MAJOR ARTICLE

Role of Secondary Prophylaxis With Valganciclovir in the Prevention of Recurrent Cytomegalovirus Disease in Solid Organ Transplant Recipients

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Background. Cytomegalovirus (CMV) is a major contributor to morbidity and mortality in solid organ transplant recipients (SOTRs). Ganciclovir and valganciclovir are highly effective antiviral drugs with a well-established role in primary prophylaxis and treatment of CMV disease. Our objective in this study was to examine the effect of secondary prophylaxis (SP) on the risk of relapse in SOTRs following an episode of CMV disease.

Methods. We performed a retrospective cohort study of SOTRs from 1995 to 2015 and used propensity score–based inverse probability of treatment weighting methodology to control for confounding by indication. A weighted Cox model was created to determine the effect of SP on time to relapse within 1 year of treatment completion.

Results. Fifty-two heart, 34 liver, 79 kidney, and 5 liver–kidney transplant recipients who completed treatment for an episode of CMV infection/disease were included. A total of 120 (70.6%) received SP (median duration, 61 days; range, 5–365) and 39 (23%) relapsed. SP was protective against relapse from 0 to 6 weeks following treatment completion (hazard ratio [HR], 0.19; 95% confidence interval [CI], 0.05–0.69). However, after 6 weeks, risk of relapse did not significantly differ between the 2 groups (HR, 1.18; 95% CI, 0.46–2.99).

Conclusions. Our findings demonstrate that use of SP following treatment of CMV disease did not confer long-term protection against relapse, although it did delay relapse while patients were receiving antivirals. This suggests that SP has limited clinical utility in the overall prevention of recurrent CMV disease.

Keywords. cytomegalovirus; transplant; relapse; valganciclovir; secondary prophylaxis.

Reactivation of latent cytomegalovirus (CMV) infection is a major cause of morbidity, graft loss, and mortality in solid organ transplant recipients (SOTRs). It can result in a diverse array of clinical manifestations that range from a nonspecific febrile illness to severe end organ disease with syndromes such as colitis, pneumonitis, and hepatitis [1]. Treatment protocols are well established and involve a reduction of immunosuppression, where possible, as well as several weeks of intravenous ganciclovir or oral valganciclovir. CMV immune globulin (CMVIG) is occasionally used as adjunctive therapy. The total duration of antiviral therapy is now typically determined by clinical response and resolution of DNAemia [2–4]. Following treatment, relapse occurs in 20%–30%. Several risk factors for relapse that relate to the extent of initial disease and level of immunosuppression have been identified [4]. These include

primary CMV infection, high initial viral load, prolonged DNAemia, persistent DNAemia at treatment completion, multiorgan disease, CMV pneumonitis, treatment for rejection, cadaveric kidney/kidney–pancreas/thoracic organ transplantation, and "extensive disease" in gastrointestinal CMV [2, 5–11].

A key strategy used by many clinicians in the hope of reducing the risk of relapse is secondary prophylaxis (SP) with valganciclovir, where a prophylactic dose is continued following successful treatment [12]. This practice has become widespread with valganciclovir, and is based primarily on extrapolation of prevention of relapse of treated CMV retinitis in patients with AIDS and the success of primary prophylaxis in SOTRs [13–18]. In fact, in the VICTOR trial, all patients received maintenance-dose valganciclovir following treatment [3]. There are no randomized trials that demonstrate efficacy of SP, and most published observational studies show no clear benefit. However, most of these studies had a small sample size, lacked a comparator group, or did not adequately control for potential confounders [6, 9, 19–22]. A recent well-performed retrospective study examined 282 SOTRs with CMV infection (48% with asymptomatic DNAemia), 80% of whom received SP for a median of 50.5 days [22]. Relapse occurred in 32% of patients who received SP vs 23% of those who did not. However, after adjusting for

confounders using multivariate logistic regression, there was no significant difference between the groups ($P = .15$). There was a trend toward a delay in relapse, with a longer time to recurrence from initial viral clearance in those receiving SP (median 69 days vs 44 days; $P = .01$). However, the authors did not control for all potential confounders such as severity of CMV disease, peak viral load, and use of antilymphocyte therapy. Concern for confounding in these studies is particularly relevant as SP is likely to be targeted to those perceived to be at highest risk of relapse, given its cost and potential for bone marrow toxicity [23, 24].

