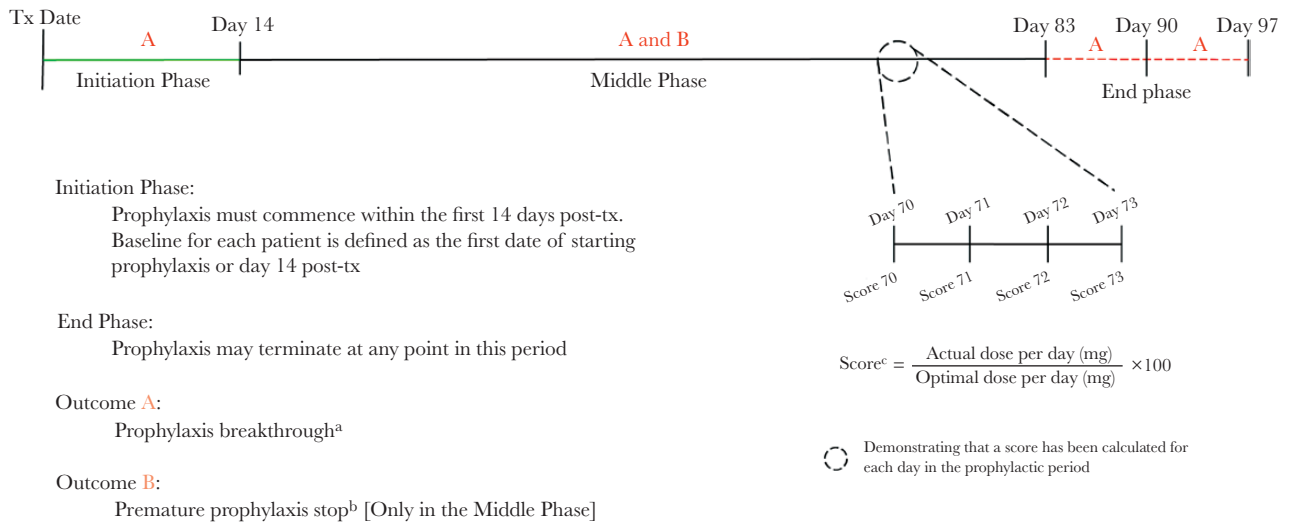

Figure 2. Illustration describing the prophylactic period, the calculation and interpretation of the score, and the definitions of the various outcomes in the study. The prophylactic period is split into 3 phases. The score is the actual dose (mg) received divided by the optimal dose (mg) multiplied by 100. The 2 outcomes of the study are prophylaxis breakthrough and premature prophylaxis stop. [a]Defined as polymerase chain reaction–verified cytomegalovirus DNAemia in either plasma or bronchoalveolar lavage while actively receiving prophylaxis. [b]Defined as >7 consecutive days' cessation of prophylaxis. [c]A score for each day within the patient's prophylactic period has been calculated.

was defined by either 2 consecutive CMV PCRs ≥273 IU/mL within 14 days of each other [14, 15] or 1 CMV PCR ≥2730 IU/mL in plasma. Alternatively, fluid from a single bronchoalveolar lavage (BAL) with CMV PCR ≥2730 IU/mL was considered an infection [16]. Serostatus constellation (D/R) was defined by the combination of the donor and recipient CMV IgG statuses before transplantation.

Immunosuppression

A full description of the immunosuppressive regimen received by each transplantation group can be found in Supplementary Figure 3 [13].

Other Clinical Parameters

Clinical, demographic, and laboratory data on recipients, including values for CMV PCR, eGFR, and other markers were collected longitudinally during the entire prophylactic period of the recipient from electronic health records. Leukopenia was defined as a white blood cell (WBC) count <3500 cells/mm^3, and elevated liver enzymes were defined as alanine transaminase (ALT) >210 U/L for males and >135 U/L for females (ie, 3× the upper limit of normal).

Statistical Analysis

Standard descriptive statistics were used to describe the categorical and continuous baseline clinical characteristics of the included patients. Patients were censored at death (as defined by medical records), after a prophylaxis score of 0 for ≥7 consecutive days (premature prophylaxis stop), loss to follow-up (last lab date +14 days), or re-transplantation within the 90-day prophylactic period. Calculated prophylaxis scores were categorized as low (score < 90), medium (score = 90–≤190) and high (score > 190). The lower boundary of 90 for a medium score was set just below the optimal score of 100; the medium score upper boundary of 190 was set just below an optimal treatment dose (ie, double the optimal prophylaxis dose), namely a score of 200.

