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Letermovir treatment of cytomegalovirus infection or disease in solid organ and hematopoietic cell transplant recipients

Kathleen A. Linder[1] | Christopher Kovacs[2] | Kate M. Mullane[3] | Cameron Wolfe[4] | Nina M. Clark[5] | Ricardo M. La Hoz[6] | Jeannina Smith[7] | Camille N. Kotton[8] | Ajit P. Limaye[9] | Maricar Malinis[10] | Morgan Hakki[11] | Aaron Mishkin[12] | Arnoldo Adrian Gonzalez[13] | Maria Dioverti Prono[14] | Darin Ostrander[14] | Robin Avery[14] | Daniel R. Kaul[1]

[1] Division of Infectious Disease, University of Michigan, Ann Arbor, Michigan, USA

[2] Department of Infectious Disease, Cleveland Clinic, Cleveland, Ohio, USA

[3] Department of Medicine, University of Chicago, Chicago, Illinois, USA

[4] Division of Infectious Disease and International Health, Duke University, Durham, North Carolina, USA

[5] Division of Infectious Disease, Loyola University, Chicago, Illinois, USA

[6] Division of Infectious Disease, University of Texas Southwestern Medical Center, Dallas, Texas, USA

[7] Division of Infectious Disease, University of Wisconsin, Madison, Wisconsin, USA

[8] Division of Infectious Disease, Massachusetts General Hospital, Boston, Massachusetts, USA

[9] Division of Allergy and Infectious Disease, University of Washington, Seattle, Washington, USA

[10] Section of Infectious Disease, Yale University, New Haven, Connecticut, USA

[11] Division of Infectious Disease, Oregon Health and Science University, Portland, Oregon, USA

[12] Division of Infectious Disease, Temple University, Philadelphia, Pennsylvania, USA

[13] West Coast ID, Safety Harbor, Florida, USA

[14] Division of Infectious Disease, Johns Hopkins University, Baltimore, Maryland, USA

Correspondence
Daniel R. Kaul, MD, Division of Infectious Diseases, F4133 University Hospital South, 1500 E. Medical Center Dr, SPC 5226, Ann Arbor, MI 48109, USA.
Email: kauld@umich.edu

Abstract

Background: Few options are available for cytomegalovirus (CMV) treatment in transplant recipients resistant, refractory, or intolerant to approved agents. Letermovir (LET) is approved for prophylaxis in hematopoietic cell transplant (HCT) recipients, but little is known about efficacy in CMV infection. We conducted an observational study to determine the patterns of use and outcome of LET treatment of CMV infection in transplant recipients.

Methods: Patients who received LET for treatment of CMV infection were identified at 13 transplant centers. Demographic and outcome data were collected.

Results: Twenty-seven solid organ and 21 HCT recipients (one dual) from 13 medical centers were included. Forty-five of 47 (94%) were treated with other agents prior to LET, and 57% had a history of prior CMV disease. Seventy-seven percent were intolerant to other antivirals; 32% were started on LET because of resistance concerns. Among 37 patients with viral load < 1000 international units (IU)/ml at LET initiation, two experienced >1 log rise in viral load by week 12, and no deaths were attributed to

CMV. Ten patients had viral load > 1000 IU/ml at LET initiation, and six of 10 (60%) had a CMV viral load < 1000 IU/ml at completion of therapy or last known value. LET was discontinued in two patients for an adverse event.

Conclusions: Patients treated with LET with viral load < 1000 IU/ml had good virologic outcomes. Outcomes were mixed when LET was initiated at higher viral loads. Further studies on combination therapy or alternative LET dosing are needed.