To determine if there is any sustained long-term benefit of SP, we performed a retrospective cohort study of SOTRs who successfully completed treatment for an episode of CMV disease. We compared the time to relapse between those who received SP and those who did not while controlling for confounding by indication using a propensity score–based inverse probability weighting approach.

METHODS

Study Design and Data Collection

The study population included heart, liver, kidney, heart–kidney, and liver–kidney transplant recipients who developed an episode of CMV infection at Tufts Medical Center between 1995 and 2015. Cases were identified by searching electronic medical records for positive test results for CMV, including viral cultures, histopathology, and viral load testing. Patients were excluded if they did not complete a course of antiviral therapy; died, were lost to follow-up, or experienced graft failure during treatment or within 2 weeks following treatment completion; or did not have sufficient clinical information available in the medical records. The Tufts Medical Center Institutional Review Board approved the study. Informed consent was not required given the minimal risk and retrospective nature of the study.

Clinical data were collected through review of hospital medical records. A panel of 3 transplant infectious disease physicians assessed all cases individually to determine if they met our predetermined inclusion and exclusion criteria and whether they received SP. Potential relapses (up to 1 year from the completion of treatment) were evaluated independently, with reviewers blinded to SP status to determine whether they met the definition for relapse.

Immunosuppression, Rejection, and Primary Cytomegalovirus Prophylaxis Protocols

Standard maintenance immunosuppression across all organ types consisted of a calcineurin inhibitor, an antimetabolite, and prednisone. There was a shift from cyclosporine/azathioprine without induction immunosuppression to tacrolimus/mycophenolate with induction using an antilymphocyte agent, routinely in kidney transplant recipients and for calcineurin inhibitor sparing in heart/liver transplant recipients with renal impairment (glomerular filtration rate <30 mL/min, calculated using the Chronic Kidney Disease Epidemiology Collaboration, equation [25]) from approximately year 2000. Antilymphocyte

agents included antithymocyte globulin, OKT3, daclizumab, and basiliximab [26–30].

Primary CMV prophylaxis was routinely used (except in donor and recipient seronegative patients) after it became available around 1995. This consisted of the administration of intravenous (IV) ganciclovir 5 mg/kg once daily, oral ganciclovir 1000 mg 3 times daily, or oral valganciclovir 900 mg once daily, with doses adjusted for renal impairment according to the package insert [23, 24]. Between 1997 and 2002, patients received 3 months of oral ganciclovir; those who were donor seropositive, recipient seronegative (D+/R–) received 7 doses of CMVIG. After 2002, most patients received 3–6 months (longer in high-risk patients) of oral valganciclovir without routine CMVIG (except for D+/R– heart transplant recipients, who continued to receive CMVIG until 2014). There was no routine viral load monitoring after primary prophylaxis, although some patients received this at the discretion of their treating physicians.

All rejection was biopsy proven; if moderate or severe, it was treated with intravenous methylprednisolone 1 g daily for 3–5 days. If there was no initial response, lymphocyte-depleting anti–T-cell therapy (most commonly antithymocyte globulin) was used for cell-mediated rejection or anti–B-cell therapy (rituximab, plasmapheresis, intravenous immunoglobulin ± bortezomib) was used for antibody-mediated rejection. A small number of patients underwent photopheresis for rejection refractory to standard therapy. Patients were defined as having received steroids for rejection if they received IV methylprednisolone or if their oral prednisone dose was increased by ≥3 fold.