Kaplan-Meier estimates were used to illustrate time to prophylaxis breakthrough and time to prophylaxis discontinuation, stratified by transplant type and D/R seroconstellation. Univariate Cox analyses were performed to determine the impact of the prophylaxis score on prophylaxis breakthrough and premature prophylaxis discontinuation. Other explanatory covariates such as age, year of transplantation, type of transplantation, gender, eGFR post-transplantation, WBC count, liver enzyme levels (ALT), and D/R seroconstellation were also investigated. Variables included in the multivariate analyses were based on significance values from univariate analyses ($P < .1$). Cox analyses based on the cumulative time spent in each of the 3 scoring categories were performed, stratified for a priori selected risk factors, including transplant type and D/R seroconstellation. Prophylaxis score, eGFR post-transplantation, WBC count, ALT levels, and cumulative time spent in each of the 3 scoring categories were included as time-updated variables. For modeling the score changes over time in figures, recipients were censored on the day of their first event (breakthrough or censoring as defined above); *t* tests were used to compare average scores at different time points.

Statistics were performed using SAS, version 9.4 (SAS Institute, Cary, NC). *P* values ≤.05 were considered significant.

RESULTS

Patient Characteristics

During the study period, 830 SOT recipients were transplanted. Of these, 245 patients were excluded (45 recipients <18 years old, 11 missing birth dates, 161 either missing or seroconstellations other than D+/R+, D+/R- or D-/R+, and 28 did not start prophylaxis within 14 days or were censored by day 14). The remaining 585 SOT recipients were included in the study, and of these, 311 (53.2%) were kidney transplants, 117 (20.0%) were liver transplants, 106 (18.1%) were lung transplants, and 51 (8.7%) were heart transplants. With regards to seroconstellation, 137 (23.4%) were D-/R+, 324 (55.4%) were D+/R+, and 124 (21.2%) were D+/R- recipients. The median age at transplantation (interquartile range [IQR]) was 50.5 (40.9–58.9) years, with 351/585 (60%) being male (Table 1).

Breakthrough on Primary Prophylaxis and Associated Risk Factors

Thirty-eight (6.5%; 95% confidence interval [CI], 4.5 to 8.5) recipients experienced breakthrough CMV infection during the 90-day prophylactic period (Table 1). All 38 recipients experienced CMV DNAemia in plasma; of these, 2 also experienced DNAemia in BAL within a week of infection diagnosis. Median time to infection from the start of follow-up (IQR) was 60 (45–72) days, with the median CMV DNAemia load, defined as the first positive value preceding an infection, in plasma being 796 (364–1592) IU/mL); 273 IU/mL is the lower limit of quantification of the assay.

Of recipients with 1 year of follow-up (FU; 32/38 with breakthrough), mutations in CMV UL97 (ie, genotypic resistance) developed in 9 of the recipients experiencing breakthrough (8/32, 25.0%; 95% CI, 10.0 to 40.0); 2 recipients (2/32, 6.3%; 95% CI, –2.1 to 14.7) with prophylaxis breakthrough progressed to CMV disease (both CMV pneumonia) during the first year post-tx, both of whom were lung tx recipients. In contrast, among nonbreakthrough patients not censored for other reasons and with a year of FU, 108 (108/439, 24.6%; 95% CI, 20.6 to 28.6) experienced CMV DNAemia (ie, an infection after the prophylaxis period), of whom 3 (3/108, 2.8%; 95% CI, –0.31 to 5.91) developed resistance. Additionally, among the 108 patients experiencing CMV DNAemia, 30 (30/108, 27.8%; 95% CI, 19.4 to 36.2) progressed to CMV disease (of whom 18 were CMV pneumonia, 8 CMV syndrome, and 4 gastrointestinal [GI] tract

Table 1. Baseline Characteristics of 585 SOT Patients, Stratified for Breakthrough Infections and Prophylaxis Discontinuation