KEYWORDS
cytomegalovirus infection, letermovir, solid organ transplantation, stem cell transplantation

1 | INTRODUCTION

Disease caused by cytomegalovirus (CMV) remains a leading viral cause of morbidity and mortality after solid organ transplant (SOT) and hematopoietic cell transplant (HCT). Available treatments for CMV infection and disease (ganciclovir, valganciclovir, foscarnet, and cidofovir) have two significant limitations. First, antiviral resistance may develop during treatment and limit efficacy. Up to 12% of CMV seronegative recipients of organs from CMV seropositive donors (D+R-) treated for CMV infection or disease develop ganciclovir resistance mutations.[1–4] Ganciclovir resistance is less common in patients receiving ganciclovir or valganciclovir for prophylaxis, occurring in 1%–3% of patients with the notable exception of D+R- lung recipients, where resistance rates as high as 16% have been reported.[3,5–8] In some cases, additional mutations at UL54 result in cross-resistance to all agents that act at the CMV DNA polymerase.[9] Outcomes associated with drug resistant CMV infections in SOT/HCT recipients are poor, with longer time to viral clearance, increased mortality, and increased incidence of renal dysfunction compared to matched controls.[4,10,11] Second, adverse events may limit use of currently approved agents. Ganciclovir and valganciclovir have hematological toxicities that may preclude use in HCT recipients with baseline low blood counts.[12] Further, decreased blood counts frequently complicate CMV treatment in SOT recipients, particularly in those receiving other agents with hematological toxicity such as mycophenolate, trimethoprim-sulfamethoxazole, and anti-thymocyte globulin. In addition, the renal toxicities of foscarnet and cidofovir are significant,[11,13,14] and many patients at risk for complex CMV syndromes are already on other nephrotoxic drugs such as calcineurin inhibitors or have pre-existing chronic or acute kidney disease.

Letermovir (LET) was approved for prevention of CMV infection/disease in CMV seropositive HCT recipients in 2017. LET prophylaxis was shown to be effective and well tolerated, without significant hematological and renal toxicity, and demonstrated a possible beneficial impact on mortality.[15,16] Furthermore, as LET acts at the level of the terminase complex rather the DNA polymerase, activity is expected against CMV isolates resistant to other agents.

Limited data are available regarding the use of LET for treatment of CMV infection or disease. An early case report describes successful treatment of multi-drug resistant CMV with multi-organ involvement with LET under a compassionate use protocol.[17] Since licensure of the drug, case reports and case series show mixed results when SOT or HCT recipients with CMV infection or disease are treated with LET, and in a number of reports resistance developed rapidly leading to treatment failure.[19–26]

Despite this paucity of data, LET represents a potentially attractive option for the treatment of CMV in certain situations. Thus, we conducted a multicenter observational study to better understand the patterns of off-label use of LET for CMV infection or disease and subsequent outcomes.

2 | METHODS

Multiple transplant centers were approached, and 13 centers interested in participating were included. Cases of LET use in SOT and HCT recipients were reviewed for inclusion. The enrollment time period varied at each medical center. Initiation of LET was between January 2018 and January 2020. Standard definitions of CMV infection and end-organ disease were followed.[27] Enrollment criteria included receipt of an HCT or SOT and the use of LET to treat an established CMV infection. Subjects who were switched from another agent to complete therapy for an ongoing episode of CMV infection/disease were included. Subjects in whom LET was started as primary prophylaxis or as secondary prophylaxis after a distant episode of CMV infection were excluded. Subjects were excluded if they received less than 7 days of LET or if poor adherence was suspected. Death was attributed directly or indirectly to CMV based on the clinical determination of the investigators at each center.

A REDCap survey was used to retrospectively collect demographic and clinical subject data including transplant type, characteristics of the CMV episode, CMV treatment information, and clinical, virological, and safety outcome information. Information was collected by investigators at each site and entered into the REDCap survey tool; data accuracy was not confirmed by the coordinating center or reviewed by more than one investigator at each site. Data analysis was conducted at the coordinating center (University of Michigan). Institutional regulatory approval was obtained at each participating site and the coordinating site.

Virological failure was defined as follows:

1. For those with baseline CMV viral loads < 1000 international units (IU)/ml at LET initiation
   a. Increase of CMV viral > 1 log at any time while on LET treatment
2. For those with baseline CMV viral load > 1000 IU/ml at LET initiation
   a. Failure to achieve 1 log reduction of CMV viral load by weeks 2–4 using the latest measurement available during that time interval
   b. CMV viral > 1000 IU/ml at weeks 5–8 and weeks 9–12, respectively, using the latest measurement available during that time period
   c. Failure to achieve viral load < 1000 IU at the end of LET treatment

Clinical failure was defined as symptomatic worsening of end organ disease or CMV syndrome or relapse of previously resolved symptoms while on treatment with LET.