Cytomegalovirus Diagnosis and Treatment

CMV infection was defined as a positive test for CMV at any body site. Viral load, viral culture, and histopathologic testing were performed using standard techniques. Over the 20-year study period, the following 3 viral load assays were used: (1) the Hybrid Capture CMV DNA assay (version 2.0), Digene Corp (now Qiagen), Silver Spring, Maryland, a whole blood assay with a detection range of 2.1 to >830 pg/mL (1997–2008); (2) a whole blood assay performed by Quest Diagnostics (Chantilly, Virginia) with a range of detection of 200 to >200 000 copies/mL (2008–2011); or (3) a plasma viral load assay (Simplexa™ CMV Assay, Focus Diagnostics, Cypress, California) with a range of detection of 1000 (values below 1000 can be detected but not quantified) to 500 000 copies/mL (2011–present). Invasive procedures (eg, gastroscopy, colonoscopy, bronchoscopy) were performed as clinically indicated to obtain tissue samples for additional testing. Tissue or cytology specimens were examined for the presence of characteristic CMV inclusion bodies with hematoxylin and eosin staining. Immunohistochemical stains using CMV-specific mouse monoclonal antibodies (Cell Marque, Sigma-Aldrich, Rocklin, California) were performed on request or clinical suspicion. Blood buffy coat, tissue, urine, and bronchoalveolar lavage samples were cultured using the

rapid shell-vial technique and conventional viral culture using human fibroblast cell lines, with CMV detection by direct immunofluorescence using conjugated monoclonal antibodies against CMV immediate early antigen 1 and 2 (Light Diagnostics, EMD Millipore Corporation, Temecula, California).

CMV end organ disease required laboratory confirmation of CMV plus clinical evidence of organ dysfunction, categorized as proven (positive pathology or cultures at a nonblood site with attributable symptoms), probable (DNAemia plus attributable symptoms), or possible (DNAemia with clinical symptoms suggestive of end organ involvement but a potential alternative diagnosis present). Patients with CMV syndrome had detection of CMV in blood plus 2 or more of the following: fever for ≥2 days, new or increased malaise, neutropenia ($<1.5 \times 10^3/$μL) or thrombocytopenia ($<150 \times 10^3/$μL), or elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (>2× upper limit of normal, non-liver recipients only).

Standard treatment of CMV infection was with intravenous ganciclovir 5 mg/kg twice daily or oral valganciclovir 900 mg twice daily, with doses adjusted for renal impairment according to the package insert [23, 24]. Duration of therapy was individualized and determined by clinical and virologic endpoints but was generally at least 2 or 3 weeks. If ganciclovir resistance was suspected, alternative antiviral agents were considered and genotypic testing was performed. The treating clinician determined the frequency of viral load monitoring following treatment completion.

Secondary Prophylaxis

SP was defined as the continuation of IV/oral ganciclovir or oral valganciclovir at the prophylactic dose following treatment completion. The decision to use SP and the duration was made by treating clinicians on an individualized basis.

Relapse

The primary outcome was time to relapse of CMV infection, defined as CMV infection or disease that occurred after the completion of successful treatment of an initial episode of CMV disease. Relapse could occur from any time following treatment completion up to 1 year, including during SP. Patients were considered to have relapsed if they (1) became symptomatic with any positive test for CMV, (2) were asymptomatic but had a single positive viral load test above the lower limit of detection of the assay, or (3) were asymptomatic but had 2 or more consecutively positive tests <1000 copies/mL (assay 3). Asymptomatic patients with a single positive but unquantifiable viral load were not counted as relapses. This definition was adapted from previous published studies and modified to suit our patient population and local diagnostic testing [7, 21, 26, 30, 31]. Censoring occurred at the time of relapse, death, graft loss (return to dialysis in kidney transplant recipients or retransplantation), loss to follow-up, or 1 year following treatment completion, whichever came first.

Statistical Analyses

Basic descriptive statistics were calculated. Categorical data were reported as percentages; continuous data were reported as means ± standard deviations if normally distributed and as medians with ranges if nonnormally distributed. Missing data for the variables of interest were negligible.

