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Original Article

Letermovir Primary Cytomegalovirus Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients: Real-Life Data from a University Hospital in Argentina

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Abstract. ***Background.*** **Cytomegalovirus (CMV) infection remains the most common clinically significant infection after allogeneic hematopoietic stem cell transplantation (allo-HCT) and is associated with considerable morbidity and mortality.**
Objectives**: The present study was designed to describe and compare the incidence of untreated CMV reactivation (uCMVr), clinically significant infection (cs-CMVi) and disease (CMVd), as well as CMV-related hospitalization and outcome of allo-HCT patients, either treated with letermovir (LET) primary prophylaxis or managed with preemptive therapy (PET).**
Methods**: This is a prospective observational cohort study of adult CMV seropositive allo-HCT patients who either received primary prophylaxis with LET within the first 100 days after HCT or were managed with PET.**
Results**: The study population comprised 105 patients (28 in the LET group and 77 in the PET group). Compared to the PET group, patients in the LET group received more allo-HCT from alternative donors (54.5% vs. 82.14%, *P=0.012*). More than half of the patients in both groups were classified as high risk for CMVd. In the LET vs. PET group, cs-CMVi and CMVd developed respectively in 0 vs. 50 (64.94%), *P=<0.0001*, and 0 vs. 6 (7.79%), *P=0.18*. In the LET group, uCMVr occurred in 5 (17.8%) and were all considered blips. Hospital admissions related to cs-CMVi or CMVd in the PET group vs. LET group were 47 (61.04%) vs. 0, respectively, *P=<0.0001*. No differences were observed in 100-day mortality.**
Conclusions**: LET primary prophylaxis proved effective in preventing cs-CMVi and CMVd and reducing hospitalizations in allo-HCT adults. Blips can occur during prophylaxis and do not require LET discontinuation.**

Keywords: Letermovir; Cytomegalovirus; Hematopoietic cell transplantation.

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Introduction. Cytomegalovirus infection (CMVi) is a frequent complication after allogeneic hematopoietic cell transplantation (allo-HCT) in CMV-seropositive recipients.[1,2] It can develop as untreated CMV reactivation (uCMVr), clinically significant infection (cs-CMVi), or tissue invasive CMV disease (CMVd). Moreover, CMVi has been shown to increase the risk of bacterial and fungal infections, cause neutropenia and acute kidney injury due to antiviral treatment, and increase hospitalizations and mortality, especially within the first 100 days after HCT.[3-7] Several decades ago, primary prophylaxis with ganciclovir for CMV-seropositive recipients within the first 100 days after HCT proved effective for the prevention of uCMVr, cs-CMVi, and CMVd. Notwithstanding that, it was associated with adverse events and delayed recovery of CMV-specific T-cell immunity, with the consequent increase in late CMV infections.[8] Therefore, preemptive therapy (PET) with ganciclovir, valganciclovir, or foscarnet to patients with CMVr has been the strategy for the prevention of CMVd in most transplant centers. However, letermovir (LET) primary prophylaxis is currently the most frequently used CMV prevention strategy in CMV seropositive allo-HCT. uCMVr correlates with a higher risk of non-relapse mortality and overall mortality, supporting the use of LET prophylaxis.[9,10] Unfortunately, LET is not available in most countries from Latin America.

In 2017, Marty F. et al. published a randomized double-blind controlled trial comparing primary prophylaxis with LET vs. placebo in CMV-seropositive patients with allo-HCT within the first 100 days after transplantation. LET Prophylsxis effectively reduced CMVr, cs-CMVi, and CMVd, with lower overall mortality at week 24 and a good safety profile, particularly without myelotoxicity.[11] In addition, two post-hoc analyses of this study demonstrated lower mortality rates at week 48 after transplantation and lower rates of CMV-associated and all-cause re-hospitalizations.[12,13] After drug approval, several comparative retrospective cohort studies, mostly conducted in the US, Europe, and Japan, confirmed the superiority of LET over PET in the prevention of cs-CMVi and CMVd. Therefore, scientific societies currently recommend primary prophylaxis with LET to prevent uCMVr, cs-CMVi, and CMVd.[2,14,15,16] Nevertheless, to the best of our knowledge, comparative studies from Latin America have not been published.