3 | RESULTS

3.1 | Baseline patient and center characteristics

We collected data on 47 patients from 13 centers. One center contributed 11 cases; all other centers contributed six or fewer cases. Baseline characteristics are described in **Table 1**. Of 47 subjects, 27 were SOT recipients, and 21 were HCT recipients (one received both). Lung recipients (including one kidney/lung) represented just over half of SOT recipients, 14/27 (52%). Eight of 27 (30%) of SOT recipients were treated for organ rejection in the 3 months preceding LET initiation, and 19 of 27 (70%) were CMV D+R−. The two most common indications for LET were intolerance to other agents 36 of 47 (77%) and 15 of 47 (32%) proven antiviral resistance (more than one indication was present in 20 patients).

3.2 | Characteristics of CMV events and CMV treatment

Table 2 describes the classification of the CMV event, genotypic findings, LET dosing, and the use of additional antiviral treatments. End organ disease was present in 17 of 47 (36%) with the gastrointestinal tract the most common involved site 13 of 17 (76%). In 8 of 17 (47%), end organ disease had resolved at the time of LET initiation. Most patients received LET 480 mg daily 41/47 (87%); 8 of 47 (17%) either had their dose increased above 480 mg ($n = 2$) or started at a dose of 720 mg daily ($n = 6$). While most patients received monotherapy with LET, combination therapy was used in seven patients.

3.3 | Treatment outcomes

Table 3 describes the clinical outcome of the entire cohort stratified by baseline CMV illness status. Nine of 17 with end organ disease were still symptomatic at the time of LET initiation. Thirteen deaths occurred by last known follow-up, including in 10 of 37 (27%) of those with viral loads < 1000 IU/ml at onset of LET treatment. Only one of these deaths was directly attributable to CMV infection. Of the three deaths indirectly attributable to CMV disease, two were due to fungal infection, and one was a consequence of renal failure after foscarnet treatment.

TABLE 1 Patient baseline characteristics

Characteristic	Number (percent)
Age, y, median (range)	56 (15–73)
Male sex	32/47 (68)
Race/ethnicity	
White[a]	35/47 (74)
Black	9/47 (9)
Asian	2/47 (4)
Other	1/47 (2)
Solid organ transplant	
Lung	13/27 (48)
Kidney	6/27 (22)
Heart	2/27 (7)
Liver	1/27 (4)
Other[b]	5/27 (19)
Stem cell transplant (no autologous)	
Haploidentical (not cord)	5/21 (24)
Cord blood	6/21 (29)
Graft vs. host disease	11/21 (52)
Previous episode of CMV infection or disease	27/47 (57)
Clinical indications for letermovir[c]	
Resistance	15 (32)
Clinically refractory	6 (13)
Intolerance to other treatments	36 (77)
Oral agent preferred	9 (19)
Other (combination therapy desired)	1 (2)
CMV treatment at letermovir initiation[d]	
(Val)ganciclovir	19 (40)
Foscarnet	16 (34)
CMV immunoglobulin	6 (13)
Leflunomide	3 (6)
Other (CMV T cells, brincidofovir, intravitreal antivirals)	4 (9)
None	8 (17)

Abbreviation: CMV, cytomegalovirus.
[a]Three Hispanic persons.
[b]One intestine, one pancreas alone, two kidney /pancreas, one kidney/lung.
[c]Twenty patients with more than one indication.
[d]Seven patients on two or three treatments; in most cases these treatments were stopped at letermovir initiation.

TABLE 2 Characteristics of CMV event and letermovir treatment

Characteristic	Number (percent)
CMV end organ disease (including all proven/probable/possible)[a]	17/47 (36)
Pneumonia	4/17 (24)
Gastrointestinal	13/17 (76)
Retinitis	3/17(18)
Other (skin)	1/17 (6)
CMV syndrome (solid organ only)	16/27 (59)
Resistance (proven by genotyping)	17/47 (36)
UL97	15/17 (88)
UL54	4/17 (24)
Letermovir dosing and route at initiation	
480 mg[b]	41/47 (87)
720 mg	6/47 (13)
Intravenous	5/47 (11)
Oral	42/47 (89)
Letermovir monotherapy[c]	40/47 (85%)

Abbreviation: CMV, cytomegalovirus.