	Characteristic	All Recipients	No Breakthrough Infection	Breakthrough Infection	*P* Value	No Stop in Prophylaxis	Stop in Prophylaxis	*P* Value
	All	585 (100.0)	547 (93.5)	38 (6.5)		550 (94.0)	35 (6.0)	
Tx type, No. (%)	Heart	51 (8.7)	50 (98.0)	1 (2.0)	.067	51 (100.0)	0 (0.0)	<.001
	Kidney	311 (53.2)	284 (91.3)	27 (8.7)		305 (98.1)	6 (1.9)	
	Liver	117 (20.0)	114 (97.4)	3 (2.6)		113 (96.6)	4 (3.4)	
	Lung	106 (18.1)	99 (93.4)	7 (6.6)		81 (76.4)	25 (23.6)	
Gender, No. (%)	Male	351 (60.0)	327 (93.2)	24 (6.8)	.681	329 (93.7)	22 (6.3)	.722
Year tx, No. (%)	2012	130 (22.2)	122 (93.9)	8 (6.1)	.613	117 (90.0)	13 (10.0)	.022
	2013	98 (16.8)	94 (95.9)	4 (4.1)		90 (91.8)	8 (8.2)	
	2014	132 (22.6)	125 (94.7)	7 (5.3)		129 (97.7)	3 (2.3)	
	2015	142 (24.3)	130 (91.6)	12 (8.4)		132 (93.0)	10 (7.0)	
	2016	83 (14.2)	76 (91.6)	7 (8.4)		82 (98.8)	1 (1.2)	
D/R status, No. (%)	D-/R+	137 (23.4)	134 (97.8)	3 (2.2)	<.001	120 (87.6)	17 (12.4)	.001
	D+/R+	324 (55.4)	309 (95.4)	15 (4.6)		310 (95.7)	14 (4.3)	
	D+/R-	124 (21.2)	104 (83.9)	20 (16.1)		120 (96.8)	4 (3.2)	
Median age (IQR), y		50.5 (40.9–58.9)	50.8 (41.1–58.9)	48.2 (35.5–59.4)	.445	50.4 (40.6–58.8)	50.9 (44.7–59.3)	.34
Prior transplant, No. (%)		23 (3.9)	23 (4.2)	0 (0.0)	.197	13 (8–80)	86 (45–90)	<.001
Median weight on day 1[a] (IQR), kg		74 (61–85)	74 (64–83)	71 (61–83)	.399	74.8 (63.5–82.5)	68 (60–73)	.01

Abbreviations: D/R, donor/recipient; IQR, interquartile range; SOT, solid organ transplantation.

[a]Three hundred sixty-eight out of 585 patients had available weight post-transplant.

disease) within the first year post-tx. This resulted in an overall viral resistance rate of 8.4% (12/143; 95% CI, 3.8 to 12.9) among those recipients in the cohort experiencing DNAemia not censored for other reasons and with a year of FU. Of recipients with a minimum of 1 day with a score <90, the median score for recipients within the defined follow-up in the first 90 (±7) days post-tx with prophylaxis breakthrough vs those without breakthrough (IQR) was 50 (50–100) and 100 (50–100), respectively. The median score for the 7 days preceding the diagnosis of the breakthrough infection (IQR) was 50 (50–100; n = 38). At 2 weeks (day 15) post-tx, differences in the mean score for those that went on to experience breakthrough (78.7; n = 34) vs those who did not experience breakthrough (100.3; n = 537) were significant ($P < .01$). Differences in the mean score after 1 month (28 days) were also significant ($P < .01$). A visual representation of the changes in score over time can be seen in Figure 3.

Recipients with a D+/R- serostatus constellation were significantly more likely to develop a breakthrough infection compared with recipients with a D+/R+ or D-/R+ serostatus constellation (16.1% vs 4.6% and 2.2%; $P < .01$) (Figure 4A). Differences were also noted in prophylaxis breakthrough rates between different organ types, with kidney and lung transplant recipients having increased rates of breakthrough (8.7% and 6.6%) as compared with liver (2.6%) and heart transplant (2.0%) recipients ($P = .067$). Gender, year of transplant, and age were not noted to be significantly different among recipients with and without breakthrough (Table 1).

