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MAJOR ARTICLE

Real-World Outcomes Associated With Letermovir Use for Cytomegalovirus Primary Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients: A Systematic Review and Meta-analysis of Observational Studies

Ami Vyas,[1] Amit D. Raval,[2] Shweta Kamat,[1] Kerry LaPlante,[1] Yuexin Tang,[2] and Roy F. Chemaly[3]

[1]Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island, Kingston, Rhode Island, USA, [2]Center for Observational and Real-World Evidence, Merck & Co., Inc., Rahway, New Jersey, USA, and [3]Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Background. A systematic review and meta-analysis of real-world observational studies was conducted to summarize the impact of letermovir cytomegalovirus (CMV) primary prophylaxis (PP) among adult allogeneic hematopoietic cell transplant (allo-HCT) recipients.

Methods. Systematic searches in Medline/PubMed, Embase, and conferences (from database inception to October 2021) were conducted to identify studies for inclusion. Random-effects models were used to derive pooled estimates on the relative effectiveness of letermovir PP compared to controls.

Results. Forty-eight unique studies (N = 7104 patients) were included, most of which were comparative, single-center, and conducted in the United States. Letermovir PP was associated with statistically significant reduction in odds of CMV reactivation (pooled odds ratio [pOR], 0.13 and 0.24; $P < .05$), clinically significant CMV infection (pOR, 0.09 and 0.19; $P < .05$), and CMV disease (pOR, 0.31 and 0.35; $P < .05$) by day +100 and day +200 after allo-HCT, respectively. Letermovir PP was associated with significantly lower odds of all-cause (pOR, 0.73; $P < .01$) and nonrelapse mortality (pOR, 0.65; $P = .01$) beyond day 200 after allo-HCT.

Conclusions. Letermovir for CMV PP was effective in reducing the risk of CMV-related complications overall and mortality beyond day 200 among adult allo-HCT recipients.

Keywords. allogeneic hematopoietic cell transplantation; cytomegalovirus; letermovir; meta-analysis.

INTRODUCTION

Cytomegalovirus (CMV) reactivation is common after allogeneic hematopoietic cell transplantation (allo-HCT) and can lead to serious complications [1, 2]. If left untreated, it can result in tissue-invasive CMV disease [3–6] and can have damaging effects including increased risk of other infections, graft failure, and death [7]. Historically, preemptive therapy (PET) for CMV infection and disease with ganciclovir, valganciclovir, or foscarnet has been utilized to avoid prolonged medication exposure, thereby limiting undesirable myelosuppressive or nephrotoxicity associated with these agents [8–12]. However, PET has shown to increase the risk of neutropenia and acute kidney injury [13], which ultimately increases the risk of mortality [14] and healthcare resource utilization [15–17].

Letermovir was approved by the United States (US) Food and Drug Administration in November 2017 and the European Medicines Agency in January 2018 for the prophylaxis of CMV infection and disease in adult CMV-seropositive (R^+) allo-HCT recipients. A phase 3 trial showed that letermovir primary prophylaxis (PP) reduced clinically significant CMV infection (cs-CMVi) at 24 weeks post-HCT compared to placebo [18]. Additional analysis of the phase 3 dataset showed that patients who received letermovir had lower all-cause mortality at week 24 (10.2% vs 15.9%, $P = .03$) and numerically lower mortality at week 48 ($P > .05$) compared to those who received placebo [19].

Several site-specific real-world studies have been published to evaluate the real-world effectiveness of letermovir PP in allo-HCT recipients, many of which have smaller sample sizes. A comprehensive systematic literature review and meta-analysis of all real-world studies published till recently is yet not available. Such a systematic review and meta-analysis will help better understand the effectiveness of letermovir PP in a

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Correspondence: Ami Vyas, PhD, MS, MBA, Department of Pharmacy Practice, University of Rhode Island College of Pharmacy, 7 Greenhouse Road, Kingston, RI 02881, USA (AVyas@URI.edu).

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larger representative patient sample across multiple study sites. Therefore, we conducted a systematic review and meta-analysis of real-world observational studies focusing on the incidence of CMV reactivation (CMVr), cs-CMVi, and CMV disease (CMVd), other clinical outcomes including mortality, and healthcare resource utilization following PP with letermovir among adult allo-HCT recipients.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [20–22].

Inclusion Criteria for the Systematic Review

Studies eligible for inclusion were prospective or retrospective observational studies published in English language and with no geographical restrictions. We included prospective or retrospective observational studies that used either case-control or cohort design. We included studies with a population of adults undergoing allo-HCT, received letermovir PP for the intervention group, and had no comparator (single-arm study) or had a control group with no letermovir PP (with or without PET). We excluded studies where letermovir was utilized as a secondary prophylaxis or for treatment of CMV infection.

Systematic Literature Search

A comprehensive systematic search of real-world evidence was conducted in Embase and PubMed using a combination of keywords that included "letermovir," "cytomegalovirus or CMV or cytomegaloviral," or "transplant or transplantation" as text words, title/abstract, or exploded terms, from their inception through October 2021. We also searched conference proceedings indexed in Embase as well as specifically searched abstracts and retrieved posters presented at Transplant Cellular Therapy meetings, European Blood and Marrow Transplantation meetings, European Hematology Association Meetings, American Society of Clinical Oncology meetings, and IDWeek meetings using the conference portal and contacting authors for access to full posters. References of the included studies and relevant systematic reviews were also searched for additional studies.

Study Selection, Data Extraction, and Study Quality Assessment

Titles and abstracts of studies were reviewed by 1 of the coauthors (A. V.) to determine eligibility for the full text review based on the predefined criteria. Then, 2 reviewers (A. V. and S. K.) independently examined the full text reports of all the articles that were deemed eligible. Disagreements were resolved through discussion.

Data from all studies that met the eligibility criteria were extracted by 1 reviewer (S. K.) and validated by a second one (A. V.). Data on specific characteristics of the studies, interventions, patients, and outcomes were extracted. For outcomes, data on CMV outcomes (including presence of CMVr, cs-CMVi, and CMVd), indirect outcomes (including graft-vs-host disease [GVHD], all-cause mortality, and nonrelapse mortality) and healthcare resource use and costs (including CMV-related hospitalization) were extracted when available at different time points from allo-HCT (D+100: follow-up of 100 days or 14 weeks; D+200: follow-up of 200 days or 24 weeks; and beyond D+200: follow-up of ≥200 days or ≥24 weeks). Any discrepancies were resolved through discussion and by a third reviewer (K. L.).

Two independent reviewers appraised methodological quality of the eligible real-world observational studies using the Newcastle-Ottawa Scale [23]. Studies with scores ≥7, 4–6, and <4 were considered high, moderate, and low quality, respectively.

Data Synthesis and Statistical Analysis

The feasibility of performing meta-analysis for each outcome was assessed. Any substantial variations in the disease characteristics, time period within which outcomes occurred, and the type of publication were assessed. Based on heterogeneity across studies, we pooled the data from the relevant studies for meta-analysis on each outcome of interest using the random-effects model. Pooled odds ratios (pORs) and the corresponding 95% confidence intervals (CIs) and *P* values for each outcome were determined. Heterogeneity between studies was examined using I^2 statistics and Cochrane χ^2 statistics. Subgroup analyses by country of study (US/non-US), full publication versus abstracts/presentations, studies with R^+-only patients versus R^+ and other risk factors, studies that included cord-blood recipients only, and high-CMV-risk patients only were performed for certain outcomes as we found moderate (30%–60%) to substantial (50%–90%) heterogeneity in the meta-analyses. Publication bias was assessed for cs-CMVi, CMVd, CMVr, and all-cause mortality (outcomes for which >10 studies were available) using Egger method. Additionally, contour-enhanced funnel plots were used to identify publication bias by examining the plot symmetry. Statistical software R was used to perform meta-analyses.

RESULTS

Of 576 retrieved citations identified, 60 citations representing 48 unique studies (see Supplementary Appendix 1 for the list of citations and unique studies) met the inclusion criteria (Figure 1).

Study and Patients' Characteristics

Most of the studies were comparative retrospective cohort studies (n = 40 [83.3%]), were single-center studies (n = 43 [89.6%]), and were conducted in the US (n = 28 [58.3%]), Italy (n = 7 [14.6%]), or Japan (n = 5 [10.4%]) (Table 1).

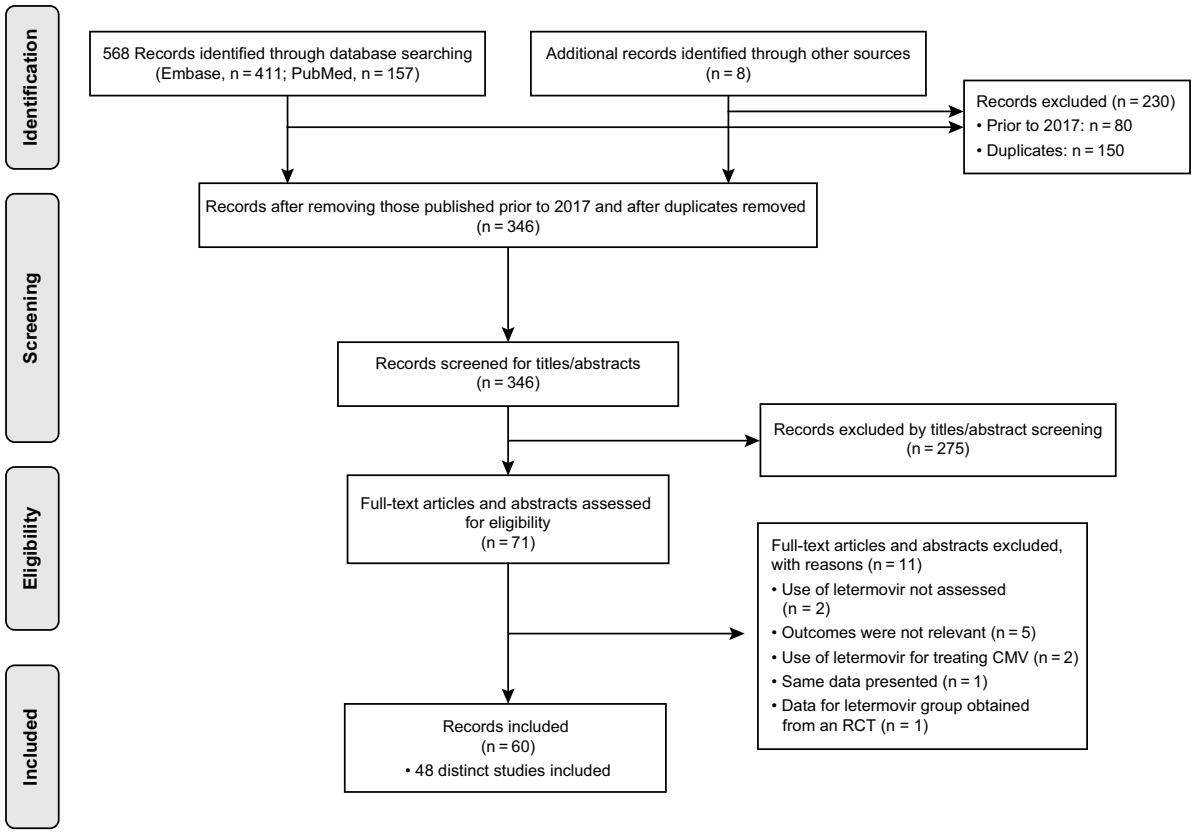

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for study selection. Abbreviations: CMV, cytomegalovirus; RCT, randomized controlled trial.

