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Effective Letemovir Prophylaxis of CMV infection post allogeneic hematopoietic cell transplantation: Results from the French temporary authorization of use compassionate program

David Beauvais^{a,*}, Christine Robin^b, Anne Thiebaut^c, Sophie Alain^d, Valérie Coiteux^a, Sophie Ducastelle-Lepretre^e, Ambroise Marçais^f, Patrice Ceballos^g, Alienor Xhaard^h, Rabah Redjoul^b, Stéphanie Nguyenⁱ, Eolia Brissot^j, Magalie Joris^k, Pascal Turlure^l, Marie-Thérèse Rubio^m, Patrice Chevallierⁿ, Nathalie Bénard^o, Camille Liautard^o, Ibrahim Yakoub-Agha^a

^a Univ Lille, CHU Lille, Hematology Department, Inserm, Infinite U1286, Lille, France

^b University Paris-Est-Créteil, Hematology Department, Assistance Publique-Hopitaux de Paris (AP-HP), Henri Mondor Hospital, Créteil, France

^c Hematology Department, CHU Grenoble, Grenoble, France

^d INSERM, CHU Limoges, RESINFIT, U1092, National Reference Center for Herpesviruses, Limoges University, Limoges, France

^e Department of Hematology, Hospices Civils de Lyon, Hôpital Lyon-Sud, Pierre-Bénite, France

^f Department of adult hematology, Assistance Publique-Hopitaux de Paris, university hospital Necker, Paris, France

^g Hematology Department, Saint-Eloi University Hospital, Montpellier, France

^h Hematology and transplantation unit, Saint Louis Hospital, APHP, Paris, France

ⁱ Department of Hematology, AP-HP, Hôpital Pitié-Salpêtrière, Sorbonne Université, Paris, France

^j Service d'Hématologie Clinique et Thérapie Cellulaire, Hôpital Saint-Antoine, Sorbonne Université, INSERM UMRs 938, Paris, France

^k Department of Haematology, Amiens University Medical Center, Amiens, France

^l CHU Limoges, Univ. Limoges, Department of Hematology, Limoges, France

^m University Hospital of Nancy, Vandoeuvre-Les-Nancy, France

ⁿ Department of Hematology, University Hospital, Nantes, France

^o Medical Affairs, MSD France, Puteaux, France

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ABSTRACT

We report the results of the French Temporary Authorization of Use (ATU) compassionate program of letemovir for primary prophylaxis conducted in 21 transplant centers. Patients were CMV seropositive allogeneic hematopoietic cell transplantation recipients and at high risk for CMV infection. Primary prophylaxis was defined as initiation of letemovir between day 0 and day +28 post-transplant. Between November 2017 and January 2019, 96 patients with a median age of 56 years received letemovir and follow-up data were available for 78 patients. The median time from transplant to letemovir initiation was 4 days, and the median duration of exposure to letemovir was 78 days, with 57 patients still on treatment at the cutoff date. Letemovir was temporarily discontinued in 4 patients (5.1%) and stopped in 39 patients (50.0%), in most cases due to planned end of treatment ($n = 16$, 20.5%). Fifteen patients (19.2%) each presented one positive CMV PCR, in median 13 days after letemovir initiation. Clinically significant CMV infection was reported in 5 patients (6.4%). No CMV disease was reported. At least one adverse drug reaction was reported for 12 patients (15.4%). In this early access program, letemovir was effective with comparable results of the phase 3 study with a low rate of clinically significant CMV infection, including in patients who were at high-risk for CMV infection.