Without adjusting for covariates, for every 10% more time spent during the defined follow-up with a score <90, the risk of a breakthrough infection increased by 15% (hazard ratio [HR], 1.15; 95% CI, 1.07 to 1.24; $P < .01$). This finding was confirmed in the multivariate analysis: Having adjusted for D/R seroconstellation, transplant type, and death as a competing risk factor, every 10% of additional follow-up time spent with a score <90 was associated with a 15.7% increased risk of breakthrough (adjusted HR [aHR], 1.16; 95% CI, 1.04 to 1.29; $P = .01$). This implies that the adjusted incidence rate ratio of CMV breakthrough is almost double (aHR, 1.98; 95% CI, 1.19 to 3.63; $P < .01$) in recipients spending 50% more follow-up time with a score <90 (Figure 5). When adjusting for type of transplant and score, a D+/R- serostatus constellation was also deemed to be an independent risk factor for developing CMV prophylaxis breakthrough (aHR, 5.37; 95% CI, 2.63 to 10.98; $P < .001$). Tx type was not significant, and no relevant interactions were observed.

Premature Prophylaxis Discontinuation

In the study population, 35 (6.0%; 95% CI, 4.1 to 7.9) recipients experienced a premature cessation of prophylaxis during the first 90 (±7) days post-transplantation for reasons other than emerging CMV infection, of whom 25 were lung tx recipients (n = 25/35, 71%; 95% CI, 56 to 86). The median time to premature discontinuation among those who discontinued prophylaxis (IQR) was 29 (18–63) days from the start of follow-up. Lung transplant recipients were more likely than liver, kidney, and heart transplant recipients to discontinue prophylaxis early (23.6% vs 3.4%, 1.9%, and 0% respectively; $P < .001$) (Figure 4B). Of lung tx recipients discontinuing prophylaxis prematurely and with a year of FU, 14 (14/25, 56.0%; 95% CI, 36.5 to 75.5) experienced CMV DNAemia (ie, infection) and 5 (5/25, 20.0%; 95% CI, 4.32 to 35.7) progressed to CMV disease (4 with CMV pneumonia, 1 with GI