[a]Four patients had end organ disease at more than one site (two lung and gastrointenstinal, one skin and gastrointestinal, and one retina and gastrointestinal).

[b]Two patients increased from 720 mg to 960 mg, one from 480 mg to 960 mg, one from 480 mg to 720 mg.

[c]Combination therapy in seven included (val)ganciclovir = 2, foscarnet = 2, CMV IgG = 4, leflunomide = 2, intravitreal foscarnet/ganciclovir = 1.

Figure 1 describes virologic outcomes in patients with CMV viral load below 1000 IU at LET initiation. In this group, 29 of 37 (78%) were on active CMV treatment at the time of LET initiation. The leading indication for LET was intolerance to alternative treatment, 29 of 37 (78%). Other indications included documented or suspected viral resistance, eight of 37 (22%), refractory infection, four of 37 (11%), or a preference for oral therapy, seven of 37 (19%). In 11 patients, more than one indication was present. In 34 of 37 (92%), LET was given as monotherapy. Only one of 34 (3%) of patients who remained on LET and had a viral load checked at 2–4 weeks had an increase in viral load of greater than one log. Of the 28 patients still on LET at weeks 5–8, all remained undetectable, and only one of 25 (4%) who continued treatment to 9–12 weeks experienced a greater than one log increase in viral load. Reasons for stopping LET included completion of therapy nine of 37 (24%), death seven of 37 (19%), persistent viremia seven of 37 (19%), insurance issues two of 37 (5%), adverse event two of 37 (5%), determination that suspected resistance was not present one of 37 (3%). The remaining nine of 37 (24%) remained on LET at last reported time point. Over the course of 12 weeks, two patients experienced a one log or greater increase in viral load while on LET. No deaths were attributed to CMV.

Table 4 includes 10 patients with viral load > 1000 IU/ml at LET initiation. In no case was LET the initial treatment for these episodes of CMV, and the median time from CMV diagnosis to initiation of LET was 63 days (range 10–318 days). In six of 10 cases, LET was used as monotherapy. The median duration of LET treatment was 16.9 weeks. In the eight patients with a CMV viral load checked at weeks 2–4 after initiation of LET, four of eight (50%) experienced a 1 log reduction in CMV viral load. At weeks 5–8, eight had a CMV viral load checked, and three of eight (38%) had a viral load < 1000 IU/ml. At weeks 9–12, six had a viral load checked, and two of six (33%) were less than 1000 IU/ml. Two additional patients who had a viral load > 1000 IU/ml at weeks 9–12 received prolonged courses of LET monotherapy (19.4 and >52 weeks) with subsequent CMV viral loads remaining below 1000 IU/ml. In one of these 10 patients, CMV LET resistance testing was sent and indicated UL 56 C325Y mutation associated with LET resistance. LET course was completed in eight patients with initial viral load > 1000 IU/ml, and of these, four had CMV viral loads < 1000 IU/ml at the time of LET discontinuation. Overall, six of 10 had a viral load < 1000 IU/ml at end of treatment or last known value.

3.4 | Tolerability and safety

Overall LET was well tolerated and was discontinued for a possible adverse event/drug interaction in two patients (diarrhea which resolved with discontinuation in one patient and increase in tacrolimus levels in one other). In five patients, the dose of tacrolimus was decreased during treatment with LET to achieve the same target trough level.