The present study was designed to describe and compare the incidence of uCMVr, cs-CMVi, and CMVd, as well as CMV-related hospitalization and outcome of allo-HCT patients, either treated with LET primary prophylaxis or managed with PET.

Materials and methods.

Setting, Patients, and Study Design. A prospective observational cohort study was performed in a university hospital in Buenos Aires, Argentina. CMV seropositive allo-HCT recipients ≥18 years of age were included from December 2012 to November 2022. They were divided into two groups according to CMV management timeframe strategy: PET (between December 1, 2012 and January 31, 2020) and LET primary prophylaxis (February 1, 2020, onward). They were followed within the first 100 days after HCT or until death, whichever occurred first. Data were obtained from electronic and paper medical records, direct patient care, and databases from the Section of Infectious Diseases, Hematology, and Virology Laboratory. Patients were excluded if they had CMVr before HCT or at the start of LET, had received antiviral therapy with anti-CMV activity, had discontinued prophylaxis before engraftment without CMVr, had died before engraftment or before starting LET, or were monitored with CMV pp65 antigenemia assay.

Demographic and clinical data were obtained, including age, sex, underlying hematological disease, HCT type and conditioning regimen, donor CMV seropositivity, administration of antithymocyte globulin (ATG) or post-HCT cyclophosphamide (PTCy) for graft-versus-host-disease (GVHD) prophylaxis, absolute lymphocyte count at day 50 after allo-HCT, and development of GVHD. Total lymphocyte counts and CMV viral load (CMV VL) at the onset of cs-CMVi were collected from patients who developed cs-CMVi.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the CEMIC Ethics Committee (Approval identification number 1461).

Since this is an observational study, patient informed consent was waived by the Ethics Committee (Data Protection Law 25326, section 7, subsection 2).

Definitions, Virologic Studies, and CMV Management. CMVi was defined as virus isolation or detection of nucleic acid in blood, plasma, or another fluid or tissue specimen. cs-CMVi was defined as CMVi or CMVd requiring antiviral treatment. The end-organ disease is the occurrence of clinical symptoms and signs of organ involvement, with CMV documented in tissue by virus isolation, rapid culture, histopathology, immunohistochemistry, DNA hybridization techniques, or CMV VL.[11,17] uCMVr was defined as CMVi requiring no treatment with antiviral drugs.

The following were considered risk factors for CMVi and CMVd: CMV-seropositive recipient with CMV-seronegative donor, acute GVHD, ex vivo T cell depletion, ATG or alemtuzumab use, prednisone (or

equivalent) at a dose of 1 mg or more per kilogram of body weight per day, mismatched or unrelated donor, haploidentical donor, cord blood transplant, lymphopenia with a total lymphocyte count <300/mm^3, older age, and PTCy.[2,14,18,19]

Patients were stratified according to the risk of developing CMVd. Those presenting one or more of the following factors were stratified as high risk: ex vivo T cell depletion, ATG or alemtuzumab use, prednisone (or equivalent) at a dose of 1 mg or more per kilogram of body weight per day for acute GVHD grade II-IV, mismatched related or unrelated donor, haploidentical donor, and cord blood transplant.[11] Allo-HCT presenting none of the above factors was considered low risk.

For the diagnosis of CMVi, CMV VL was measured in plasma with real-time polymerase chain reaction (qRT-PCR) assay (LightMix, TIB Molbiol) in LightCycler 2.0 or COBAS 480 from January 2012 to November 2021, with a detection threshold of 20 copies/ml and a quantification threshold of 200 copies/ml. From December 2021 onward, CMV VL detection was done with RealStar altona Diagnostic in COBAS 480 with a detection threshold of 100 IU/ml and a quantification threshold of 500 IU/ml. Weekly monitoring started at the time of engraftment or on day 10, whichever occurred first in the PET group and on day 4 to 10 in the LET group, and continued through day 100 post-HCT or beyond in those patients that remained at risk for CMVi.