To adjust for potential nonrandom use of SP in our cohort, we developed a propensity score and applied it using inverse probability of treatment weighting methodology [32]. Balance between the groups was checked by calculating standardized mean differences (SMDs) across all covariates included in the propensity score (see Supplementary Material). After applying the weights, we performed a Cox proportional hazards analysis to estimate the hazard ratio (HR) associated with SP for the primary outcome. While developing the Cox models, a violation of the proportional hazards assumption was identified, indicating that the effect of SP varied over time. Because more than one-third of patients initially assigned to receive SP had stopped it by 6 weeks, we addressed this by calculating separate HRs for 0 to 6 weeks and 6 weeks to 1 year. Choosing these time periods minimized misclassification but also allowed sufficient time for some events to occur. We also performed a sensitivity analysis, treating SP as a time-dependent variable in a Cox model without propensity score weighting. All analyses were performed with the R statistical software platform, version 3.2.4 (RStudio version 0.99.903).

RESULTS

A total of 246 patients were initially identified from the laboratory database search. However, after review, 10 patients were not eligible for the study and 66 met our exclusion criteria, leaving 170 patients in our final cohort (Figure 1). The average age
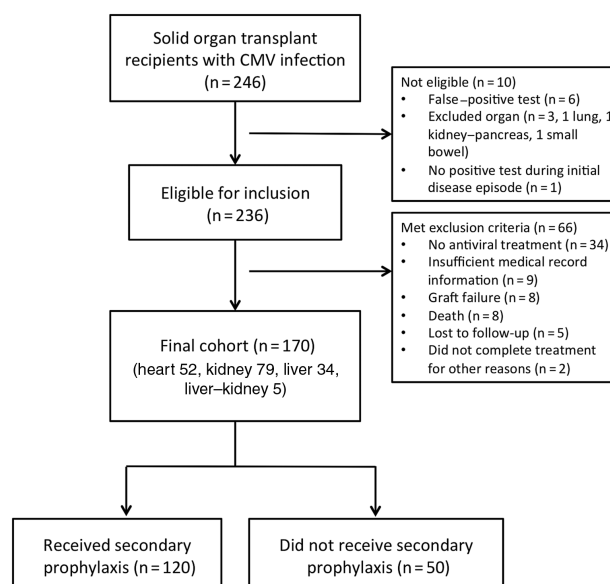
Figure 1. Number and flow of study participants. Abbreviation: CMV, cytomegalovirus.

Table 1. Baseline Characteristics of the Overall Cohort of Solid Organ Transplant Recipients With Cytomegalovirus Disease

Characteristic	Number (%) n = 170
Age at CMV onset (y), mean ± SD	52.5 ± 13.6
Male sex	111 (65.2)
White race (vs nonwhite)	127 (74.7)
Year of CMV disease, median, range	2007, 1995–2016
Previous transplant[a]	16 (9.4)
Transplanted organ	
Heart	52 (30.6)
Liver	34 (20)
Liver–kidney	5 (2.9)
Kidney (living related donor)	15 (8.8)
Kidney (living unrelated donor)	16 (9.4)
Kidney (deceased donor)	48 (28.2)
Receiving hemodialysis during CMV treatment	5 (2.9)
CMV serostatus at time of transplant	
Donor positive, recipient negative	85 (50.0)
Donor positive, recipient positive	53 (31.2)
Donor negative, recipient negative	6 (3.5)
Donor negative, recipient positive	24 (14.1)
Donor unknown, recipient positive	2 (1.2)
Induction immunosuppression with antilymphocyte agent	81 (47.6)
Number of immunosuppressive drugs at treatment completion	
1	13 (7.6)
2	85 (50)
3	72 (42.4)
Antilymphocyte agent within 1 year prior to treatment completion	61 (35.9)
Steroid-treated rejection within 1 year prior to treatment completion	38 (22.4)
Steroid-treated rejection after CMV (to 1 year or relapse)	15 (8.8)
Any antilymphocyte agent after CMV (to 1 year or relapse)	1 (0.6)
Days from transplant to CMV onset, median, range	214.5, 25–7918
Days of symptoms prior to proven onset, median, range	11.5, 0–365
Site of disease	
Asymptomatic	6 (3.5)
CMV syndrome	44 (25.9)
Disseminated	2 (1.2)
Gastrointestinal	111 (65.3)
Lung	7 (4.1)
Type of end organ disease episode	
None	50 (29.4)
Possible	15 (8.8)
Probable	74 (43.5)
Proven	31 (18.2)
Peak viral load, median, range[b]	
Assay 1 (pg/mL, n = 88)	35, 0–831
Assay 2 (copies/mL, n = 23)	5101, 0–200 001
Assay 3 (copies/mL, n = 46)	1343, 0–500 001
Days from diagnosis to start of treatment, median, range	3, –11 to 72
Admitted for CMV	134 (78.8)
Length of stay (days, n = 134), median, range	6, 1–46
Seen in infectious disease outpatient clinic	133 (78.2)
Treatment duration (days), median, range	28.5, 3–201
Treatment type	