4 | DISCUSSION

The FDA-approved indication for LET is prevention of CMV infection and disease in CMV seropositive HCT recipients. This paper describes the off-label use of LET in both SOT and HCT recipients at 13 academic medical centers. The most frequent rationales for off-label LET use in descending order were intolerance to other available treatments, CMV resistance, and preference for an oral agent. In the majority of treated patients, low levels of DNAemia (below 1000 IU/ml) had been achieved with valganciclovir, ganciclovir, or foscarnet at the time of initiation of LET. In this situation, patients on LET typically maintained a CMV viral load < 1000 IU/ml, and progression or development of worsening symptoms was uncommon occurring in only one patient. While 10 of 37 patients in this group died, this was largely due to other factors (e.g., relapse of leukemia in HCT recipient) rather than direct or indirect effects of CMV infection. It is not known how much of this success is due to LET, and how much is due to other factors, including reduction in immunosuppression, or spontaneous viral clearance. In contrast, in patients with CMV viral load > 1000 IU/ml at initiation of LET, success rates were lower. While both groups were heavily pretreated for CMV prior to LET initiation, the group with higher viral loads at LET initiation exhibited high rates of baseline CMV disease and resistance. Interestingly, two patients in the group with higher viral loads at LET initiation that did not achieve viral load < 1000 IU/ml at 9–12 weeks did maintain viral suppression with extended (19.4 and > 52 weeks) courses of LET

TABLE 3 Clinical outcomes by baseline CMV illness status

	CMV Syndrome or DNAemia $n = 30$ (64%)		End organ disease$n = 17$ (36%)	
	<1000 IU/ml atLET start ($n = 26$)	>1000 IU/ml at LET start ($n = 4$)	<1000 IU/ml at LET start ($n = 11$)	>1000 IU/ml at LET start ($n = 6$)
Persistent or worsening symptoms while on LET	0	0	1 (9%)	3 (50%)
Death[a]	8 (31%)	0	2 (18%)	3 (50%)
Death direct result of CMV	0	0	0	1
Death indirect result of CMV	1[b] (3%)	0	0	2[b] (33%)

Abbreviations: CMV, cytomegalovirus; IU, international units; LET, letermovir.

[a]Death at last known follow-up.

[b]Two deaths due to invasive fungal infection, one as a consequence of renal failure due to foscarnet.

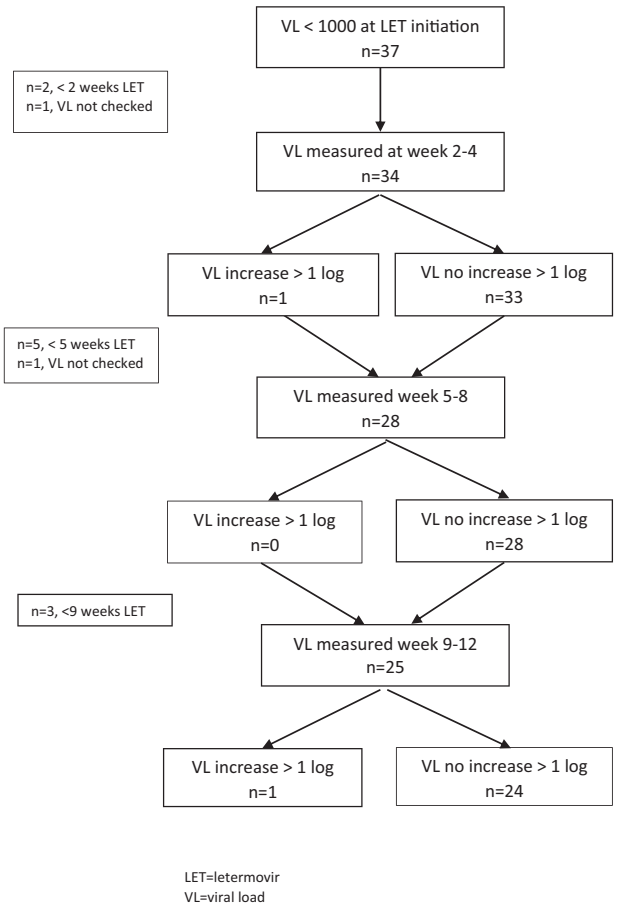

FIGURE 1 Virological outcomes viral load at letermovir initiation < 1000 IU/ml

monotherapy. Overall, four of eight (50%) patients in whom LET was stopped had viral load < 1000 IU/ml when treatment was discontinued. Again, other interventions may have contributed to these outcomes.