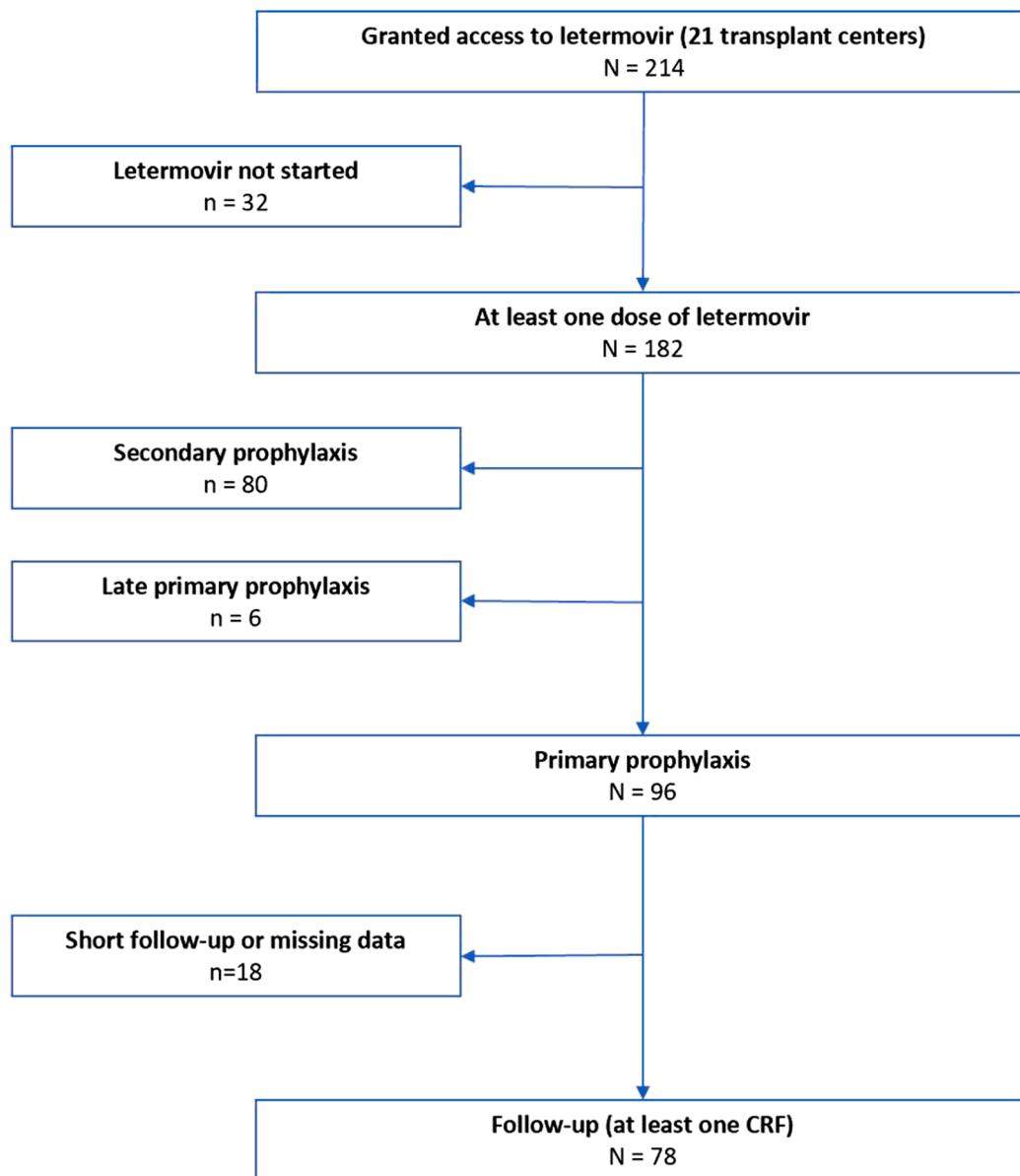
* Corresponding author: UAM allogreffe de cellules souches hématopoïétiques, CHU Lille – Hôpital Huriez, 1 rue Michel Polonovski, F-59037 Lille CEDEX, France.
E-mail address: david.beauvais@chru-lille.fr (D. Beauvais).

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CRF: case report form

Fig. 1. Flow-chart of letermovir use for study population.

1. Introduction

Cytomegalovirus (CMV) infection is a frequent and potentially severe complication after allogeneic hematopoietic cell transplantation (allo-HCT), as approximately half of allo-HCT recipients are CMV-seropositive [1–6]. CMV infection occurrence depends on multiple risk factors such as level of immunosuppression, donor type and CMV-serostatus, and graft-versus-host disease (GVHD) prophylaxis and treatment [7,8]. Until recently, based on regular monitoring of CMV DNA in the blood during the first months after transplantation, the preemptive strategy was the most widely used [9]. Treatments using specific antiviral agents such as ganciclovir, valganciclovir and foscarnet were initiated according to local procedures given that guidelines do not recommend a specific threshold [10]. A curative strategy, using the same aforementioned drugs, was used in cases of CMV end-organ disease such as pneumonia and gastroenteritis, but has become rarer thanks to the preemptive strategy [11]. In the same way as for other human herpes

viruses (i.e. herpes simplex virus; varicella zoster virus), a preventive strategy has been considered with valaciclovir and ganciclovir/valganciclovir as well as with new drugs such as brincidofovir and maribavir; however, these approaches were either ineffective or too toxic [12–15].

Letermovir is an oral or intravenous specific inhibitor of the CMV terminase complex that works by binding to the terminase components (UL51, UL56, or both) [16]. Positive results from a randomized, double-blind phase 3 study including 565 patients led the Food and Drug Administration and the European Medicines Agency to approve letermovir in 2017 in CMV-seropositive recipients of allo-HCT up to 100 days post-transplant [17–20]. In France, the Temporary Authorization of Use (ATU) compassionate program allows early treatment access. Letermovir ATU was initiated in November 2017 and ended in January 2019 and access to the drug was granted in CMV-seropositive allo-HCT recipients who were considered at high-risk for CMV infection. One hundred and eighty-two patients received treatment and were divided into three

groups according to the type of prophylaxis (primary, late primary, secondary). This article reports the results of primary prophylaxis in the French letermovir ATU cohort.