Table 1. Continued

Characteristic	Number (%) n = 170
PO only	72 (42.4)
IV and PO	64 (37.6)
IV only	34 (20)
CMV immune globulin used as part of initial treatment	17 (10)
Laboratory results at treatment completion, mean ± SD	
Total white blood cell count (×10³/μL, n = 140)	4.6 ± 2.6
Absolute lymphocyte count (×10³/μL, n = 133)	1.01 ± 0.66
Absolute neutrophil count (×10³/μL, n = 133)	3.01 ± 1.9
Chronic kidney disease epidemiology collaboration estimated glomerular filtration rate (mL/min/1.73m², n = 140)	56.9 ± 25.2
Received SP	120 (70.6)
Duration of SP (days), median, range	60.5, 5-365[c]
Drug received for SP	
IV ganciclovir	2 (1.7)
PO ganciclovir	16 (13.3)
Valganciclovir	102 (85)

Abbreviations: CMV, cytomegalovirus; IV, intravenous; PO, oral; SD, standard deviation; SP, secondary prophylaxis.

[a]Patients who received a transplanted organ prior to the index transplant procedure associated with the episode of CMV.

[b]Refer to descriptions of assays in the Methods section.

[c]Three patients received secondary prophylaxis for more than 1 year but were truncated at 365 days for the purposes of analysis.

at CMV onset was 52.5 ± 13.6 years; there was a male predominance, and three-quarters were white (Table 1). Median time to CMV onset was 7 months. There were 79 (46.5%) kidney, 52 (30.6%) heart, 34 (20%) liver, and 5 (2.9%) combined liver–kidney transplant recipients. A total of 120 patients (70.6%) had evidence of end organ disease, most commonly in the gastrointestinal tract. As defined above, 31 had a proven disease site, 74 a probable site, and 15 a possible site. The majority of patients commenced or completed therapy with oral valganciclovir, though one-fifth received IV ganciclovir alone. Median treatment duration was 28.5 days. Five patients had clinically suspected ganciclovir resistance, 4 of whom received SP. One had a confirmed UL97 mutation but responded to high-dose ganciclovir, and another was treated empirically with foscarnet.

Almost three-quarters of the study cohort received SP; however, there was wide variation in duration, with a mean of 77 ± 70 days (median, 60.5; range, 5–365). One-third of patients had stopped by 6 weeks, half had stopped by 2 months, and three-quarters had stopped by 3 months. Three patients who received SP for more than 1 year were truncated at 365 days for analysis, and none of them relapsed within the year. Patients who received SP were more likely to be white, had their CMV infection more recently, received antilymphocyte therapy within 1 year, commenced antiviral therapy intravenously, and were less likely to have undergone transplantation more than once. These differences are summarized in Table 2. After applying the weights, the SMDs of these variables all decreased, and most other variables had an SMD <0.1.