Twenty-two studies (45.8%) were full publications whereas 26 studies (54.2%) were conference proceedings. The patient sample size ranged from 12 to 204 patients in the letermovir arm and 18 to 637 patients in the control arm. Table 2 lists the CMV serostatus and inclusion–exclusion criteria of patients in each included study. Of the 40 comparative studies, 21 studies had PET historical group as a comparator, 13 had nonletermovir historical group as a comparator, 4 had CMV prophylaxis historical group as a comparator, and 2 had matched historical group as a comparator.

Twenty-seven studies included any type of allo-HCT (56.3%), 3 studies included cord-blood transplant recipients only (6.3%), and 18 studies (37.5%) included haploidentical, cord-blood, or unrelated donor cell recipients, with GVHD, and/or in the setting of posttransplant GVHD prophylaxis or T-cell depletion therapy. Of the 48 studies, 22 (45.8%) included patients who were at high risk of CMV infection and/or disease as per the authors of these studies (Table 3). The median days for initiation of letermovir PP was in the range of 0–42 days posttransplant, while the duration of letermovir prophylaxis ranged between 79 and 191 days.

The median age of patients ranged from 42 to 65 years in the letermovir arm and from 26 to 65 years in the comparator arm (Supplementary Appendix 2). Overall, most of the studies had a higher proportion of patients at high risk of CMVr or CMVd in the letermovir arm compared to the control arm (see footnote of Supplementary Appendix 2).

Quality Assessment of Included Studies

Of all of the studies included in this systematic review, 12 studies (25.0%) were high-quality studies, while 4 studies (8.3%) were low-quality studies and the remaining 32 studies (66.7%) were of moderate quality (Supplementary Appendix 3).

CMV-Related Outcomes

CMV-related outcomes included CMVr, cs-CMVi, and CMVd. In the individual studies that provided a definition of CMVr, CMVr was defined as any DNAemia or viremia in 20 studies, CMV antigenemia in 2 studies, CMV viral load of >500 IU/mL in 1 study, and polymerase chain reaction (PCR) >137 DNA IU/mL in 1 study. In the individual studies that provided a definition of cs-CMVi, cs-CMVi was defined as CMV viremia requiring PET or CMV disease in 30 studies, or CMV viral load >1250 IU/mL in peripheral blood in 1 study. Last, in the individual studies that provided a definition of CMVd, CMVd was defined as CMV end-organ disease in 8 studies, CMV

Table 1. Characteristics of the Included Real-World Studies[a] of Letermovir Primary Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients

Study ID[b]	Country	LET Identification Period	Control Identification Period	Historic Control vs Parallel Control	Total Sample Size, No.	LET, No.	Comparator, No.
Comparative retrospective cohort studies							
Anderson, 2020	US	Mar 2018–Jan 2019	Sep 2012–May 2016	Historic	131	25	106
Derigs, 2021	Germany	Mar 2018–Mar 2019	Jan 2017–Mar 2018	Historic	160	80	80
Sassine, 2021	US	Mar 2016–Feb 2018	Mar 2018–Oct 2018	Historic	537	123	414
Hill, 2021	US	Oct 2018–Dec 2019	2014–2017	Historic	61	21	40
Hosoi, 2020	Japan	Oct 2018–Mar 2020	Oct 2016–Mar 2018	Historic	44	22	22
Johnsrud, 2020	US	Jan 2018–Dec 2019	Jan 2013–May 2019	Historic	745	108	637
Zavras, 2019	US	Dec 2017–2018	2017	Historic	193	98	95
Lin, 2020	US	Jan 2018–2019	2014–2017	Historic	64	32	32
Malagola, 2020	Italy	Dec 2018–Apr 2020	Nov 2017–Nov 2018	Historic	86	45	41
Marzolini, 2021[c]	UK	Jul 2019–Aug 2020	Jan 2006–Feb 2017	Historic	344	110	234
Mori, 2021[c]	Japan	Jan 2015–Mar 2019[d]	…	Historic	685	114	571
Royston, 2021	Switzerland	May 2019–May 2020	Jan 2015–May 2019	Historic	78	26	52
Serio, 2021	Italy	Feb 2012–Sep 2020[d]	…	Historic	35	13	22
Sperotto, 2021	Italy	Jan 2016–Mar 2020[d]	…	Historic	110	55	55
Studer, 2020	Switzerland	2019–2020	2010–2018	Historic	381	28	353
Sharma, 2020	US	2018	Dec 2009–Dec 2018	Historic	133	32	101
Terao, 2021	Japan	2018–Aug 2020	Jan 2014–2018	Historic	48	25	23
Wolfe, 2021	US	Jul 2018–Jun 2020	Jun 2016–Jul 2018	Historic	262	119	143
Archambeau, 2019	US	Mar 2018–Feb 2019	Mar 2017–Feb 2018	Historic	109	42	67
Bradshaw, 2021	US	NR	NR	Historic	91	28	63
Cutini, 2021	Italy	2019–2020	2016–2018	Historic	121	31	90
Dadwal, 2019	US	Feb 2018–Jun 2018	Jan 2017–Feb 2018	Historic	338	59	279
Desnica, 2021	Croatia	Jun 2019–Jun 2020[d]	NR	Historic	NR	90	NR
Dwabe, 2020	US	2018–2020[d]	NR	NR	116	71	45
Faraci, 2021	Italy	2019–Apr 2020	Jan 2015–2019	Historic	93	19	74
Freyer, 2021	US	Feb 2019–May 2020	Feb 2013–Jan 2019	Historic	37	19	18
Hedvat, 2019	US	Nov 2017–Mar 2019	Jul 2016–Nov 2017	Historic	150	50	100
Jinnouchi, 2020	Japan	NR	After 2008	Historic	62	31	31
Karam, 2019	US	2017–2019[d]	…	Historic	104	63	41
Koch, 2021	Germany	Jan 2017–Aug 2020[d]	…	Historic	48	27	21
Lau, 2020	US	Dec 2017–Jun 2019	Mar 2013–Dec 2017	Historic	82	20	62
Loecher, 2020	US	Jun 2018–Jun 2019	Jun 2017–Jun 2018	Historic	67	31	36
Markowski, 2019	US	Jan 2014–Dec 2018[d]	…	Historic	85	15	70
Merchant, 2019	US	Dec 2017–Aug 2018	NR	Historic	65	30	35
Muhsen, 2021	US	Jan 2016–Jun 2020[d]	…	Historic	79	24	55
Myers, 2021	US	NR	NR	Historic	192	38	154
Ngyuen, 2020	Germany	2018+	2013–2017	Historic	347	12	335
Satake, 2020	Japan	May 2018–Aug 2019	Jan 2009–Apr 2018	Historic	NR	27	NR
Shahan, 2021	US	Jul 2019–Oct 2020	Mar 2018–Jun 2019	Historic	59	26	33
Smith, 2021[c]	UK	Jul 2019–Oct 2020[e]	Jan 2004–Feb 2014	Historic	184	60	124
Single-arm retrospective cohort studies							
Abidi, 2021[f]	US	NR	…	NA	26	26	…
Bansal, 2021	US	Jan 2018–Jan 2020	…	NA	20	20	…
Cassaniti, 2021[c]	Italy	NR	…	NA	75	75	…
Chen, 2021	US	Nov 2017–Dec 2019	…	NA	60	60	…
Ferrari, 2019	US	Jan 2018–Sep 2018	…	NA	25	25	…
Kodiyanplakkal, 2019	US	Jan 2018–Jan 2019	…	NA	31	31	…
Paviglianiti, 2021[c]	Italy	Jan 2019–Jun 2020	…	NA	204	204	…
Patel, 2020	US	May 2018–Dec 2019	…	NA	20	20	…
Total sample size	…	…	…	…	7104	2350	4754

Abbreviations: LET, letermovir; NA, not applicable; NR, not reported; UK, United Kingdom; US, United States.

[a]Full publication studies: Anderson 2020, Bansal 2020, Cassaniti 2021, Chen 2021, Derigs 2020, Sassine 2021, Hill 2021, Hosoi 2020, Johnsrud 2020, Zavras 2019, Lin 2020, Malagola 2020, Marzolini 221, Mori 2020, Paviglianiti 2021, Royston 2021, Serio 2021, Sperotto 2021, Studer 2020, Sharma 2020, Terao 2021, Wolfe 2021. Abstract/poster studies: Abidi 2021, Archambeau 2019, Bradshaw 2021, Cutini 2021, Dadwal 2019, Desnica 2021, Dwabe 2020, Faraci 2021, Ferrari 2019, Freyer 2021, Hedvat 2019, Jinnouchi 2020, Karam 2019, Koch 2021, Kodiyanplakkal 2019, Lau 2020, Loecher 2020, Markowski 2019, Muhsen 2021, Myers 2021, Ngyuen 2020, Patel 2020, Satake 2020, Shahan 2021, Smith 2021.

[b]Citations of all the included studies are found in Supplementary Appendix 1.

[c]Multicenter study.

[d]Identification period for both letermovir and comparator groups.

[e]Study focused on adult patients, but LET group included patients in the age range 16–74 years.

[f]Prospective cohort study.