LET was started after undetectable CMV VL within the previous 48 hours. It was administered from days 5 to 10 and continued through day 100 post-HCT. Since all patients received cyclosporine for GVHD prophylaxis, 240 mg/day of LET was indicated. Only oral formulation was used.

Patients with a positive qRT-PCR result meeting the institutional threshold for PET or with diagnosed CMVd were started on appropriate antiviral therapy according to institutional guidelines.

Regarding CMV VL, the thresholds to consider antiviral treatment for CMVi in the LET group were ≥200 copies/ml in high-risk patients and ≥500 copies/ml in low-risk patients. On the other hand, in the PET group, thresholds were detectable non-quantifiable PCR in high-risk patients and ≥500 copies/ml in low-risk patients.[20] For those managed with CMV VL measured in IU/ml, thresholds were converted to the equivalent in copies/ml. Detectable CMV VL was confirmed with another sample two days later before starting antiviral treatment.

All patients received prophylaxis with acyclovir 800 mg twice daily or valacyclovir 500 mg/day from admission through at least 1-year post-HCT, sulphamethoxazole-trimethoprim three days a week at least six-month post-HCT and until the end of severe immunosuppression, and antifungal prophylaxis through at least day 75 post-HCT according to IDSA and GITMO guidelines.[21-23] GVHD grading was based on consensus guidelines.[24]

Statistical Analysis. Descriptive statistics characterized the study population. For continuous variables, centrality (median) and dispersion (IQR) measures were used according to the distribution of variables. Categorical variables were analyzed using absolute frequency and percentage. Groups were compared using the U Mann-Whitney test for continuous variables and the Fisher exact test or the chi-square test for categorical variables. Kaplan-Meier curves for uCMVi, cs-CMVi, and CMVd were estimated for patients who received primary prophylaxis with LET vs. PET. For all tests, a 95% level of statistical significance was used. Analyses were performed with the SPSS (Statistics for Windows, Version 22.0. Armonk, NY, USA) software packages.

Results. A total of 124 allo-HCT patients were evaluated during the study period (36 in the LET group and 88 in the PET group), and 19 were excluded since they failed to meet the eligibility criteria. In the PET group, 5 were CMV-seronegative, 2 died before engraftment, and 4 were monitored with CMV pp65 antigenemia assay. In the LET group, 3 were CMV-seronegative, 3 died before starting LET and had not developed CMVi, 1 developed cs-CMVi, which required PET with foscarnet before starting LET, and 1 discontinued LET before engraftment due to hemodialysis requirements.

The total study population consisted of 105 patients (28 in the LET group and 77 in the PET group) whose baseline characteristics are described in **Table 1**. There was a predominance of males, with a median age of 42 years. The most frequent underlying diseases were acute myeloblastic leukemia, acute lymphoblastic leukemia, and myelodysplasia; the disease was active in many patients. Compared to the PET group, patients in the LET group received more allo-HCT from alternative donors (54.5% vs. 82.14%, *P=0.012*), as well as a reduced-intensity conditioning regimen. In contrast, the PET group more frequently underwent the myeloablative regimen. In both groups, the drugs most commonly used for conditioning regimens were fludarabine (91, 86.67%) and mefalan or busulfan (90, 85.71%). Only patients in the PET group received ATG as part of the conditioning regimen. Regarding GVHD prophylaxis, 101 (96.19%) patients received cyclosporine, with no differences between groups. Likewise, mycophenolate was more frequently administered in the LET group (24, 85.71% vs. 45, 58.44%, *P=0.009*), as well as PTCy (data shown in **Table 1**).

The median time to granulocyte engraftment in the LET vs. PET group was 18 days (IQR: 17-23) vs. 16 days (IQR: 12-20), respectively, *P=0.018*. Acute GVHD developed in almost half of the patients with no

Table 1. Characteristics of the cohort and differences between patients with preemptive therapy and letermovir primary prophylaxis.