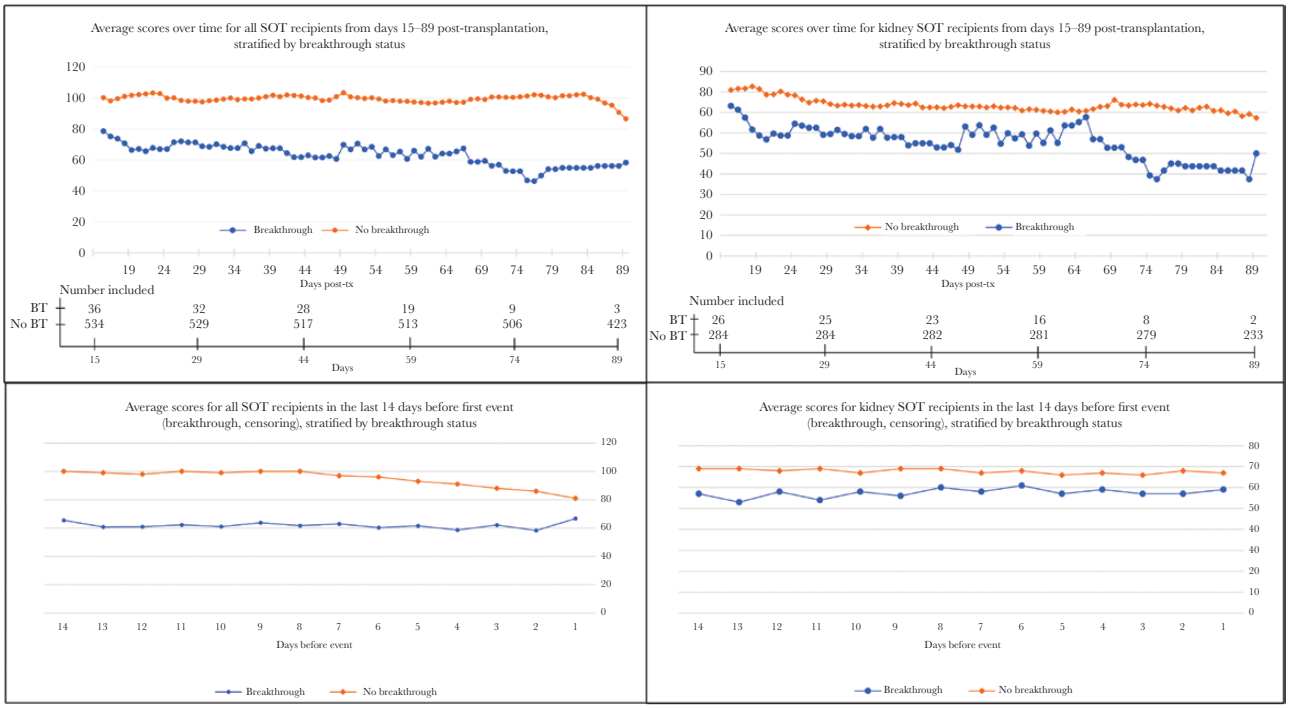

Figure 3. Graphs illustrating the changes in score over time between days 15 and 89 and the last 14 days before the first event (breakthrough, censoring) experienced by recipients, stratified by breakthrough status. Graphs over time for only kidney transplant recipients are also included. Patients without prophylaxis breakthrough had visibly higher scores over time than recipients experiencing breakthrough. Abbreviations: BT, breakthrough; No BT, no breakthrough; SOT, solid organ transplantation.

tract disease). Additionally, premature prophylaxis discontinuation rates were significantly different depending on D/R CMV IgG serostatus constellation; 12.4% (95% CI, 6.9 to 17.9) of D-/R+ recipients experienced a stop in prophylaxis compared with 4.3% (95% CI, 2.1 to 6.5) and 3.2% (95% CI, 0.1 to 6.3) of D+/R+ and D+/R- recipients, respectively ($P = .001$).

The main risk factor for prophylaxis discontinuation was lung transplantation (HR, 20.2; 95% CI, 3.34 to 121.9; $P = .001$), adjusted for year of transplantation, donor/recipient CMV IgG seroconstellation, time spent with a score >190, WBC count, liver enzyme levels (ALT), eGFR, and death as a competing risk factor. D-/R+ seroconstellation was also an independent risk factor for prophylaxis discontinuation (aHR, 3.57; 95% CI, 1.55 to 8.20; $P = .003$). Age and gender did not differ significantly in those with premature prophylaxis cessation vs those without.

Reasons for Premature Discontinuation of Prophylaxis

The main reasons for premature discontinuation of prophylaxis were liver toxicity (n = 10), patient- and/or physician-related reasons (n = 12), and myelosuppression (n = 6) (Table 2). Fifty-three percent of lung tx recipients experienced leukopenia during the first 90 days post-transplant. This contrasts with 47%, 17%, and 41% for heart, kidney, and liver transplant recipients, respectively ($P < .01$). Current leukopenia (aHR, 4.10; 95% CI, 1.13 to 14.9; $P = .03$) was predictive of prophylaxis discontinuation; it was also predictive of discontinuing prophylaxis 14 days later (aHR, 3.94; 95% CI, 1.10 to 14.14; $P = .04$). Elevated ALT levels were not significant in either time range. Higher doses of (val)ganciclovir were not significantly associated with increased rates of leukopenia or elevated ALT levels.

DISCUSSION

In this study, we introduced a novel and simple method for evaluating the optimal dosage for universal prophylaxis. Using this method, our data demonstrate that recipients receiving prophylaxis in dosages below the recommendations of the manufacturers (adjusted for eGFR) are at an increased hazard of subsequent CMV prophylaxis breakthrough, particularly if the recipients had CMV IgG D+/R- mismatch. Furthermore, 25% of the lung transplant recipients discontinued prophylaxis before day 90, mainly because of toxicity. Our results highlight the importance of adjusting the administered dosage of prophylaxis according to the current eGFR, as well as the continued need for newer and less toxic agents against CMV.