While the literature on off-label LET use is sparse and consists primarily of case reports or small case series,[17,19–25] some larger case series describe successful use of LET when started in patients with very low CMV viral loads or as secondary prophylaxis.[28,29] An analysis of 70 recipients from the phase III trial of LET as prophylaxis after HCT with detectable CMV at entry noted similar outcomes compared to study participants with no detectable CMV at LET initiation.[28] CMV viral loads were all quite low in this group (median 150 IU/ml, range 150–716). In a report of the French compassionate access experience with 80 HCT recipients receiving LET as secondary prophylaxis, four of 80 (5.5%) experienced CMV disease ($n = 3$) or infection without disease ($n = 1$).[29] Only one patient had a viral load above the limit of quantification of the assay at LET initiation. Nonetheless, these reports are consistent with the generally favorable virologic outcomes we observed when LET was started in patients with CMV viral loads < 1000 IU/ml. However, spontaneous clearance of untreated low level CMV viremia has been well described, and the effect of LET in this situation is uncertain.[30,31]

While about one-third of patients had documented resistance mutations, intolerance of currently available treatment for CMV (largely renal toxicity of foscarnet or cidofovir and hematologic toxicity of ganciclovir) was the most commonly cited reason for using LET. LET is generally well tolerated, with discontinuation rates similar in placebo versus LET arm in clinical trials, and hematological or renal toxicity is rare.[32] In the current series, only two of 47 (4%) discontinued LET (one due to diarrhea and the other due to drug interaction with tacrolimus).

There is little information on the safety and effectiveness of alternative treatment strategies including increased LET dosing or combination with other antiviral agents. The approved dose for prophylaxis is 480 mg daily, but in this series, due to either refractory disease or disease in the retina and concerns about drug penetration, eight patients received either initial increased dosing (720 mg) or had their dose increased when disease was not responding. Currently there are no data to guide dosing of LET when used outside of the licensed prophylaxis indication. Combination therapy was applied in seven cases and often used multiple drugs including CMV immune globulin and leflunomide which likely have limited activity. Due to the small numbers of cases involved and the fact that combination therapy and increased LET doses were often used in the most challenging clinical situations, we cannot comment on the relative effectiveness of these strategies. Of note, the antiviral drug maribavir is being developed specifically for

TABLE 4 Characteristics and outcomes of patients with CMV viral loads > 1000 IU/ml at letermovir initiation

Age	Gen	Race	Transpl	Days from transplant to CMV episode	CMV disease	Prior CMV treatments	Days from CMV diagnosis to LET	LET indication	LET dose	Other CMV agents used with LET	Mut	Viral load at LET start	Viral load wk 2–4	Viral load wk 5–8	Viral load wk 9–12	Duration LET wks	Viral load < 1000 at LET end	Last known status
50	M	Black	Lung	272	GI (probable)	(val)gan, fos	15	resistance, toxicity	480 mg qd; increased to 960 mg qd	(val)gan	UL97	23854	10975	85257	2939	19.4	Yes	Alive
29	M	White	Intestine	1753	GI (proven)	(val)gan, fos	36	Resistance	480 mg qd	None	UL97	2000	NA	NA	NA	1.14	No	Dead
63	F	White	Lung	136	GI (probable)	(val)gan, fos	123	Toxicity	480 mg qd	None	None	2350	BLQ	167	BLQ	46.4	Yes	Alive
65	F	Black	Lung	415	None	(val)gan, fos	318	Resistance, toxicity	480 mg qd	None	UL97	18270	4788	4662	4473	> 52 (ongoing)	NA	Alive
55	M	Black	Kidney	68	None	(val)gan	20	Refractory, toxicity	480 mg qd	None	None	4000	BLQ	BLQ	BLQ	26.4	Yes	Alive
50	M	Black	Kidney	214	None	cdv, CMV IgG	49	Resistance, toxicity	480 mg qd	None	UL97	41923	41736	43109	NA	11.0	No	Alive
35	M	White	Stem cell	190	Lung (probable)	fos	10	Combination therapy	480 mg qd	fos	None	160000	BLQ	NA	NA	2.3	Yes	Dead
56	M	White	Kidney	97	None	(val)gan	286	Resistance, oral preferred	720 mg qd	None	UL97, UL54	4318	NA	BLQ	NA	>22 (ongoing)	NA	Alive
70	F	White	Lung	260	Lung (proven), GI (proven)	(val)gan, fos, CMV IgG	77	Resistance	720 mg qd, increased to 960 qd	CMV IgG	UL54	994000	5950	1100	7690	18	No	Dead
50	M	Asian	Lung	735	GI (possible), retina (proven)	(val)gan, fos, mbv, CMV IgG, i.v. gan, i.v. fos	163	Resistance, toxicity	720 mg qd	CMV IgG, lefluno-mide	UL54	1657	701	1246	5548 (C325 LET)	15.7	No	Alive