Table 2. Patient Characteristics of the Included Real-World Studies of Letermovir Primary Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients

Study ID[a]	Included CMV Serostatus	Inclusion Criteria	Exclusion Criteria
Comparative retrospective cohort studies			
Anderson, 2020	R^+	Allo-HCT + (HAPLO/UCB/MMURD/prednisone for acute GVHD)	Died within 30 days post-HCT or had active CMV DNAemia at the time of LET initiation or <100 days follow-up
Derigs, 2021	R^+	Allo-HCT	…
Sassine, 2021	R^+	Allo-HCT	R^- recipients
Hill, 2021	R^+	Allo-HCT + UCB	Received CMV treatment at index HCT
Hosoi, 2020	NR	Allo-HCT	Engraftment failure, died, or relapsed within 60 days post-HCT
Johnsrud, 2020	R^+ or D^+	Allo-HCT + (HAPLO/UCB/MMURD/ATG/$CD34^+$ selected graft/considered at high risk by the provider)	Previous transplant; no CMV measurements; participated in RCT
Zavras, 2019	R^+	Allo-HCT + (PB/BM)	UCB recipients
Lin, 2020	R^+	Allo-HCT + (PB/BM) + (HAPLO/HLA MMURD) + PTCy	UCB recipients
Malagola, 2020	R^+ or D^+	Allo-HCT	…
Marzolini, 2021	R^+	Allo-HCT + (alemtuzumab)	…
Mori, 2021	$D^{+/-}$ or $R^{+/-}$	Allo-HCT	Received other prophylactic agent for CMV reactivation, graft failure, or died before engraftment
Royston, 2021	R^+	Allo-HCT	…
Serio, 2021	R^+ or D^+	Allo-HCT	…
Sperotto, 2021	R^+	Allo-HCT + (HAPLO/MMURD/MUD/ATG regimen and/or prednisone treatment)	Died within 29 days post-HCT
Studer, 2020	R^+	Allo-HCT	Survived at least until day +180 without LET prophylaxis
Sharma, 2020	R^+	Allo-HCT + (HAPLO/UCB)	Baseline CMV reactivation, graft failure, death, or relapse before day 100, or participated in CMV prophylaxis trial
Terao, 2021	R^+ or D^+	Allo-HCT + HAPLO + PTCy + PB; Allo-HCT + MRD + PB	…
Wolfe, 2021	R^+	Allo-HCT + acute GVHD	…
Archambeau, 2019	R^+ or D^+	Allo-HCT	CrCl <10 mL/min; severe liver impairment; foscarnet/ganciclovir use within 90 days posttransplant
Bradshaw, 2021	R^+	Allo-HCT	R^- recipients, LET missed/held for ≥5 doses, CMV reactivation prior to LET PP
Cutini, 2021	R^+	Allo-HCT + hematologic malignancies	…
Dadwal, 2019	R^+	Allo-HCT	…
Desnica, 2021	$R^{+/-}$	Allo-HCT	…
Dwabe, 2020	$R^{+/-}$	Allo-HCT	…
Faraci, 2021	R^+/D^-	Allo-HCT	Not able to take oral therapy at day +7 posttransplant or those with major pharmacokinetic interactions
Freyer, 2021	R^+	Allo-HCT + HAPLO + PTCy	…
Hedvat, 2019	R^+	Allo-HCT	…
Jinnouchi, 2020	NR	Allo-HCT	…
Karam, 2019	R^+	Allo-HCT + (HAPLO/UCB/MUD/ATG)	…
Koch, 2021	R^+	Allo-HCT	…
Lau, 2020	R^+	Allo-HCT + CB	…
Loecher, 2020	R^+	Allo-HCT	…
Markowski, 2019	NR	Allo-HCT + (HAPLO/ MUD/MRD) + PTCy	…
Merchant, 2019	R^+ or D^+	Allo-HCT + (HAPLO/UCB/MUD with ATG/ ruxolitinib use/prednisone use)	Active CMV reactivation prior to LET initiation or anti-CMV treatment posttransplant
Muhsen, 2021	R^+	Allo-HCT + unrelated donor + alemtuzumab	…
Myers, 2021	$D^{+/-}$ or $R^{+/-}$	Allo-HCT	…
Ngyuen, 2020	NR	Allo-HCT	…
Satake, 2020	NR	Allo-HCT	…
Shahan, 2021	R^+	Allo-HCT	…
Smith, 2021	R^+	Allo-HCT	…
Single-arm retrospective cohort studies			
Abidi, 2021	R^+	Allo-HCT + (HAPLO/UCB/pre-HCT CMV cell-mediated immunity)	<180 days follow-up posttransplant

Table 2. Continued

Study ID[a]	Included CMV Serostatus	Inclusion Criteria	Exclusion Criteria
Bansal, 2021	R^+	Allo-HCT + (acute/chronic GVHD)	Those without GVHD within 100 days after LET PP
Cassaniti, 2021	R^+	Allo-HCT	Baseline CMV viremia with D0–D5 post-HCT or received CMV treatment at index transplant
Chen, 2021	R^+	Allo-HCT + (HAPLO/MMRD/MMURD/UCB/ GVHD prophylaxis)	Use of secondary prophylaxis; quantifiable CMV DNAemia prior to LET initiation; R^- with high-risk HCT procedure; participation in RCT; <10 days LET PP
Ferrari, 2019	R^+ or D^+	Allo-HCT	Pediatric patients
Kodiyanplakkal, 2019	R^+	Allo-HCT + (rATG/alemtuzumab)	CMV DNA prior to PP
Paviglianiti, 2021	R^+	Allo-HCT	Incomplete data
Patel, 2020	R^+	Allo-HCT + HAPLO	CMV end-organ disease within 6 mo of HCT, history of viremia at any point prior to transplant, received PET within 7 days of transplant

Abbreviations: –, negative; +, positive; Allo-HCT, allogeneic hematopoietic stem cell transplantation; ATG, antithymocyte globulin; BM, bone marrow; CB, cord blood; CMV, cytomegalovirus; CrCl, creatinine clearance; D, donor; GVHD, graft-versus-host disease; HAPLO, haploidentical; HCT, hematopoietic stem cell transplant; HLA, human leukocyte antigen; LET, letermovir; MMURD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; NR, not reported; PB, peripheral blood; PET, preemptive therapy; PP, primary prophylaxis; PTCy, posttransplant cyclophosphamide; R, recipient; rATG, rabbit antithymocyte globulin; RCT, randomized controlled trial; UCB, umbilical cord blood.

[a]Citations of all the included studies are found in Supplementary Appendix 1.

tissue-invasive disease or dysfunction in 2 studies, or presence of appropriate clinical signs and symptoms and/or radiographic findings in an appropriate risk patient plus detection of CMV by rapid culture, direct fluorescent antibody tests, cytology, or detection of CMV by PCR in 1 study.

Table 4 and Figures 2–4 show the pORs for clinical outcomes comparing letermovir PP to the control group among allo-HCT recipients. Letermovir PP was associated with 87% (pOR, 0.13 [95% CI, .08–.22]; $I^2 = 74\%$), 76% (pOR, 0.24 [95% CI, .18–.32]; $I^2 = 0\%$), and 78% (pOR, 0.22 [95% CI, .15–.32]; $I^2 = 55\%$) decreased odds of CMVr at D+100, D +200, and beyond D+200, respectively ($P < .01$; Table 4 and Figure 2). Regarding cs-CMVi, letermovir PP was associated with a 91% (pOR, 0.09 [95% CI, .05–.14]; $I^2 = 76\%$) and 81% (pOR, 0.19 [95% CI, .14–.25]; $I^2 = 47\%$) decreased odds in the random-effects model at D+100 and D+200, respectively ($P < .01$; Figure 3). For CMVd, letermovir PP was associated with a 69% (pOR, 0.31 [95% CI, .12–.77]; $I^2 = 0\%$) and 65% (pOR, 0.35 [95% CI, .16–.78]; $I^2 = 0\%$) decreased odds in the random-effects model at D+100 and D+200, respectively (Figure 4). The findings from the subgroup analyses are available in Table 5.

Time to CMV Reactivation and Duration of CMV Viremia

At D+100, time to CMVr in the letermovir group ranged from a median of 10 days (interquartile range [IQR], 5–38 days) [24] to 38 days (IQR was not reported in these 2 studies) [25, 26]. At D+200, time to any detectable CMV viremia ranged from a median of 19 days (IQR, 14–67 days) [27] to 67 days (IQR, 32–100 days) [28]. At D+100, duration of CMVr was lower in the letermovir group compared to the control group in several studies that reported the data and ranged from a median of 3 days (IQR, 1–24 days) [29] to 29 days (IQR, 26–38 days) [30] in the letermovir group compared to a range of 27 days (IQR, 3–99 days) [29] to 42 days (IQR, 31–54 days) in the control group [30]. The findings remained consistent for the D+200 follow-up as well.

Graft-Versus-Host Disease and Mortality Outcomes

The odds of grade ≥2 GVHD was significantly lower in patients who received letermovir PP compared to those who did not (control group) at D+100 (pOR, 0.52 [95% CI, .32–.86]; $I^2 = 0\%$) (Table 4); however, this finding was not significant for D+200 (pOR, 1.03 [95% CI, .67–1.61]). Letermovir was associated with 30% reduced odds of all-cause mortality at D+100 (pOR, 0.70 [95% CI, .46–1.07]; $P = .1$, $I^2 = 0\%$) (Table 4 and Figure 5). Beyond D+200, letermovir was associated with a significant 27% decreased odds of all-cause mortality (pOR, 0.73 [95% CI, .60–.90]; $P < .01$, $I^2 = 0\%$). The findings remained consistent for nonrelapse mortality (pOR, 0.70, $P = .23$ for D+100, and pOR, 0.65, $P = .01$ for beyond D+200) (Table 4 and Figure 6).

Healthcare Utilization and Costs

The odds of CMV-related hospitalization were significantly lower with letermovir PP at D+100 (pOR, 0.08 [95% CI, .02–.36]; $P < .01$; Table 4); however, the finding was nonsignificant for D+200 follow-up. The duration of CMV-related hospitalization was 35 days in the letermovir group compared to 20 days in the comparator group as reported in 1 study [25]. One US-based study reported letermovir costs of $38 461 for up to D+200 follow-up [31], whereas another US-based study reported letermovir costs of $21 686 for the letermovir group compared to PET costs of $22 466 for the comparator group at D+100 [32].

Table 3. Details of Letermovir Primary Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients

Study ID[a]	Inst. Protocol for LET	Time to Initiate LET, days, Median (Range)/ [IQR]	Duration of LET, days, Median, (Range)/[IQR]	Preparative/ Conditioning Regimen Type	GVHD Prophylaxis	High Risk of CMV	Protocol on Time of Initiation	PET Protocol/Threshold	Comparator Type	Definition of Comparator
Comparative retrospective cohort studies										
Anderson, 2020	…	10 [10–10]	89 [56–93]	MAC, RIC, or NMA	NR	HAPLO, MMURD, UCB, acute GVHD requiring prednisone	D10–D100	CMV VL ≥200 IU/mL on 2 consecutive tests	HC: PET	PET treatment as per local protocol
Derigs, 2021	R^+	19	NR	MAC or RIC	Cyc + MTX; Cyc + MMF; TAC + MTX; TAC + MMF	…	D0–D100	CMV VL >3200 IU/mL	HC: PET	VAL, GAN, FOS
Sassine, 2021	R^+	NR	NR	MAC or RIC or NMA	TAC/MTX; ATG/TAC/ MTX; PTCy/TAC; PTCy/TAC/MMF; TAC/MMF; ATG/TAC/ MMF	…	D5–D100 +	CMV monitoring twice weekly by PCR in plasma	HC: PET	VAL, GAN, FOS
Hill, 2021	…	NR	97 [88–98]	MAC or NMA	NR	CB	D1–D100	CMV VL ≥150 IU/mL between days D1–D98 and ≥500 IU/mL thereafter	HC: CMV prophylaxis	High-dose VAL; patients who could not tolerate VAL continued on high-dose VALA
Hosoi, 2020	…	NR	NR	MAC or RIC	TAC + MTX; TAC + MMF; Cyc + MTX; Cyc + MMF	…	NR	…	HC: non-LET	…
Johnsrud, 2020	(R^+/D^+ or R^+/D^- or R^-D^+) and (HAPLO/UCB/ ATG/$CD34^+$/ MMRD/ MMURD)	NR	100 (3–347)	MAC or RIC or NMA	CNI; CNI + MMF; CNI + MTX; SIRO	HAPLO, CB, ATG regimen, $CD34^+$ selected graft, MMRD/MMURD	D1–D100	CMV VL >400 IU/mL	HC: PET	VAL, GAN, FOS
Zavras 2019	…	NR	NR	MAC or RIC	NR	HAPLO, mismatched, T-cell–depleted graft	D7–D100 +	>2 consecutive values of CMV VL >300 IU/mL	HC: PET	VAL, GAN, FOS
Lin, 2020	…	7 (5–12)	191 (16–796)	MAC, RIC, or NMA	PTCy	(HAPLO or HLA MMURD) + PTCy	D7–D180	2 consecutive values of CMV VL >300 IU/mL or a single CMV VL >1000 IU/mL	HC: PET	VAL, FOS
Malagola, 2020	R^+ or (R^+/D^-, mismatch donor, GVHD)	NR	100 [40–100]	MAC or RIC	Local guidelines and protocols	R^+, R^+/D^-, mismatched donor, GVHD	D0–D100 +	2 consecutive tests with CMV VL >1000 copies/mL	HC: PET	VAL, GAN, FOS
Marzolini, 2021	…	NR	NR	MAC or RIC	Alemtuzumab	…	D0–D100	…	HC: non-LET	Alemtuzumab-based T-cell–depleted and no LET
Mori, 2021	Physician's choice guided by stem cell course, HLA parity, or CMV serostatus	0 (0–35)	92 (5–108)	MAC or RIC	Cyc/TAC; MTX; MMF; mPSL; ATG; PTCy	HAPLO, HLA Mismatched, CB, grade ≥2 GVHD requiring corticosteroid	D0–D100 +	≥2 CMV antigen-positive cells per 50 000 WBCs detected	HC: PET	IV GAN, FOS, oral VAL
Royston, 2021	(R^+/D^-) or (R^+ with early grade 2+ GVHD requiring prednisone treatment)	NR	98[b] (4–258)	MAC or RIC	NR	D^-/R^+, R^+ with early grade ≥2 GVHD requiring corticosteroids	D1–D100	CMV VL >150 IU/mL and/or evidence of CMV syndrome/ disease	Matched HC: PET	VAL, GAN, FOS
Serio, 2021	…	7 (3–10)	NR	MAC or RIC	Cyc; Cyc + MTX; Cyc + MMF + Cys; ATG	R^+	D7–D100	…	HC: PET	VAL
Sperotto, 2021	…	NR (1–8)	NR	MAC or RIC	Cyc + MTX + ATG; TAC + MTX + ATG;TAC + MMF + Cys	R^+, HAPLO, MMURD, ATG regimen, prednisone treatment	D3–D100	CMV VL >150 copies/mL for high risk; >300 copies/mL for low-risk CMVr and CMVd	HC: PET	VAL, GAN, FOS
Studer, 2020	…	NR	98 (5–153)	MAC or NMA	MAC + Cyc + MTX; MAC + Cyc + MTX + ATG; Flu + Bu + Cyc + MTX + ATG; FluTBI + Cyc + MMF	…	D0–D100	CMV DNAemia >1000 copies/mL determined twice	HC: PET	VAL, GAN, FOS

Table 3. Continued

Study ID[a]	Inst. Protocol for LET	Time to Initiate LET, days, Median (Range)/ [IQR]	Duration of LET, days, Median, (Range)/[IQR]	Preparative/ Conditioning Regimen Type	GVHD Prophylaxis	High Risk of CMV	Protocol on Time of Initiation	PET Protocol/Threshold	Comparator Type	Definition of Comparator
Sharma, 2020	R^+ with CBT	NR	NR	MAC or NMA	Cyc + MMF	R^+ (HAPLO, CB)	D0–D100	CMV DNAemia > 10 000 IU/mL whole blood, any repeat PCR value >5000 IU/mL following an initial positive, or evidence of end-organ involvement	HC: CMV prophylaxis	VALA; prior to Nov 2016, GAN
Terao, 2021	…	NR	95	MAC or RIC	MTX + CNI, MMF + CNI; high-dose PTCy + TAC + MMF	…	…	…	HC: non-LET	…
Wolfe, 2021	Allo-HCT	NR	97	MAC or RIC	TAC + MTX; TAC + SIRO; TAC + MMF; PTCy	GVHD	NR	As used in Marty et al RCT	HC: PET	VAL, GAN, FOS
Archambeau, 2019	…	NR	NR	…	NR	R^+ or D^+	NR	…	HC: non-LET	…
Bradshaw, 2021	R^+	NR	NR	MAC or RIC	NR	…	NR	…	HC: PET	VAL, GAN, FOS
Cutini, 2021	…	NR	NR	…	NR	…	D2–D100	…	HC: non-LET	…
Dadwal, 2019	…	13 (4–26)	NR	MAC or NMA	Cellcept, MTX, TAC/ SIRO	HAPLO, CB, ATG use, GVHD onset prior to CMV infection and LET	NR	CMV VL >1250 IU/mL in high-risk and >3750 IU/mL in low-risk HCT	HC: PET	GAN, FOS
Desnica, 2021	…	9 (5–28)	NR	RIC or others	…	…	NR	…	HC: PET	Not specified
Dwabe, 2020	…	NR	NR	MAC or RIC	NR	CMV positive, T-cell–depleting therapies (PTCy and/or ATG), a related donor with at least 1 mismatch at 1 of the specified 3 HLA gene loci (HLA-A, -B, or -DR), an unrelated donor with at least 1 mismatch at 1 of the specified 4 HLA gene loci (HLA-A, -B, -C, and -DRB1), HAPLO, CB, grade ≥2 GVHD	NR	…	Non-LET	…
Faraci, 2021	…	11 (5–27)	89 (40–113)	…	NR	R^+/D^-	NR	…	HC: PET	Not specified
Freyer, 2021	…	NR	NR	RIC or others	TAC, MMF, PTCy	HAPLO + PTCy	D10–D100	CMV VL ≥137 IU/mL[c]	HC: CMV prophylaxis	High-dose VALA
Hedvat, 2019	…	2[b] (−6–24)	NR	MAC or others	TAC/MTX; TAC/MMF/ Cys	…	NR	…	HC: PET	Not specified
Jinnouchi, 2020	…	NR	NR	MAC or RIC	TAC + MTX; TAC + MTX + ATG	…	NR	At least 1 pp65 antigen-positive cell per 50 000 leukocytes[c]	Matched HC: non-LET	…
Karam, 2019	…	NR	NR	…	NR	HAPLO, MUD, CB, or ATG use	NR	…	HC: PET	Not specified
Koch, 2021	…	NR	NR	…	NR	…	NR	CMV copies >1250 IU/mL in PB[c]	HC: non-LET	…
Lau, 2020	…	NR	IV: 15 (0–35) Oral: 79 (0–94)	…	Cys/Flu/Thio/TBI + Cyc/ MMF, tocilizumab (LET group only)	CB	D7–D100	…	HC: PET	VAL, GAN, FOS
Loecher, 2020	…	NR	96 [66–116]	MAC or RIC	NR	…	D10–D100	…	HC: non-LET	…
Markowski, 2019	…	NR	NR	…	PTCy	…	NR	…	HC: non-LET	…
Merchant, 2019	…	32 (5–40)	NR	…	NR	(HAPLO, CB, MUD recipient with thymoglobulin administration, ruxolitinib initiation, prednisone equivalent)	NR	CMV VL >500 IU/mL[c]	HC: CMV prophylaxis	High-dose VALA
Muhsen, 2021	…	15 (12–41)	124 (43–270)	…	NR	MMURD/MUD + T-cell depletion with alemtuzumab	NR	…	HC: PET	Not specified
Myers, 2021	…	NR	NR	MAC or others	NR	…	NR	…	HC: non-LET	…
Ngyuen, 2020	…	NR	NR	…	NR	R^+/D^- and/or HLA mismatch	NR	CMV VL >10 copies/μg DNA in 2 consecutive PCRs[c]	HC: PET	Not specified

Table 3. Continued

Study ID[a]	Inst. Protocol for LET	Time to Initiate LET, days, Median (Range)/[IQR]	Duration of LET, days, Median, (Range)/[IQR]	Preparative/ Conditioning Regimen Type	GVHD Prophylaxis	High Risk of CMV	Protocol on Time of Initiation	PET Protocol/Threshold	Comparator Type	Definition of Comparator
Satake, 2020	…	NR	NR	RIC	NR	Related HLA 1 loci mismatch (HLA-A, -B, -DRB1), HAPLO, unrelated HLA 1 loci mismatch (HLA-A, -B, -DRB1), UBC, ex-vivo T-cell–depleted graft, grade ≥2 GVHD with prednisone use	Starting on D0	…	HC: non-LET	…
Shahan, 2021	…	NR	NR	…	NR	…	NR	…	HC: non-LET	…
Smith, 2021	…	NR	NR	MAC or RIC	NR	…	NR	…	HC: non-LET	…
Single-Arm Retrospective Studies										
Abidi, 2021	R^+	…	NR	…	Cyc + MMF	R^+ (Haplocord, Dualcord)	Through D100	…	NA	…
Bansal, 2021[d]	R^+	NR	182 (107–576+)	MAC or RIC	TAC/MTX; TAC/MMF/ PTCy; alemtuzumab; TAC/MMF	Acute GVHD or Chronic GVHD	D5–D100 +	Within 100 days post-HCT: CMV VL ≥500 IU/mL or for 2 consecutive values of ≥137 IU/mL + physician judgment; past 100 days HCT: CMV VL ≥137 IU/mL for 2 consecutive values or for a single value ≥1000 IU/mL + physician judgment	NA	…
Cassaniti, 2021	…	4 [1–14]	105 [101–114]	MAC or RIC	Cyc + MXT; Cyc + MXT + MMF/ATG; Cyc + PTCy + MMF; PTCy + SIRO	…	D0/28–D100	CMV VL >10 000 copies/mL whole blood	NA	…
Chen, 2021	R^+ at high risk of CMVr based on graft source, conditioning regimen, GVHD prophylaxis	8 (0–43)	92 (10–504)	MAC or RIC	PTCy + TAC + MMF; TAC + MTX; MTX + TAC + SIRO; TAC + MMF; TAC + MMF + MTX; PTCy; TAC + SIRO; PTCy + MMF + SIRO	Based on Marty et al RCT	D7–D100 +	CMV VL >137 IU/mL (151 copies/mL)	NA	…
Ferrari, 2019	R^+ or R^-/D^+	5 (0–20)	79 (20–110)	MAC or others	TAC or Cyc, MTX, MMF	…	Through D100	…	NA	…
Kodiyanplakkal, 2019	R^+	…	NR	MAC or RIC	Alemtuzumab	T-cell depletion with alemtuzumab for related and HLA-identical unrelated transplant recipients; ATG for UCB transplant recipients	NR	…	NA	…
Paviglianiti, 2021	R^+	…	93 (5–100)	MAC or RIC	Cyc + MTX; Cyc; Cyc + MMF; TAC	HAPLO, CB, HLA-related donor with at least 1 mismatch at HLA-A, -B, or -DR loci, unrelated donor with at least 1 mismatch at HLA-A, -B, -C. or -DRB, ex-vivo T-cell–depleted grafts, ≥2 grade GVHD requiring corticosteroids	D0–D100	2 consecutive values of CMV DNAemia level >1000 copies/mL in plasma or 10 000 copies/mL in whole blood	NA	…
Patel, 2020	…	…	NR	MAC or RIC	TAC + MMF + PTCy	HAPLO	D16–D100	…	NA	…