	Total cohort (n=105) n (%)	**Preemptive therapy (n=77)** n (%)	**Letermovir prophylaxis (n=28)** n (%)	***p****
Age (years) – Median (IQR)	42 (33-54)	44 (33-53)	40 (34-55)	0.81
Male sex	64 (60.95)	48 (62.34)	16 (57.14)	0.62
Underlying disease				
Acute myeloid leukemia	42 (40)	32 (41.56)	10 (35.72)	0.58
Acute lymphoblastic leukemia	14 (13.33)	11 (14.29)	3 (10.71)	0.75
Myelodysplastic syndrome	11 (10.48)	6 (7.79)	5 (17.86)	0.15
Myelofibrosis	10 (9.52)	8 (10.39)	2 (7.14)	1
Non-Hodgkin lymphoma	9 (8.57)	8 (10.39)	1 (3.57)	0.43
Hodgkin lymphoma	5 (4.76)	3 (3.9)	2 (7.14)	0.60
Other	14 (13.34)	9 (11.68)	5 (17.86)	0.51
Stage of underlying disease				
Complete remission	33 (31.43)	23 (29.87)	10 (35.71)	0.56
Partial remission	17 (16.19)	12 (15.58)	5 (17.86)	0.77
Relapse	19 (18.1)	15 (19.48)	4 (14.29)	0.77
Refractory	32 (30.48)	25 (32.47)	7 (25)	0.46
Chronic phase	4 (3.81)	2 (2.6)	2 (7.14)	0.28
Stem cell source				
Peripheral blood	87 (82.86)	63 (81.82)	24 (85.71)	0.77
Bone marrow	18 (17.14)	14 (18.18)	4 (14.29)	0.77
HLA matching and donor type				
Matched related	40 (38.1)	35 (45.45)	5 (17.86)	0.01
Matched unrelated	33 (31.43)	21 (27.27)	12 (42.86)	0.12
Mismatched unrelated	4 (3.81)	4 (5.19)	0 (0)	0.57
Haploidentical	28 (26.67)	17 (22.08)	11 (39.29)	0.07
Type of conditioning				
Myeloablative	73 (69.52)	62 (80.52)	11 (39.29)	<0.0001
Non-myeloablative	3 (2.86)	0 (0)	3 (10.71)	0.01
Reduced intensity	29 (27.62)	15 (19.48)	14 (50)	0.002
Anti-thymocyte globulin use	23 (21.9)	23 (29.87)	0 (0)	<0.0001
Post-transplant cyclophosphamide	43 (40.95)	18 (23.38)	25 (89.29)	<0.0001
Acute GVHD	49 (46.67)	37 (48.05)	12 (42.86)	0.63
CMV seropositive donor	67 (63.81)	52 (67.53)	15 (53.57)	0.18
Lymphocytes at day 50 (cells/mm^3) Median (IQR)	459 (208-768)	590 (279-951)	421 (204-662)	0.04
Risk of CMV disease				
High risk	70 (66.67)	54 (70.13)	16 (57.14)	0.21
Low risk	35 (33.33)	23 (29.87)	12 (42.86)	