In line with the manufacturers' recommendations, the current guidelines recommend 900 mg of valganciclovir daily for universal prophylaxis after SOT [2, 3, 5]. However, several recent studies suggest an equivalent efficacy with a lower dose (450 mg for valganciclovir) [6, 12]. An important difference is that these studies used CMV disease and not CMV DNAemia as the primary end point. However, progression to CMV disease is largely preventable (apart from certain subpopulations experiencing pneumonia, retinitis, and GI tract disease due to

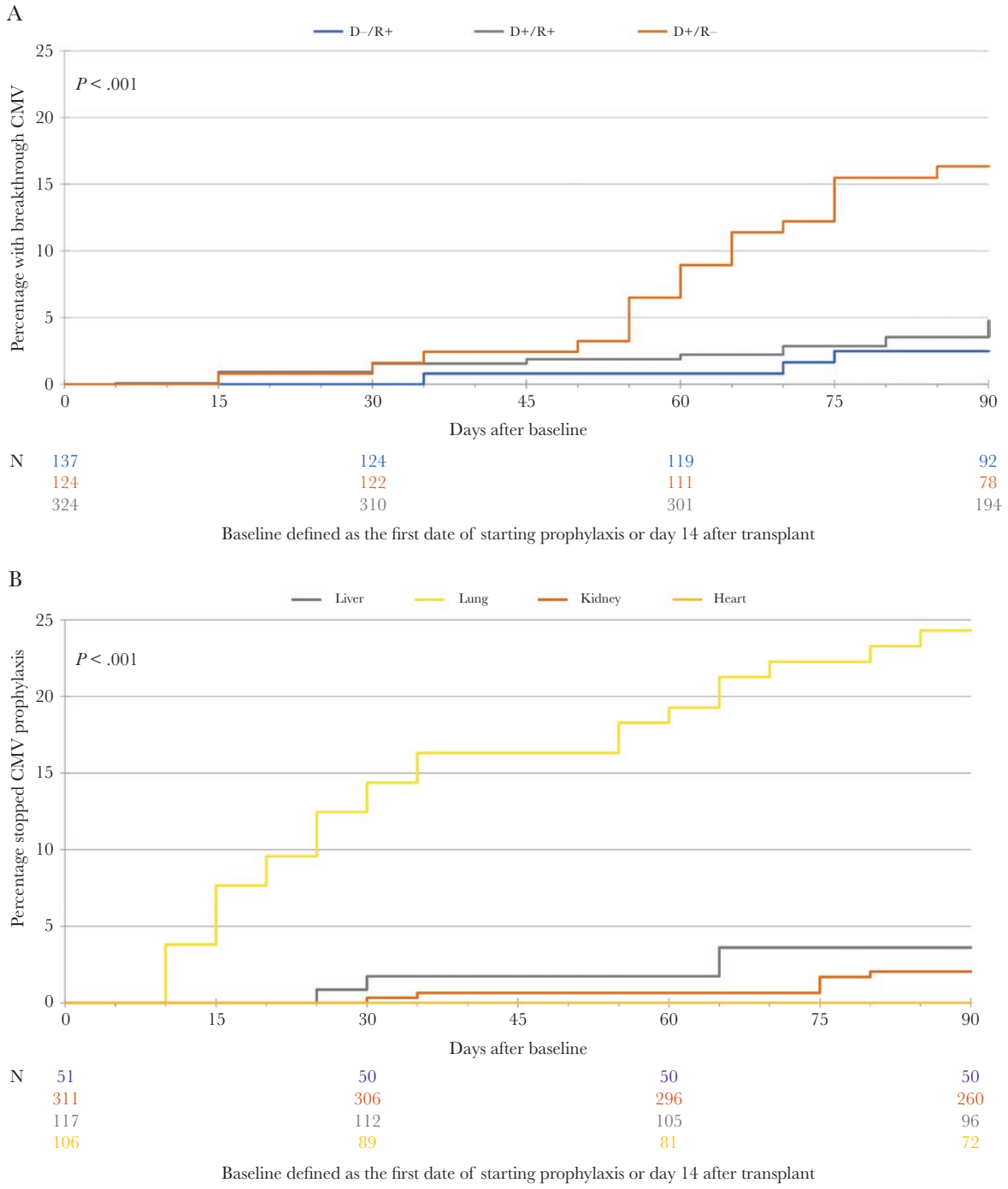

Figure 4. A, Kaplan-Meier curve depicting the time to prophylaxis breakthrough stratified by seroconstellation within the first 90 days post-transplantation. Donor (D)+/recipient (R)- solid organ transplantations (SOTs) had a significantly higher rate of breakthrough compared with the D-/R+ and D+/R+ SOTs. B, Kaplan-Meier curve depicting the time to stopping cytomegalovirus prophylaxis (without experiencing prophylaxis breakthrough) stratified by SOT type within the first 90 days post-transplantation. Lung transplant recipients were significantly more likely than heart, liver, and kidney recipients to stop prophylaxis early. Abbreviation: CMV, cytomegalovirus.