Abbreviations: allo-HCT, allogeneic hematopoietic stem cell transplant; ATG, antithymocyte globulin; Bu, busulfan; CB, cord blood; CBT, cord blood transplantation; CMV, cytomegalovirus; CMVd, cytomegalovirus disease; CMVr, cytomegalovirus reactivation; CNI, calcineurin inhibitor; Cyc, cyclosporine A; Cys, cyclophosphamide; D, donor; Flu, fludarabine; FluTBI, fludarabine with total body irradiation; FOS, foscarnet; GAN, ganciclovir; GVHD, graft-versus-host disease; HAPLO, haploidentical donor; HC, historical cohort; HCT, hematopoietic stem cell transplant; HLA, human leukocyte antigen; Inst, institution; IQR, interquartile range; IV, intravenous; LET, letermovir; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MMRD, mismatched related donor; MMURD, mismatched unrelated donor; mPSL, methylprednisolone; MTX, methotrexate; MUD, matched unrelated donor; NMA, nonmyeloablative conditioning; NR, not reported; PB, peripheral blood; PCR, polymerase chain reaction; PET, preemptive therapy; PTCy, posttransplant cyclophosphamide; R, recipient; RCT, randomized controlled trial; RIC, reduced-intensity conditioning; SIRO, sirolimus; TAC, tacrolimus; TBI, total body irradiation; Thio, Thiotepa; UCB, umbilical cord blood; VAL, valganciclovir; VALA, valacyclovir; VL, viral load; WBC, white blood cell.

[a]Citations of all the included studies are found in Supplementary Appendix 1.

[b]Mean value.

[c]CMV viremia/CMV reactivation.

[d]All studies with LET use for primary prophylaxis except the Bansal 2020 study focused on letermovir use for extended primary prophylaxis.

Table 4. Pooled Absolute Event Rates[a] and Odds Ratios for Clinical Outcomes Comparing Letermovir With Controls Among Allogeneic Hematopoietic Cell Transplant Recipients

	Absolute Effect—Letermovir		Absolute Effect—Control		Random-Effects Model				Publication Bias
Outcome	No. of Studies/Sample Size	Pooled % (95% CI)	No. of Studies/Sample Size	Pooled %(95% CI)	No. of Studies/Sample Size	Pooled OR (95% CI)	*P* Value	NNT(95% CI)	EggerTest
CMV reactivation									…
D+100	25/1204	24% (19%–28%)**	18/2221	62% (52%–71%)**	18/3054	0.13 (.08–.22)**	<.01	2.29 (2.00–2.85)	Significant[b]
D+200	15/806	32% (24%–37%)**	5/942	69% (62%–75%)**	5/1297	0.24 (.18–.32)	<.01	2.92 (2.49–3.60)	NA
Beyond D +200	17/849	32% (36%–36%)**	8/1601	69% (57%–79%)**	8/2109	0.22 (.15–.32)*	<.01	2.75 (2.28–3.61)	NS
Clinically significant CMV infection									…
D+100	27/1548	11% (9%–12%)*	21/2857	57% (48%–65%)**	21/3993	0.09 (.05–.14)**	< .01	2.16 (2.00–2.45)	NS
D+200	19/1165	23% (17%–28%)**	14/1951	64% (52%–74%)**	14/2771	0.19 (.14–.25)*	<.01	2.56 (2.26–3.02)	NS
CMV disease									
D+100	16/894	1% (0%–3%)	12/1272	5% (3%–7%)	10/1838	0.31 (.12–.77)	.0125	38.92 (30.52–121.89)	NS
D+200	12/674	2% (1%–5%)	7/938	9% (7%–11%)*	7/1261	0.35 (.16–.78)	.01	22.00 (16.67–68.01)	NA
All-cause mortality									
D+100	9/757	10% (7%–17%)*	5/1337	12% (9%–16%)**	5/1723	0.70 (.46–1.07)	.1	30.52 (–133.60 to 16)	NA
Beyond D +200	17/1060	22% (18%–27%)**	15/1845	30% (22%–39%)**	15/2685	0.73 (.60–.90)	<.01	15.99 (10.11–44.78)	NS
Nonrelapse mortality									
D+100	5/449	7% (4%–13%)*	4/640	10% (6%–18%)**	3/889	0.70 (.39–1.25)	.23	40.20 (–51.20 to 19.37)	NA
Beyond D +200	8/708	11% (8%–14%)*	6/1341	18% (12%–26%)**	6/1829	0.65 (.47–.90)	.01	17.04 (10.79–64.21)	NA
Grade ≥2 GVHD									
D+100	6/199	18% (10%–30%)**	6/272	30% (16%–48%)**	6/471	0.52 (.32–.85)	<.01	8.23 (5.34–30.43)	NA
D+200	3/354	20% (0%–10%)**	2/179	50% (38%–62%)*	2/329	1.03 (.67–1.61)	>.05	–116.21 (–8.51 to 10.10)	NA
CMV-related hospitalization									
D+100	3/238	0% (0%–3%)	3/817	8% (3%–21%)*	3/1055	0.08 (.02–.36)	<.01	12.72 (11.81–18.57)	NA
D+200	2/81	2% (0%–10%)	2/136	6% (0%–39%)**	2/217	0.22 (.04–1.31)	>.05	14.10 (–39.66 to 11.18)	NA

Heterogeneity was examined as I^2 statistic along with other parameter as per the Cochrane Handbook for systematic reviews: *30%–60% may represent moderate heterogeneity; **50%–90%, substantial heterogeneity; 75%–100%, considerable heterogeneity. CMV reactivation indicates any CMV DNAemia or viremia; clinically significant CMV infection indicates CMV DNAemia or viremia requiring preemptive therapy. Follow-up periods were as follows: D+100, follow-up of 100 days or 14 weeks; D+200, follow-up of 200 days or 24 weeks; beyond D+100, follow-up of ≥100 days or ≥14 weeks; beyond D+200, follow-up of ≥200 days or ≥24 weeks.

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; GVHD, graft vs host disease; NA, not applicable; NNT, number needed to treat; NS, not significant; OR, odds ratio.

[a]Event rate indicates number of patients with outcome over the sample size in each treatment group.

[b]A trim and fill analysis eliminated publication bias ($P = .67$).

Table 5. Pooled Odds Ratios on Clinical Outcomes Comparing Letermovir With the Control Group in Different Subgroups of Allogeneic Hemopoietic Cell Transplant Recipients

			Relative Effect (RE Model)				
Outcome	Duration[a]	Subgroups	No. of Studies	No. of Patients	Pooled OR (95% CI)	*P* Value	I^2
CMV reactivation	D+100		18	3054	0.13 (.08–.22)	<.01	74%
		Full publication	10	2083	0.19 (.12–.32)	<.01	60%
		Abstracts	8	971	0.09 (.03–.22)	<.01	80%
		US-based studies	11	1988	0.27 (.20–.36)	<.05	27%
		Non-US-based studies	7	1066	0.05 (.02–.14)	<.01	77%
		R^+-only studies	9	1670	0.11 (.04–.29)	<.01	85%
		Studies with R^+ and others	9	1384	0.17 (.11–.27)	<.01	44%
		High-risk population	8	1361	0.15 (.08–.26)	<.01	58%
		Cord blood only (100% cord blood)	2	194	0.24 (.08–.69)	<.05	46%
		Posttransplant cyclophosphamide	3	155	0.09 (.02–.43)	<.05	57%
	D+200		5	1297	0.24 (.18–.32)	<.01	0%
		Full publication	3	926	0.28 (.20–.39)	<.01	0%
		Abstracts	2	371	0.16 (.07–.35)	<.01	43%
		US-based studies	3	502	0.20 (.13–.30)	<.01	11%
		Non-US-based studies	2	795	0.28 (.19–.40)	<.01	0%
		R^+-only studies	3	904	0.25 (.18–.36)	<.01	42%
		Studies with R^+ and others	2	393	0.22 (.14–.35)	<.01	0%
		High-risk population	2	241	0.28 (.16–.51)	<.05	0%
	Beyond D+200		8	2109	0.22 (.15–.32)	<.01	55%
		Full publication	4	1270	0.22 (.14–.35)	<.01	53%
		Abstracts	4	839	0.22 (.09–.54)	<.05	68%
		US-based studies	3	502	0.20 (.13–.30)	<.01	11%
		Non-US-based studies	5	1607	0.24 (.13–.45)	<.05	70%
		R^+-only studies	5	1372	0.25 (.13–.47)	<.05	59%
		Studies with R^+ and others	3	737	0.18 (.11–.28)	<.01	37%
		High-risk population	2	241	0.28 (.16–.51)	<.05	0%
Clinically significant CMV infection	D+100		21	3993	0.09 (.05–.14)	< .01	76%
		Full publication	11	3139	0.08 (.05–.14)	<.01	69%
		Abstracts	10	854	0.08 (.03–.22)	<.01	81%
		US-based studies	14	2523	0.11 (.06–.20)	<.01	72%
		Non-US-based studies	7	1490	0.06 (.02–.13)	<.01	79%
		R^+-only studies	10	2127	0.11 (.05–.25)	<.01	81%
		Studies with R^+ and others	11	1866	0.06 (.04–.11)	<.01	56%
		High-risk population	11	1638	0.10 (.05–.22)	<.01	73%
		Cord blood only (100% cord blood)	3	276	0.05 (.01–.32)	<.01	48%
		Posttransplant cyclophosphamide	2	101	0.07 (.02–.21)	<.01	0%
	D+200		14	2771	0.19 (.14–.25)	<.01	47%
		Full publication	8	1986	0.17 (.11–.27)	<.01	65%
		Abstracts	6	785	0.21 (.15–.30)	<.01	0%
		US-based studies	9	1485	0.20 (.16–.27)	<.01	21%
		Non-US-based studies	5	1286	0.16 (.09–.28)	<.01	70%
		R^+-only studies	6	1641	0.22 (.17–.29)	<.01	0%
		Studies with R^+ and others	8	1130	0.16 (.10–.27)	<.01	60%
		High-risk population	6	524	0.17 (.09–.33)	<.01	55%
CMV disease	D+100		10	1838	0.31 (.12–.77)	.0125	0%
		Full publication	7	1507	0.22 (.07–.65)	<.05	0%
		Abstracts	3	331	0.75 (.11–5.37)	>.05	17%
		US-based studies	6	1405	0.37 (.11–1.26)	>.05	0%
		Non-US-based studies	4	433	0.23 (.06–.98)	<.05	0%
		R^+-only studies	5	675	0.49 (.13–1.84)	>.05	0%
		Studies with R^+ and others	5	1163	0.19 (.05–.71)	<.05	0%
		High-risk population	6	1258	0.23 (.07–.75)	<.05	0%
		Cord blood only (100% cord blood)	2	143	0.30 (.04–2.51)	>.05	0%