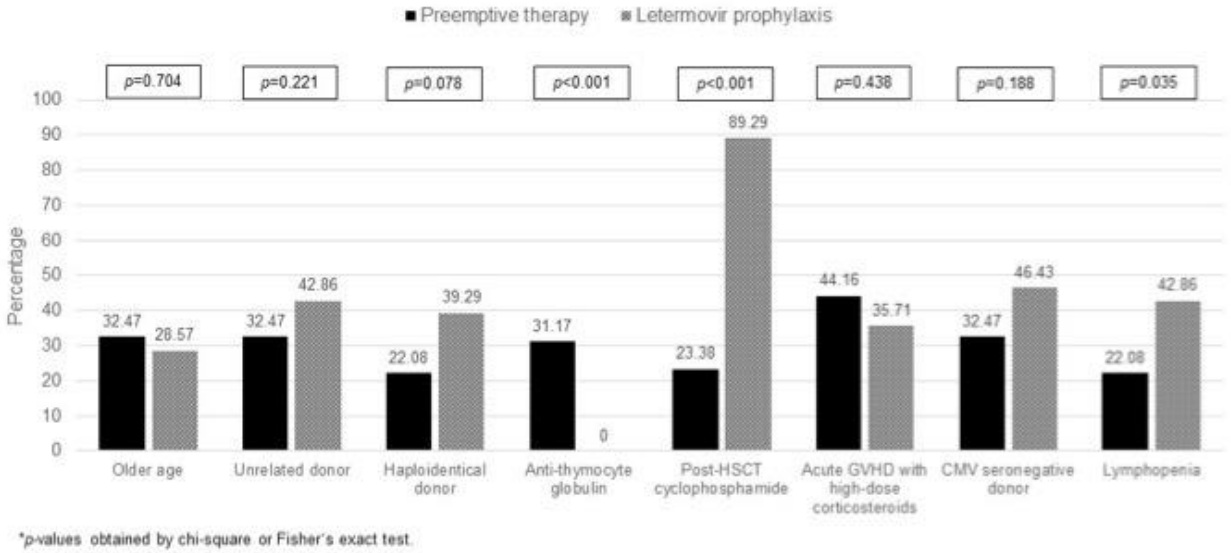
Abbreviation: IQR, interquartile range; GVHD, graft versus host disease. *p-values obtained by chi-square or Fisher's exact test for categorical variables and Mann-Whitney U-test for continuous variables.

differences between groups, as did acute GVHD grades II-IV with high doses of corticosteroid requirements. The GVHD target organs involved were the skin in 34 patients (32.38%), gastrointestinal tract in 29 (27.62%), liver in 6 (5.71%), and lung in 1 (0.95%).

Most patients had several risk factors for CMVi and CMVd, which are outlined in **Figure 1**. The median number of risk factors for PET vs. LET groups were 3 (IQR: 1-5) vs. 4 (IQR: 3-5), respectively, *P=0.72*, and more than half of the patients in both groups were classified as high-risk for CMVd.

In the LET group, prophylaxis duration was 96 days (IQR: 90-100), with adherence of 100%, and 21 patients evidencing disruption of the gastrointestinal barrier in the pre-engraftment and post-engraftment periods (mucositis in 12, 42.6%, and GVHD in 9, 32.14%). Only one patient discontinued LET for 5 days due to oral mucositis. Two (7.4%) patients presented mild LET-related adverse events (nausea and dysgeusia). Three patients (10.7%) discontinued LET before day 100 post-

Figure 1. Risk factors for CMV infection and disease



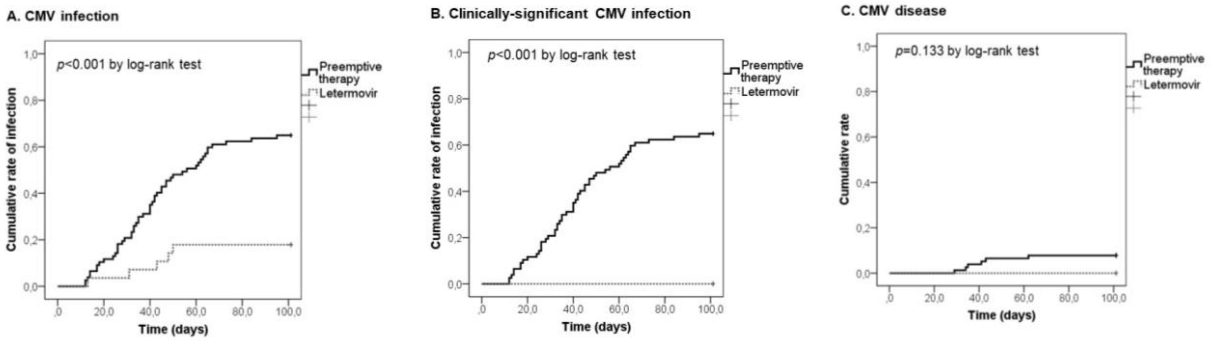


Figure 2. Cumulative rate of CMVi (A), cs-CMVi (B), and CMVd (C) in LET vs. PET groups.