Abbreviations: BLQ, below the limit of quantitation; cdv, cidofovir; CMV, cytomegalovirus; fos, foscarnet; GI, gastrointestinal; IgG, immunoglobulin; i.v., intravitreal; LET, letermovir; mbv, maribavir; mut, mutation; NA, not applicable; qd, daily; transpl, transplant; (val)gan, (val)ganciclovir; wk, week.

resistant/refractory CMV infection with phase 2 data published and phase 3 trial data pending analysis.[33]

The population described in this study is quite complex with multiple risk factors for complex CMV syndromes, resistant virus, and poor outcomes. Lung transplant recipients are overall at higher risk for CMV resistance and more severe disease, and represent under 7% of total SOT done in the USA.[34] Lung transplant recipients, however, were just over half the SOT recipients in this series. In the HCT population, haploidentical (non-cord) or cord blood recipients tend to have difficulty controlling CMV and also accounted for over half of the HCT recipients in our series. Further, 27 of 41 (66%) of the recipients in this series had a previous episode of CMV infection or disease. Thus, the high death rate of just over a quarter of patients is not surprising and likely reflects that clinicians are choosing to use LET off-label in the most challenging situations when other options have been exhausted.

This study had a number of important limitations. Different institutions used different CMV assays and specimen types (plasma vs. whole blood) that cannot be precisely compared across centers. Furthermore, since undetectable CMV viral loads are often not obtained even after successful treatment due to increasingly sensitive CMV assays, we used a one log reduction by weeks 2–4 and a CMV viral load < 1000 IU/ml at later time points to define virological success. In addition, we used a relatively wide interval of time points since different centers varied in how frequently CMV viral loads were assessed. We focused on an on-treatment analysis given the complexity of these patients and a desire to determine if in situations where patients were able to continue treatment a virologic response was seen.

In summary, clinicians in transplant centers are using off-label LET primarily for patients intolerant of or resistant to available treatments. In situations where other less well tolerated agents can be used to reduce viral load to <1000 IU/ml, LET may be associated with favorable outcomes when used as "step down" therapy. Our series suggests that in situations where viral loads cannot be effectively reduced below 1000 IU/ml with other therapies, results are mixed. Randomized trials are required to confirm these observations, and further research to determine the effectiveness and safety of combination therapy and/or higher doses of LET is needed to better understand how to treat this challenging group of patients.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors meet the ICMJE definition of authorship

DATA AVAILABILITY STATEMENT

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

ORCID

Christopher Kovacs https://orcid.org/0000-0002-2017-5751
Kate M. Mullane https://orcid.org/0000-0002-8921-8561
Cameron Wolfe https://orcid.org/0000-0002-5365-5030
Nina M. Clark https://orcid.org/0000-0001-5670-4443
Ricardo M. La Hoz https://orcid.org/0000-0002-1560-3192
Jeannina Smith https://orcid.org/0000-0001-9379-6332
Camille N. Kotton https://orcid.org/0000-0001-7320-2234
Ajit P. Limaye https://orcid.org/0000-0002-5350-9025
Maricar Malinis https://orcid.org/0000-0002-5720-9994
Morgan Hakki https://orcid.org/0000-0002-1214-9609
Aaron Mishkin https://orcid.org/0000-0001-8330-7734
Maria Dioverti Prono https://orcid.org/0000-0002-5326-9551
Robin Avery https://orcid.org/0000-0001-7692-3619
Daniel R. Kaul https://orcid.org/0000-0003-0990-4148

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