Table 5. Continued

Outcome	Duration[a]	Subgroups	Relative Effect (RE Model)				
			No. of Studies	No. of Patients	Pooled OR (95% CI)	*P* Value	I^2
	D+200		7	1261	0.35 (.16–.78)	.0105	0%
		Full publication	5	1044	0.31 (.13–.75)	<.05	0%
		Abstracts	2	217	0.91 (.03–24.37)	>.05	65%
		US-based studies	4	412	0.69 (.17–2.77)	>.05	0%
		Non-US-based studies	3	849	0.25 (.09–.67)	<.05	0%
		R^+-only studies	3	902	0.35 (.13–.94)	<.05	41%
		Studies with R^+ and others	4	359	0.36 (.10–1.38)	>.05	0%
		High-risk population	4	359	0.36 (.10–1.38)	>.05	0%
All-cause mortality	D+100		5	1723	0.70 (.46–1.07)	.10	0%
		Full publication	4	1573	0.61 (.38–.95)	<.05	0%
		Abstracts	1	150	1.81 (.57–5.71)	.31	NA
		US-based studies	4	1563	0.73 (.46–1.17)	.3	19%
		Non-US-based studies	1	160	0.55 (.15–1.95)	>.05	NA
		R^+-only studies	3	847	0.78 (.38–1.61)	.21	35%
		Studies with R^+ and others	2	876	0.66 (.34–1.25)	.4	0%
		High-risk population	2	876	0.66 (.34–1.25)	.4	0%
	Beyond D+200		15	2685	0.73 (.60–.90)	<.01	0%
		Full publication	9	1933	0.72 (.57–.92)	<.05	0%
		Abstracts	6	752	0.81 (.48–1.39)	.12	43%
		US-based studies	9	1569	0.83 (.65–1.07)	.43	1%
		Non-US-based studies	6	1116	0.59 (.42–.82)	<.05	0%
		R^+-only studies	10	2017	0.75 (.59–.96)	<.05	14%
		Studies with R^+ and others	5	668	0.70 (.49–1.00)	<.05	0%
		High-risk population	6	632	0.79 (.54–1.17)	.67	0%
Nonrelapse mortality	D+100		3	889	0.70 (.39–1.25)	.23	0%
		US-based studies	2	729	0.72 (.38–1.38)	.31	3%
		Non-US-based studies	1	160	0.58 (.13–2.53)	>.05	NA
		R^+-only studies	2	697	0.57 (.29–1.14)	.58	0%
		Studies with R^+ and others	1	192	1.14 (.38–3.43)	.49	NA
		High-risk population	1	192	1.14 (.38–3.43)	.49	NA
		Beyond D+200	6	1829	0.65 (.47–.90)	.01	0%
		Full publication	4	1513	0.62 (.43–.90)	<.05	0%
		Abstracts	2	316	0.77 (.37–1.60)	>.05	0%
		US-based studies	3	930	0.69 (.46–1.05)	>.05	0%
		Non-US-based studies	3	899	0.59 (.35–1.00)	<.05	0%
		R^+-only studies	4	1436	0.61 (.42–.89)	<.05	0%
		Studies with R^+ and others	2	393	0.78 (.41–1.47)	>.05	0%
		High-risk population	1	131	0.70 (.27–1.82)	>.05	NA
Grade ≥2 GVHD	D+100		6	471	0.52 (.32–.86)	.0098	0%
		Full publication	2	177	0.34 (.11–1.08)	>.05	50%
		Abstracts	4	294	0.66 (.34–1.30)	>.05	0%
		US-based studies	4	365	0.69 (.39–1.23)	>.05	0%
		Non-US-based studies	2	106	0.25 (.10–.65)	<.05	0%
		R^+-only studies	3	222	0.33 (.15–.77)	<.05	11%
		Studies with R^+ and others	3	249	0.66 (.36–1.23)	>.05	0%
		High-risk population	4	365	0.69 (.39–1.23)	>.05	0%

Heterogeneity was examined as I^2 statistic along with other parameter as per the Cochrane Handbook for systematic reviews: 30%–60% may represent moderate heterogeneity; 50%–90%, substantial heterogeneity; 75%–100%, considerable heterogeneity. CMV reactivation indicates any CMV DNAemia or viremia; clinically significant CMV infection indicates CMV DNAemia or viremia requiring preemptive therapy.

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; GVHD, graft-versus-host disease; NA, not applicable; OR, odds ratio; RE, random effects; US, United States.

[a]Durations: D+100, follow-up of 100 days or 14 weeks; D+200, follow-up of 200 days or 24 weeks; beyond D+200, follow-up of ≥200 days or ≥24 weeks.

DISCUSSION

This systematic review aimed to understand the current and real-world effectiveness of letermovir use as primary prophylaxis for CMV infection and disease in adult allo-HCT recipients, using data from real-world observational studies since the approval of letermovir. Our systematic review

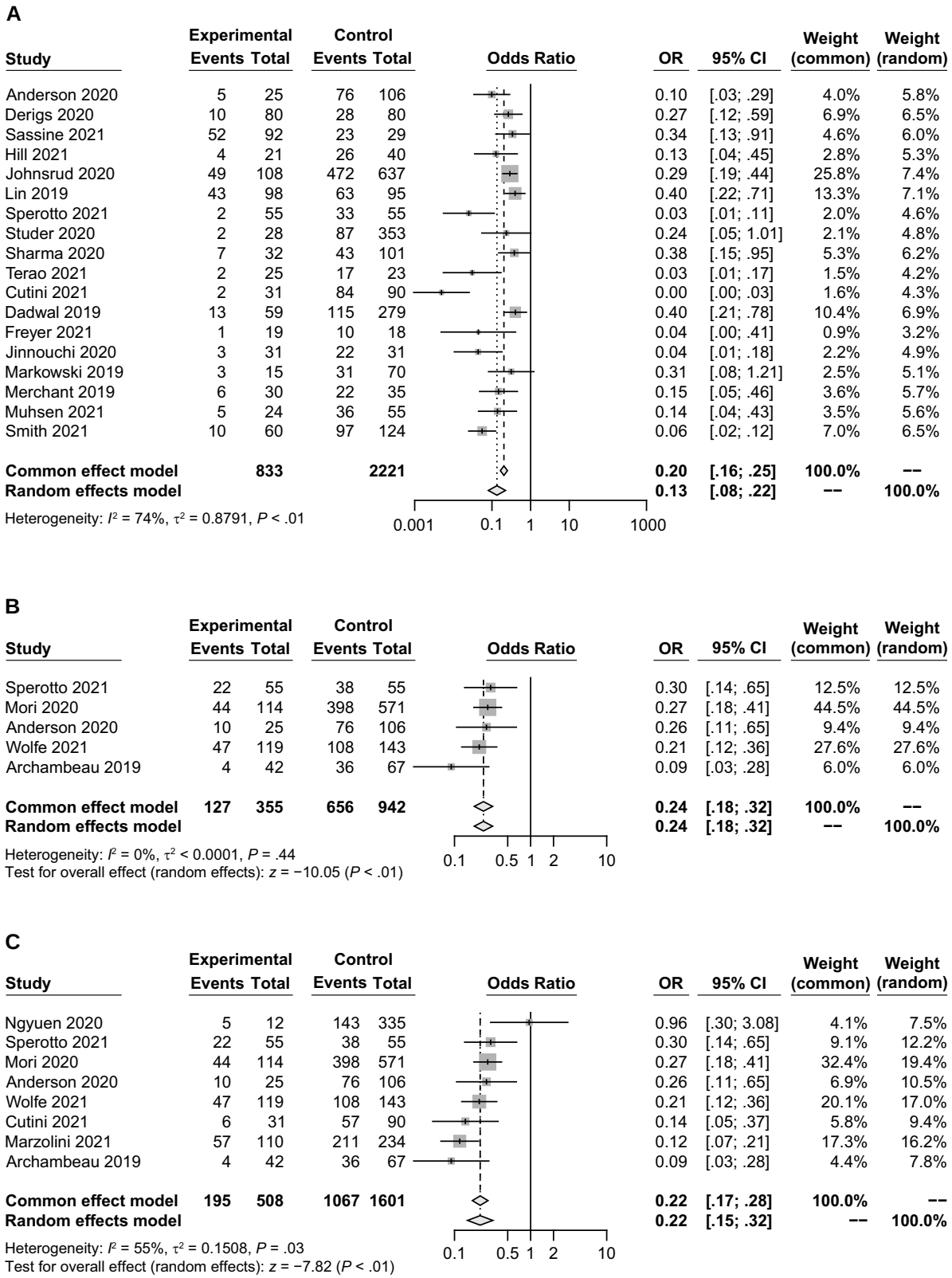

Figure 2. Cytomegalovirus reactivation at D+100 follow-up (*A*), D+200 follow-up (*B*), and beyond D+200 follow-up (*C*). Abbreviations: CI, confidence interval; OR, odds ratio.