low or undetectable plasma viral loads), as it is a downstream effect of insufficient treatment of CMV DNAemia. Proper screening programs and preemptive intensification of treatment in case of breakthrough infection while on prophylaxis can to a large extent prevent this progression to CMV disease from CMV DNAemia [16–18]. Similar to our observations, a study by Stevens et al. [9] that looked at prophylaxis breakthrough rates among kidney recipients found low-dose valganciclovir, defined as 450 mg daily (adjusted for renal function), to be suboptimal in preventing prophylaxis breakthrough in the first 6 months post-tx. The kidney transplant department at our institution has subsequently increased their prophylactic dosages.

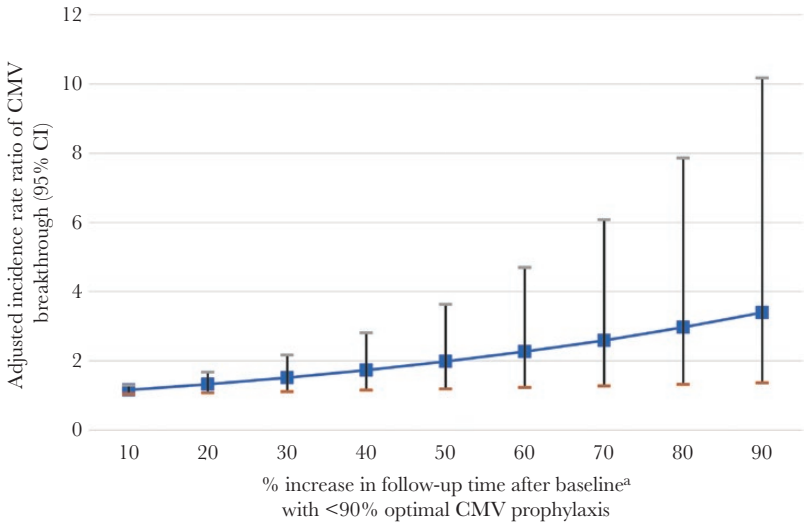

Figure 5. Graph showing the adjusted incidence rate ratio of cytomegalovirus (CMV) breakthrough with increasing follow-up time (FUT) with <90% optimal CMV prophylaxis. Recipients spending 50% more follow-up time with a score <90 were almost twice as likely to experience prophylaxis breakthrough. A score of 100 was defined as optimal; a score <90 (ie, 90% of optimal prophylaxis) would thus be suboptimal. A 10% increase in cumulative follow-up time with a score <90 would entail a patient having a 10% increase in the number of days where their score had a value <90. For example, if a patient's FUT time was 90 days, a 10% increased cumulative FUT would be 9 more days with a score <90. [a]Baseline was defined as the first day of starting prophylaxis or day 14 post-transplant. Abbreviation: CI, confidence interval.

Additionally, recipients with a D+/R- CMV IgG mismatch were at a significantly higher risk of prophylaxis breakthrough, highlighting the continued need to monitor this recipient population closely.

As far as we know, this study is the first to evaluate the effect of longitudinally collected (val)ganciclovir dosages on CMV prophylaxis breakthrough rates by taking changes in eGFR, dosages, and frequency of administration into account using a score. Clinically, such a scoring system could be a useful clinical tool determined in real time to assist the clinician in ensuring that recipients are getting an optimal level of prophylaxis.

Rates of viral resistance among SOTs having experienced viremia are usually between 5% and 12% [3, 19, 20], in concurrence with our results. Viral resistance to ganciclovir poses a major issue clinically, as patients who later develop CMV disease due to resistant CMV have poorer clinical outcomes [21, 22]. Additionally, the treatment of CMV infections in these patients is problematic [19, 21, 23]. Presently, recommended alternative therapies include foscarnet and a reduction in immunosuppression, although no controlled trials have definitively confirmed this [3, 19]. Striking a balance between adequate treatment dosages and avoiding treatment-limiting adverse effects remains difficult. As such, the potential addition of new drugs [24–26] and vaccines [27] to the CMV treatment arsenal is welcomed.