Table 2. Comparison of Weighted and Unweighted Patient Groups, Stratified by Use of Secondary Prophylaxis, Showing Variables Included in Propensity Score Model

| Characteristic	Unweighted Sample			Weighted Sample		
	Did Not Receive SP (n = 50)	Received SP (n = 120)	SMD	Did Not Receive SP (n = 44.37)	Received SP (n = 117.44)	SMD
Age at CMV onset, y, mean ± SD	52 ± 12	53 ± 14	0.009	53 ± 15	53 ± 14	0.02
Male sex, no. (%)	33 (66.0)	78 (65.0)	0.021	29.3 (66.0)	77.2 (65.7)	0.005
White race (vs nonwhite), no. (%)	34 (68.0)	93 (77.5)	0.215	29.2 (65.9)	84.6 (72.1)	0.133
Previous transplant, no. (%)	7 (14.0)	9 (7.5)	0.211	6.0 (13.4)	12.2 (10.4)	0.095
Year of CMV disease, mean ± SD	2005.64 ± 6.53	2007.37 ± 4.69	0.304	2007.78 ± 5.70	2007.77 ± 5.06	0.001
Transplanted organ, no. (%)						
Heart	17 (34.0)	35 (29.2)	0.115	13.8 (31.1)	35.3 (30.1)	0.175
Liver/liver–kidney	18 (36.0)	45 (37.5)		19.9 (44.8)	45.2 (38.5)	
Kidney (living unrelated)	4 (8.0)	12 (10.0)		3.4 (7.7)	11.0 (9.4)	
Kidney (deceased/LR)	11 (22.0)	28 (23.3)		7.3 (16.4)	26.0 (22.1)	
Receiving hemodialysis during CMV treatment, no. (%)	2 (4.0)	3 (2.5)	0.085	1.0 (2.3)	2.8 (2.4)	0.009
Recipient CMV seronegative, no. (%)	27 (54.0)	64 (53.3)	0.013	20.5 (46.3)	58.5 (49.8)	0.071
Antilymphocyte therapy within 1 year of treatment completion, no. (%)	13 (26.0)	48 (40.0)	0.301	18.3 (41.2)	45.5 (38.7)	0.05
Number of immunosuppressive drugs at treatment completion, mean ± SD	2.34 (0.66)	2.35 (0.60)	0.016	2.34 (0.68)	2.32 (0.60)	0.04
Steroid-treated rejection within 1 year of treatment completion, no. (%)	14 (28.0)	24 (20.0)	0.188	11.0 (24.7)	24.6 (20.9)	0.09
Days from transplant to CMV onset, mean ± SD	777 ± 1462	582 ± 1050	0.153	572 ± 1071	599 ± 1056	0.025
End organ disease, no. (%)	34 (68.0)	86 (71.7)	0.08	30.8 (69.4)	80.8 (68.8)	0.012
Peak viral load, mean ± SD						
Assay 1, number	23 (46.0)	65 (54.2)	0.164	18.4 (41.5)	59.1 (50.3)	0.178
Assay 1, value (pg/mL)	73 ± 181	81 ± 189	0.047	105 ± 235	82 ± 195	0.106
Assay 2, number	3 (6.0)	20 (16.7)	0.341	5.1 (11.4)	16.2 (13.8)	0.07
Assay 2, value (copies/mL)	3069 ± 19852	6621 ± 32999	0.13	2676 ± 15779	5631 ± 29796	0.124
Assay 3, number	15 (30.0)	31 (25.8)	0.093	17.6 (39.7)	37.5 (31.9)	0.164
Assay 3, value (copies/mL)	22544 ± 96136	31604 ± 105979	0.09	21363 ± 78095	26970 ± 98092	0.063
Treatment duration, days, mean ± SD	43 ± 36	37 ± 28	0.179	42 ± 30	39 ± 29	0.086
Treatment type						
PO only	25 (50.0)	47 (39.2)	0.353	20.8 (47.0)	53.9 (45.9)	0.025
IV and PO	13 (26.0)	51 (42.5)		16.6 (37.4)	44.3 (37.7)	
IV only	12 (24.0)	22 (18.3)		6.9 (15.6)	19.2 (16.4)	
CMV immune globulin used as part of initial treatment, no. (%)	6 (12.0)	11 (9.2)	0.092	2.4 (5.5)	8.7 (7.4)	0.078
Chronic kidney disease epidemiology collaboration estimated glomerular filtration rate, mL/min/1.73m^2, mean ± SD	57.1 ± 28.2	56.8 ± 24.5	0.01	58.6 ± 28.1	56.6 ± 25.9	0.074