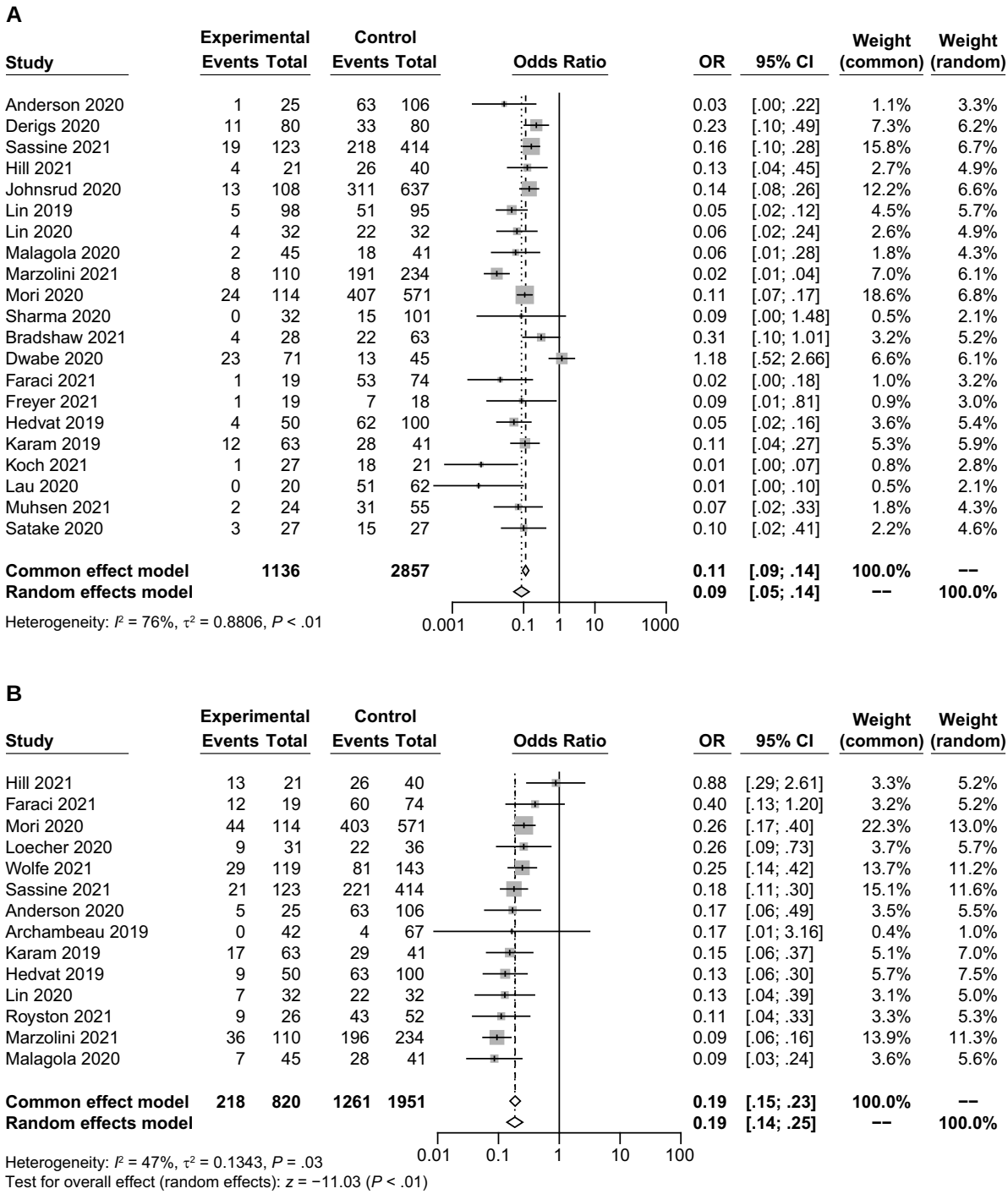

Figure 3. Clinically significant cytomegalovirus infection at D+100 follow-up (*A*) and D+200 follow-up (*B*). Abbreviations: CI, confidence interval; OR, odds ratio.

identified several noteworthy findings. Real-world use of letermovir demonstrated significant decline in CMVr, cs-CMVi, and CMVd at D+100 and D+200, compared to any control group, usually the historical control group. In addition, letermovir PP significantly reduced the odds of all-cause and non-relapse mortality beyond D+200 compared to historical controls.

Patients on letermovir PP had significantly lower odds of experiencing CMVr at D+100, and beyond. Our study findings for D+100 is consistent with a published summary of reported data of 19 real-world studies which described that letermovir PP was associated with significantly lower CMVr [33]; however, the latter study did not perform meta-analysis of the CMV-related outcomes. Importantly, our findings underscore

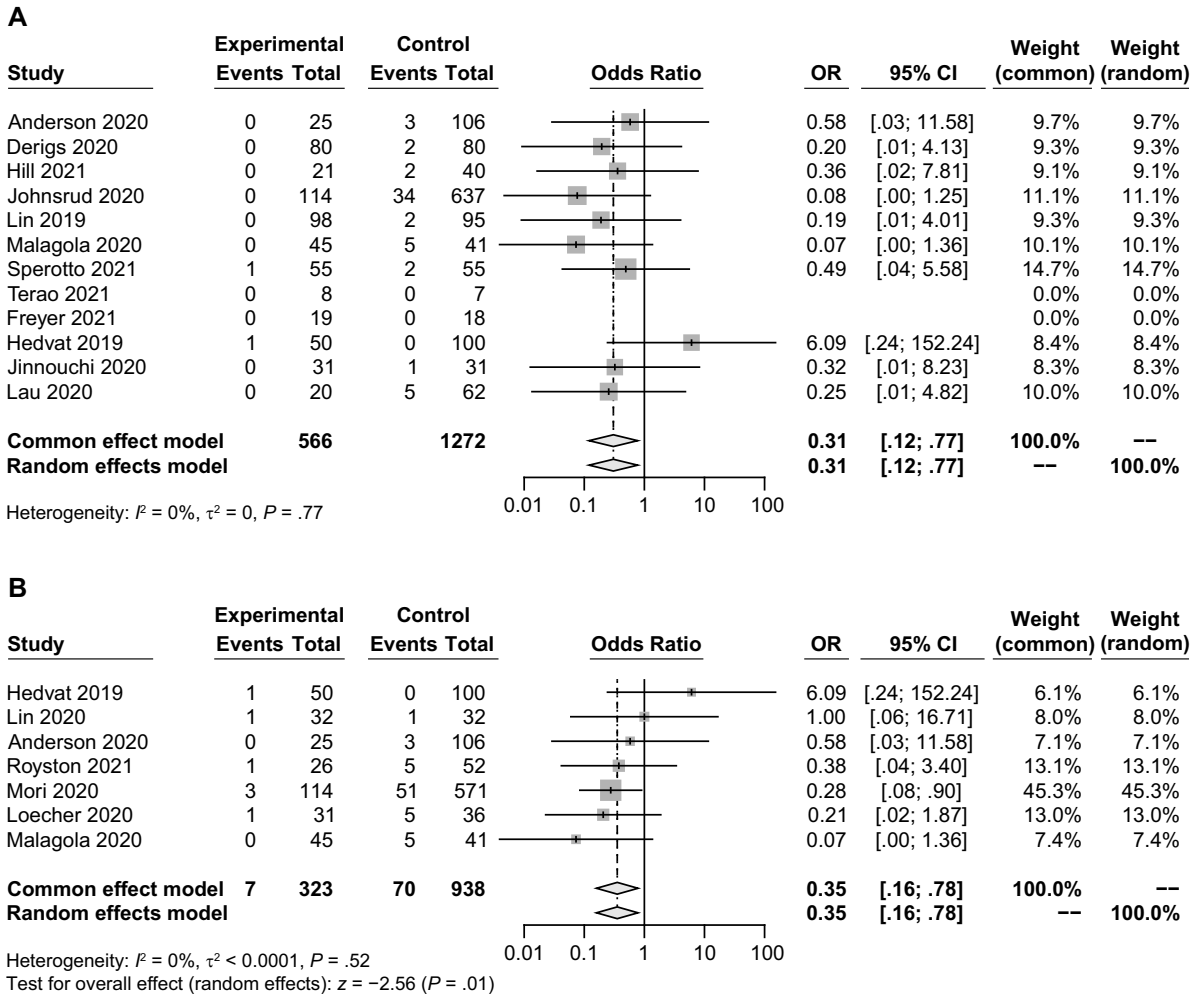

Figure 4. Cytomegalovirus disease at D+100 follow-up (*A*) and D+200 follow-up (*B*). Abbreviations: CI, confidence interval; OR, odds ratio.

the prolonged and sustained positive impact of letermovir even after its discontinuation, which was consistent with that reported in the phase 3 study [18]. Due to differences in characteristics of the included studies, we found moderate to substantial heterogeneity for the CMVr finding. To assess the source of heterogeneity, subgroup analyses by publication type, location of studies, and CMV risk of populations were conducted. At D +100, it was found that studies presented at conferences or meetings (80% vs 60% heterogeneity for presentations vs full publications), and non-US studies (77% for non-US studies vs 27% for the US-based studies) contributed substantially to the high heterogeneity. However, there was consistency in the effectiveness of letermovir PP in the subgroup analyses. Similar findings about sources of heterogeneity were found for D+200 and beyond as well. Variation in methods, patient characteristics, and initiation of PET to define CMVr in the included studies may have contributed to this heterogeneity in our meta-analysis findings. Another important finding was that letermovir PP also had a relatively stronger positive effect on patients at high risk of CMV infection and who received posttransplant cyclophosphamide with comparatively lower heterogeneity than that reported for the overall analyses. This finding about effectiveness of letermovir in high-risk patients is consistent with the phase 3 trial by Marty et al [18]. and highlights the importance of effectiveness beyond 100 days posttransplantation with letermovir [18].

Letermovir PP was also associated with significant reduction in the incidence of cs-CMVi compared to control groups arms, at D+100 and D+200 showcasing again sustained effectiveness post–letermovir discontinuation. Our findings are consistent with the results of the phase 3 clinical trial [18] that reported lower incidence of cs-CMVi by week 24 posttransplantation for patients who received letermovir PP. The proportion of patients with cs-CMVi in the letermovir group was 11% at D+100 follow-up in the studies that reported the data. This proportion increased to 23% in the D+200 period, which indicates that some patients may experience late CMV infections following letermovir cessation. Despite this finding, letermovir was found