The premature discontinuation of prophylaxis rate due to adverse events was high in lung transplant recipients, further highlighting the vulnerability in this group. In a study by

Table 2. Reasons for Prophylaxis Discontinuation by Solid Organ Transplantation Type

	SOT				
Reason for Discontinuation	Heart	Lung	Kidney	Liver	Total
Liver-related	0	9	1	0	10
Kidney-related	0	3	0	0	3
Liver- and kidney-related	0	1	0	0	1
Patient- and/or physician-related[a]	0	7	2	3	12
Subsitute medication received[b]	0	0	0	1	1
Myelosuppression	0	5	1	0	6
Skin irritation	0	0	1	0	1
Fecal issues	0	0	1	0	1
Total	0	25	6	4	35

Abbreviation: SOT, solid organ transplantation.

[a]Misunderstanding or unknown reason for stop.

[b]Valaciclovir.

Wiita et al., in which recipients received indefinite lengths of prophylaxis, 50.8% of recipients had to discontinue prophylaxis primarily due to leukopenia, albeit at a median time of 8 months post-tx [28]. Similarly, in a study by Zamora, 32% of lung transplant recipients receiving valganciclovir prophylaxis required discontinuation due to leukopenia and neutropenia [29]. The rate of discontinuation among our lung transplant recipients was high relative to that observed in liver, kidney, and heart SOTs. However, differences in the rate of such events alone probably do not explain the stark differences in prophylaxis discontinuation rates. Although lung transplant recipients may be at an increased risk of certain adverse events, lung transplant clinicians at our institution are probably also more prone to reacting to adverse changes in recipient biochemistry. Differences in immunosuppression, particularly the use of ATG and anti-infective prophylaxis (eg, voriconazole) in certain subpopulations, could also explain such differences; subsequently, voriconazole is no longer part of the standard prophylaxis regimen at the lung transplant department. Variability in clinical judgement was likely also contributing, and this is supported by the evidence that D-/R+ SOT recipients are significantly more likely to stop prophylaxis early; in these low-risk recipients, clinicians may be more inclined to discontinue prophylaxis in the presence of leukopenia.

This study has some limitations. This is a single-center study, where several different SOTs have been included to increase statistical power. This may have introduced some heterogeneity to the data. However, all analyses were stratified for the type of transplantation. Furthermore, the data collection on administered anti-CMV drugs was performed retrospectively, which has inherent weaknesses. Adherence to prophylaxis is assumed and has not been quantified; this may influence the incidence of CMV breakthrough infections. CKD-EPI was used to measure renal function (as per institutional protocols), as opposed to Cockroft-Gault, which is used in manufacturers' recommendations. Exact immunosuppression doses for each patient were not collected but will be investigated in future studies.

Despite this, the strengths of this study include the large size of the cohort and the precision of the data. Data points for CMV medication and other relevant lab values were tracked on a day-by-day basis, allowing changes in medication and recipient biochemistry to be considered using the score; the simplicity of the score is a major strength, as is the use of a longitudinal rather than cross-sectional approach. Additionally, data regarding CMV prophylaxis were collected by a single person, preventing interobserver variability in data collection.

In conclusion, recipients receiving prophylactic dosages below those recommended by the manufacturers are at an increased risk of experiencing prophylaxis breakthrough. This suggests that low-dose prophylactic regimens are suboptimal in preventing CMV breakthrough in solid organ transplant recipients and highlights the importance of dose adjustment to the latest renal function value (eGFR). The high rate of premature prophylaxis discontinuation, particularly among lung transplant recipients, also justifies the urgent need for novel, less toxic drugs.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M.P. Khurana was responsible for study design, data collection, data analysis and interpretation, and the writing of the manuscript. I.P. Lodding and J.D. Lundgren were responsible for study design, data analysis and interpretation, and the writing of the manuscript. A. Mocroft was involved in the statistical analysis, study design, and writing of the manuscript. F. Gustafsson, M. Perch, A. Rasmussen, and S.S. Sørensen provided scientific input and were involved with the writing of the manuscript.

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