Abbreviations: CMV, cytomegalovirus; IV, intravenous; LR, living related; PO, oral; SD, standard deviation; SMD, standardized mean difference.

Thirty-nine patients (23%) relapsed within the 1-year follow-up period, with 26/120 (21.7%) patients who received SP experiencing relapse compared to 13/50 (26%) of those who did not receive SP. Four patients relapsed while taking SP; none developed confirmed ganciclovir resistance. Seven patients had asymptomatic DNAemia, 17 had CMV syndrome, and 15 had evidence of end organ disease. Twenty-one patients (12.4%) were censored before 1 year, with 12 deaths, 1 graft failure, 3 lost to follow-up, 4 followed for less than 1 year at the time of analysis, and 1 who restarted SP after initially stopping it. Median time to relapse was 79.5 days (range, 28–314) in those who received SP and 35 days (14–357) in those who did not receive SP.

Figure 2 shows Kaplan-Meier plots of the probability of relapse-free survival in patients who did and did not receive SP, unweighted and after adjustment by weighting. In both groups, most relapses occurred within 100 days. While there appears to be a trend toward decreased probability of relapse among those patients who received SP, these differences were not statistically significant (P = .22 in weighted sample).

Results of the weighted and unweighted Cox models are shown in Table 3. Applying the weights had only a modest effect
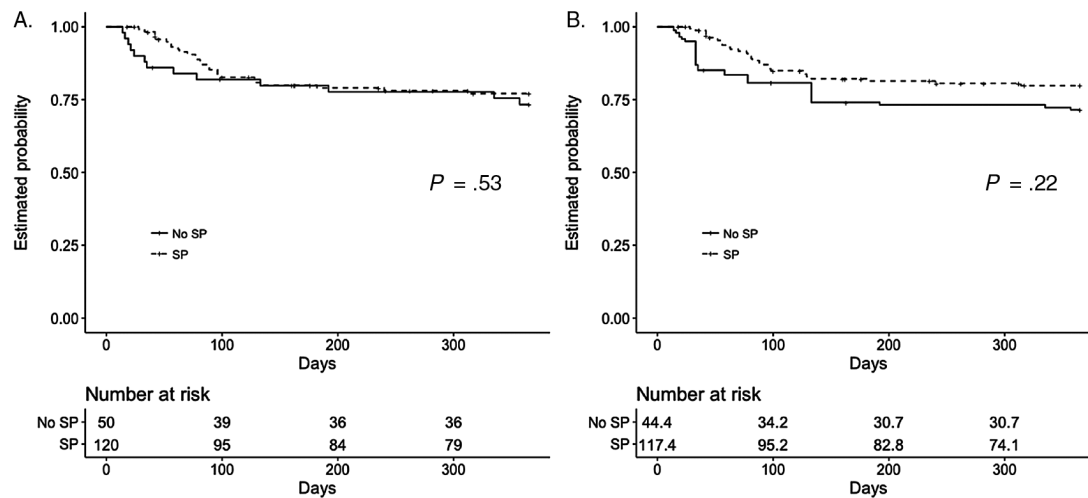
Figure 2. Kaplan-Meier plots showing the estimated probability of relapse-free survival in patients who did and did not receive secondary prophylaxis before (*A*) and after (*B*) adjustment for confounders by propensity score–based inverse probability weighting. *P* values refer to log-rank test results. Abbreviation: SP, secondary prophylaxis.

on the HRs for SP, decreasing them slightly. The weighted HR for the effect of SP on relapse was 0.19 (95% confidence interval [CI], 0.05–0.69) for 0 to 6 weeks and 1.18 (95% CI, 0.0.46–2.99) for 6 weeks to 1 year after treatment completion. This indicates a statistically significant protective effect of SP during the early period (*P* = .01) but no significant difference in likelihood of relapse between those who received and those who did not receive SP during the later period.