HCT with no CMVi: the first on day 50 due to refractory acute GVHD grade IV, the second on day 57 due to thrombotic microangiopathy requiring hemodialysis and disseminated adenoviral disease, and the third on day 22 due to underlying disease progression.

Cs-CMVi and CMVd developed in 0 vs. 50 (64.94%), *P=<0.0001*, and 0 vs. 6 (7.79%), *P=0.18*, in the LET vs. PET groups, respectively. Five (17.8%) patients in the LET group presented uCMVr, while all episodes in the PET group were cs-CMVi or CMVd. These data are shown in **Figure 2**. More than one CMVi occurred in 2 (7.14%) patients in the LET group and 16 (20.78%) in the PET group. All the patients with uCMVr had detectable non-quantifiable CMV VL, which became negative in the subsequent weekly control without discontinuation of LET. The patients who developed cs-CMVi had a median CMV VL of 1648 copies/ml (IQR: 478-6240). The median time of occurrence of uCMVr and cs-CMVi after HCT was 43 days (IQR: 22-49) and 40 days (IQR: 26-56), respectively, *P=0.84*, while the median lymphocyte counts during the episodes were 532/mm^3 (IQR: 198-731) and 461/mm^3 (220-837), *P=0.84*.

The episodes of cs-CMVi or CMVd were treated with ganciclovir in 32 cases (64%), valganciclovir in 13 (26%), foscarnet in 19 (38%), and cidofovir in 2 (4%). Seventeen (34%) episodes received more than one antiviral drug. The median duration of treatment was 19 days (IQR: 14-33). The 6 patients with CMVd had gastrointestinal (GI) tract involvement, and 2 had CMV VL undetectable at the time of diagnosis. Hospital admission related to cs-CMVi or CMVd in the PET vs. LET group was 47 (61.04%) vs. 0, respectively, *P=<0.0001*. The 100-day mortality in the LET vs. PET groups was 3 (10.71%) vs. 14 (18.18%), *P=0.55*, in no case related to CMVi.

Discussion. This study describes the incidence of uCMVr, cs-CMVi, and CMVd in CMV-seropositive allo-HCT recipients who received primary prophylaxis with LET or were managed with PET within the first 100 days post-transplant. Our cohort mainly comprises patients with several risk factors for CMVi, many of them with an increased risk of developing CMVd. Only the patients managed with PET developed cs-CMVi and CMVd; many of them required hospitalization for CMV antiviral treatment. Patients on LET developed a low rate of uCMVr and few mild adverse events with no need for

drug discontinuation. There was no difference in 100-day mortality between groups.

Several real-world retrospective single-center or multicenter cohort studies have been reported that compared LET primary prophylaxis with controls receiving PET. They could replicate the same results as those obtained in the randomized pivotal phase 3 trial. In one of the largest single-center retrospective studies, Johnsrud et al. compared LET prophylaxis within the first 100 days after allo-HCT in 114 patients at high risk for CMVd with a control group of 637 who received PET. Patients with LET prophylaxis developed no CMVd (0% vs. 5.4%, *P=0.006*) and required lower hospitalization rates (0.93% vs. 15.23%, P=*<0.001*).[25] This data agrees with that described in our cohort.

The clinical benefits of LET prophylaxis were evaluated in a systematic review and meta-analysis of all the published real-world studies.[26] They demonstrated a significant decrease in CMVr, cs-CMVi, and CMVd at day 100 and 200 post-HCT, compared to any control group, usually the historical control group. Furthermore, LET significantly reduced the all-cause and non-relapse mortality beyond day 200 post-HCT. Notwithstanding that, considerable heterogeneity in the clinical criteria used to define CMVir and cs-CMVi and related events among these studies could induce a bias in the final results and should, therefore, be assessed.