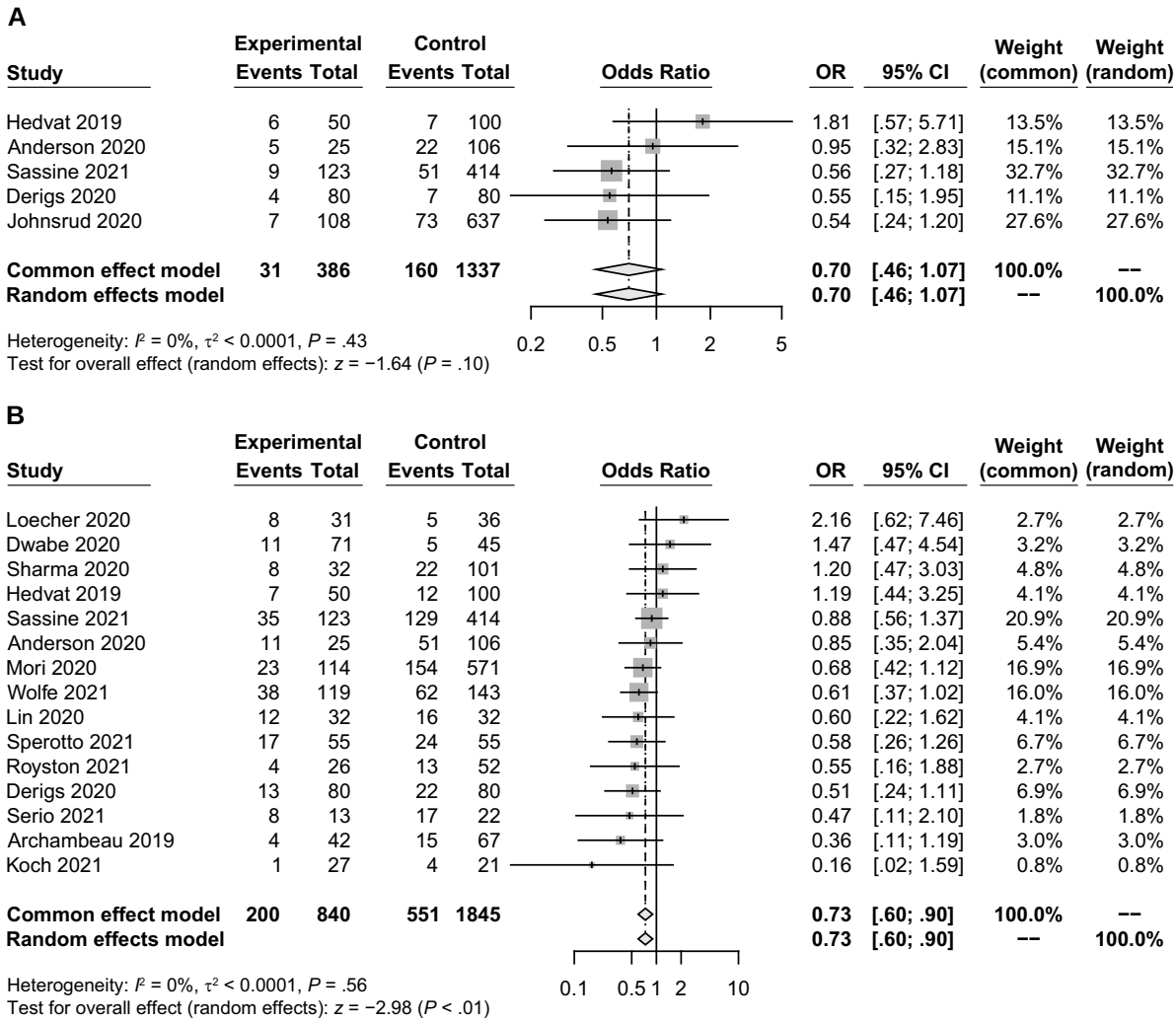

Figure 5. All-cause mortality at D+100 follow-up (*A*) and beyond D+200 follow-up (*B*). Abbreviations: CI, confidence interval; OR, odds ratio.

to significantly reduce cs-CMVi at D+200 compared to the control group. The odds ratio estimates were not significantly different when subgroup analysis was performed only for the high-risk population. The heterogeneity was substantial for D+100 follow-up (76%) whereas moderate heterogeneity was found for D+200 follow-up period (47%). In subgroup analyses, conference presentations and non-US studies contributed substantially to the high heterogeneity. An important observation in our meta-analysis was that at D+100, letermovir had a significantly stronger effect for cord-blood recipients only, those who received cyclophosphamide posttransplantation, or those who were at the high-risk of CMV. Lau et al included CMV-seropositive cord-blood transplant recipients and found significantly lower incidence of cs-CMVi at D+100 in the letermovir group compared to the historical control group (0% vs 82%, $P < .0001$) [32].

Overall, letermovir use was also associated with significantly reduced risk of CMVd at both D+100 and D+200 follow-up periods, with no heterogeneity in the pooled results. In the studies included in the meta-analysis, patients who received letermovir PP had lower rates of CMVd that ranged from 0% to 6%. Surprisingly, in the subgroup analyses, conference presentations and US-based studies showed a nonsignificant effect of letermovir PP on CMVd at both D+100 and D+200 follow-up. A likely explanation of these findings is inclusion of relatively smaller number of studies with comparatively lower sample sizes in these subgroups.

Letermovir PP was associated with a significant decrease in all-cause mortality and nonrelapse mortality beyond D+200, with no heterogeneity reported between the included studies. Our findings are different than that reported in the phase 3 trial for letermovir PP at D+200, although a trend was observed [18]. By combining studies and increasing the sample size, we identified enough number of outcome events, thereby resulting in significant outcomes beyond D+200 . Additionally, immune reconstitution following allo-HCT improves over

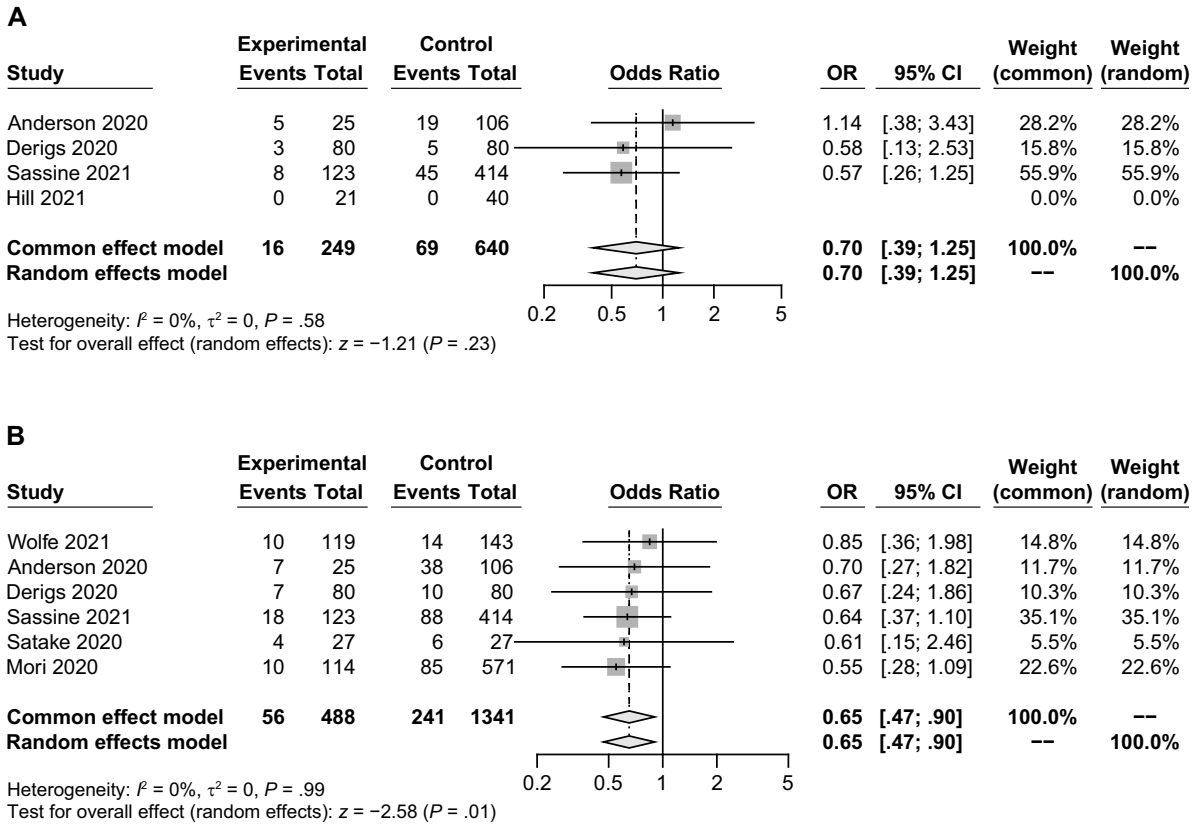

Figure 6. Nonrelapse mortality at D+100 follow-up (*A*) and beyond D+200 follow-up (*B*). Abbreviations: CI, confidence interval; OR, odds ratio.

time. The reduction or delay in CMVr may allow the reconstituted immune system to control the deleterious outcomes of CMVr [10, 34]. Hence, letermovir PP may bestow mortality benefit compared to the control group by reducing the risk of or delaying CMVr. Furthermore, letermovir PP may reduce, shorten duration, or delay PET with antiviral agents that are associated with serious toxicities, thereby providing observed mortality benefit for the letermovir PP group. Our findings for the mortality outcomes remained consistent in many subgroups: Abstracts reported nonsignificant findings for all-cause mortality and nonrelapse mortality, while full publications demonstrated significant findings in favor of letermovir use. Overall, US-based studies showed that letermovir PP was not significantly associated with lower all-cause and non-relapse mortality, in contrast with the non-US studies. This finding could be explained by the inclusion of high-risk allo-HCT population in many of the US-based studies compared to the non-US studies. In fact, 4 of 9 US studies that reported all-cause mortality beyond D+200 had a slightly higher mortality rate in the letermovir group compared to the control group. Furthermore, all-cause and nonrelapse mortality among high-risk allo-HCT recipients was not statistically significant between the letermovir PP and control groups.

To the best of our knowledge, this is the first comprehensive systematic review and meta-analysis of all of the published real-world studies that summarized the role of letermovir PP for CMV-related outcomes among adult allo-HCT recipients. Our review provides real-world evidence that is consistent with 1 of the pivotal trial studies on letermovir PP among adult CMV-seropositive allo-HCT recipients [18]. This review includes studies conducted in several countries, predominantly in the US, Italy, and Japan. Importantly, we summarized findings in this systematic review by several subgroup analyses including publication type, location of studies, and high-risk population. This systematic review focused on real-world studies, some with limited sample sizes and shorter follow-up period. The studies also varied in terms of patient characteristics. We have addressed these limitations by exploring these differences through statistical analysis in random-effects model and subgroup analysis/meta-regression.

In summary, our systematic review of real-world studies among adult allo-HCT recipients supports that compared to the control group, letermovir use for CMV PP was effective in reducing the risk of CMV-related complications including CMVr, cs-CMVi, CMVd, all-cause and nonrelapse mortality, and CMV-related hospitalization at different time points

post–allo-HCT. Finally, the use of letermovir for CMV PP reduced the incidence of CMV-related complications, the use of PET with anti-CMV agents that are associated with severe adverse events and may have prevented the direct and indirect effects of CMV infections that most probably led to improved clinical outcomes in adult allo-HCT recipients.

Notes

Author contributions. All authors contributed substantially to the reviewing and editing of the manuscript.

Patient consent. As our study is a systematic review and meta-analyses of published studies, it does not include factors necessitating patient consent.

Disclaimer. The funders played no role in the writing of the first draft of the manuscript.

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Potential conflicts of interest. A. D. R. was an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, at the time of the conduct of this study, and is a stockholder of Merck & Co., Inc., Rahway, NJ, USA. A. V. received funding from Merck & Co, Inc for performing the analysis. K. L. received investigator-initiated research grants from Merck & Co, Inc, Pfizer, Shionogi, Entasis, National Institutes of Health (NIH), Veteran's Affairs Heath Services Research & Development, and Merits; and served as a consultant for Paratek and Ferring Pharmaceuticals. Y. T. was an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, at the time this study was conducted, and is a stockholder of Merck & Co., Inc., Rahway, NJ, USA. R. F. C. received research grants paid to his institution from the National Cancer Institute, NIH, AiCuris, Ansun Biopharma, Genentech, Chimerix, Janssen, Karius, Merck, Oxford Immunotec, Takeda, and Viracor-Eurofins; and honoraria/consulting fees from Ansun Biopharma, Genentech, Qiagen, Janssen, Merck, Oxford Immunotec, Partner Therapeutics, Pulmotec, Takeda, Shionogi, Adagio, Viracor-Eurofins, and Karius. S. K. reports no potential conflicts.

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.

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