Our sensitivity analysis of SP as a time-dependent variable without propensity score weighting showed a strong protective effect while patients remained on therapy (HR, 0.17; 95% CI, 0.06–0.51; *P* < .01).

DISCUSSION

Our findings suggest that the use of SP with valganciclovir following the successful treatment of an episode of CMV disease in SOTRs is associated with reduced risk of early relapse but that this benefit is not sustained long term. Given the risk of long-term toxicities and costs of valganciclovir, our work represents an important contribution to the understanding of the potential benefits of SP. Patients who received SP appeared to have a prolonged time to relapse. However, even after we adjusted for confounding by indication using our statistical approach, we could not detect a significant difference in the overall likelihood of relapse occurring within 1 year. Given that the median duration of SP was only 2 months, this suggests that relapse is unlikely while patients are actively taking SP, but there is limited residual protective effect after cessation. These results are consistent with prior studies of SP, which have generally shown no overall long-term benefit [6, 9, 19, 21, 22].

A major strength of this study was the use of propensity score methodology to control for confounding by indication, which encompassed the measurable clinical factors associated with both use of SP and relapse, which were included in our propensity score model [33]. Failure to control for these confounders has been a limitation of previous studies. In the absence of data from randomized clinical trials, which are unlikely to be forthcoming due to feasibility constraints, applying propensity scores through inverse probability weighting enables the balancing of measured covariates between treatment groups, allowing for a more accurate estimation of true treatment effect, while preserving the original sample size. This methodology is being used in diverse areas of medicine to more closely emulate a randomized clinical trial when only retrospective observational data are available. It offers an advantage over conventional regression models when the number of confounding variables is large relative to the number of outcomes, as they were in this study [34–36].

Our study has some limitations that should be considered when interpreting our findings. While this was a large study, considering the rarity of the disease, statistical power was limited by the sample size of 170 patients, only 50 of whom did not receive SP. Given the retrospective nature of our study, it is possible that there may have been unmeasured confounders that could have influenced treatment allocation that were

Table 3. Unweighted and Weighted Hazard Ratios Showing the Effect of Secondary Prophylaxis in the Early and Late Time Periods

Time period	Unweighted		Weighted	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Early (0–6 weeks)	0.22 (0.06–0.76)	.02	0.19 (0.05–0.69)	.01
Late (6–52 weeks)	1.51 (0.61–3.72)	.37	1.18 (0.46–2.99)	.73

Abbreviations: CI, confidence interval; HR, hazard ratio.

not accounted for in our propensity score model. There were changes in CMV diagnostics, treatment, and immunosuppression protocols over the 20-year study period; changes in viral load testing were particularly challenging to incorporate in a standardized fashion into our models. Patients did not have routine virologic surveillance following primary prophylaxis or treatment completion, so it is possible some cases of asymptomatic viremia were missed. Finally, while we accounted for the time-varying nature of SP, there was wide variation in duration of SP that individual patients received, complicating our analysis.

In conclusion, the results of our study suggest that SP can be used to delay early relapse following CMV infection. However, the effect only persists while patients are maintained on antiviral therapy, which corresponded to a time-limited benefit of approximately 6 weeks in our cohort. While these findings do not support the routine use of short-term SP for all patients, some high-risk patients may benefit from a prolonged course of SP. Future studies to identify predictors of relapse are needed in order to individualize therapy and target those most likely to benefit.

Supplementary Data

Supplementary materials are available at *Clinical 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

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