Unlike most studies that compare LET with the historical control group, ours included a population with clearly defined criteria, and the entire cohort underwent prospective evaluation and follow-up. Other relevant issues need to be outlined. Since the implementation of monitoring with CMV VL and PET strategy, CMVd mainly developed as a gastrointestinal disease worsening GI GVHD. This is a big challenge for diagnoses since the overall incidence of CMVd could be as high as 25%. However, only 42% of the patients with CMV gastroenteritis had preceding evidence of CMV viremia by qRT-PCR VL.[27] In addition, GI CMVd has to be shown as an independent risk factor for reduced overall survival.[28] In agreement with this data, all CMVd in our study were GI; in 2 of 6 patients, CMV VL was negative at the time of diagnosis.

Two studies showed that patients on PET vs. no PET had an increment of readmissions (55% vs. 34%, *P=0.0001*) and higher antiviral-related adverse events (neutropenia: relative risk [RR] 1.81, 95%CI, 1.48-2.21, and acute kidney injury: RR 2.75, 95%CI, 1.71-4.42).[5,6] Although our study did not evaluate antiviral-related adverse events, we found a higher rate of CMV admissions in the PET group. This data stressed the importance of LET prophylaxis in lowering morbidity in allo-HCT patients.

Unlike Marty's study, we observed that the median time to granulocyte engraftment was longer in the LET group. The slight delay in hematopoietic recovery has been described in haploidentical HCT and those who received PTCy.[29,30] This could explain what was observed in the LET cohort.

Another interesting issue is that no patients in the LET group developed cs-CMVi. In our opinion, this could be due to two reasons. First, compared to Marty's study, in high-risk patients, we chose a higher CMV VL threshold to start PET.[11] Second, our cohort had 100% LET adherence. This is crucial in HIV patients, since virological failure correlates with poor adherence to antiretroviral medications.[31] Given that adherence could not be evaluated in retrospective real-life LET studies, larger prospective studies should be undertaken to address this issue.

Finally, we highlight that all uCMVr in our LET cohort became negative in the subsequent weekly control without discontinuation of LET. These uCMVr were blips defined as the presence of CMV DNA VL at any level in a single plasma specimen, preceded and succeeded by a negative (undetectable) PCR specimen, usually drawn seven days apart.[32] These events were first described in patients without LET prophylaxis and can be frequently observed.[33] Notwithstanding that, this has also been reported in patients under LET.[34] However, as these events usually occur in allo-HCT patients, LET prophylaxis should not be discontinued even in patients at high risk for CMVd until the blip is ruled out.

There are some drawbacks to the present study. 1) The number of patients in each cohort, which limits statistical analysis and hinders assessment of survival in the LET group. Although a more extended follow-up period (beyond day 200 post-HCT) would be more appropriate to evaluate overall mortality, this was not an objective of the study. 2) During the study period, there was a change in the expression of CMV DNA in IU instead of copies/ml, which could lead to a different interpretation of the results. Nevertheless, this was adjusted using a conversion factor. 3) T cell depletion induced by ATG was only observed in the PET group. Thus, this cohort has a higher risk of CMVd. Notwithstanding that, most patients in the LET group received PTCy, which also led to functional and selective T cell depletion by impairment of CD4+ and CD8+ alloreactive T cells.[35] Therefore, patients who received PTCy had lower lymphocyte counts.

The strengths of our research rely on its prospective design, with a high proportion of the cohorts presenting several risk factors for CMVi, as well as increased risk for developing CMVd.

Conclusions. our study showed the clinical benefits of LET prophylaxis for preventing cs-CMVi and CMVd, with a reduction in hospitalization. Likewise, it provided new insight into the incidence of blips that required no discontinuation of LET prophylaxis.

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Authors' Contributions. FH participated in the study's conception and design. FH, DT, MQ, ANR, ET, LR, PD, and CV collected clinical and virology data. DT and ANR analyzed the data. FH and DT wrote the original draft. MQ, ANR, ET, LR, PD, CV, and PB reviewed and proofread the paper. All authors have read and agreed to the published version of the manuscript.

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