2. Materials and methods

CMV infection was defined as the detection of CMV DNA in the blood and clinically significant CMV infection by the use of a preemptive therapy. Patients eligible for the letermovir ATU program met the following inclusion criteria: allo-HCT recipient; CMV seropositive; high risk for CMV infection; incompatibility of preemptive therapy with other available antivirals due to potentially deleterious effects. Primary prophylaxis was defined as initiation of letermovir between day 0 and day +28 post allo-HCT without previous CMV infection since allo-HCT. Blood CMV DNA had to be negative before treatment access. The authorization for treatment was mostly granted within 24 h on working days by the *Agence Nationale de Sécurité du Médicament* (ANSM) after having completed an eligibility form including inclusion/exclusion criteria and clinical and laboratory parameters as well as transplant characteristics. A handwritten case report form (CRF) had to be completed by transplant centers at the following time-points post-transplant: letermovir initiation; day +15; day +30; and then once a month until letermovir discontinuation, whatever the reason. Treatment exposure calculation was based on the date of treatment discontinuation when available or the date when the French ATU program ended (cutoff date). Follow-up duration was equivalent to treatment exposure duration as data collection stopped at the time of treatment discontinuation. In case of adverse events, a specific CRF was completed. All CRFs were anonymously sent to a Clinical Research Organization mandated by MSD France for data monitoring and analysis. Data collection ended on January 20, 2019. This French compassionate program was led according to local regulations and the patients were fully informed of their data privacy rights.

Letermovir was stored and delivered to patients by the hospital pharmacy. According to the phase 3 study by Marty et al., letermovir had to be started before day 28 after transplantation. The dose was either 480 mg/day or 240 mg/day (in cases of concomitant use with cyclosporine), with or without food intake [18]. Letermovir was stopped at the physician's discretion, because of clinically significant CMV infection (defined by the use of preemptive treatment, based on a blood CMV DNA threshold between 3.0 and 3.5 log UI/mL, varying by center) or CMV disease, clinician-assessed related adverse event or on day +100 post transplantation. Depending on patient's general condition and gastrointestinal absorption, oral or intravenous forms were made available to the patient. Monitoring letermovir efficacy (weekly CMV DNA whole blood test by real-time PCR) and safety was carried out routinely in both the clinic and laboratory as part of patient analysis.

Descriptive statistical analysis was performed using SAS software package, release 9.2 or higher (SAS Institute, Cary, North Carolina, USA). Quantitative variables were described by median (interquartile range, IQR), and qualitative variables as percentage per modality with 95% confidence interval calculated using the Wilson score interval with continuity correction [21]. Missing values were shown but not factored into percentage calculation.

3. Results

Between November 2017 and January 20, 2019, letermovir access was requested for 217 patients and granted for 214 patients from 21 transplant centers. Thirty-two patients did not start letermovir due to discontinuation of the ATU program ($n = 16$), death ($n = 5$), CMV infection ($n = 3$), non-compliance eligibility criteria ($n = 3$) and unknown reason ($n = 5$). One hundred and eighty-two patients received at least one dose of letermovir including 96 patients for primary prophylaxis. The median time from treatment access to letermovir initiation was 10 days (IQR 7–16). No follow-up report was available for 18

Table 1

Patient characteristics in the primary prophylaxis cohort ($n = 96$).

	n (%) / median	95% CI / IQR
Age, years	56.0	40.0 – 64.0
Sex		
Female	43 (44.8)	34.8 – 55.3
Male	53 (55.2)	44.7 – 65.3
Primary reason for transplant		
Acute myeloid leukemia	45 (46.9)	36.7 – 57.3
Acute lymphoblastic leukemia	16 (16.7)	10.1 – 26.0
Lymphoma	12 (12.5)	6.9 – 21.2
Myelodysplastic syndrome	9 (9.4)	4.6 – 17.5
Myelofibrosis	4 (4.2)	1.3 – 10.9
Myeloma	1 (1.0)	0.1 – 6.5
Chronic myeloid leukemia	1 (1.0)	0.1 – 6.5
Chronic lymphoid leukemia	1 (1.0)	0.1 – 6.5
Aplastic anemia	0 (0)	–
Other diseases	7 (7.3)	3.2 – 14.9
Donor CMV serostatus		
Seronegative	56 (60.9)	50.1 – 70.7
Seropositive	36 (39.1)	29.3 – 49.9
Missing data	4	
High risk factors of CMV infection*	95 (100)	96.2 – 100.0
Unrelated donor	56 (58.9)	48.4 – 68.8
Antithymocyte globulin use	54 (56.8)	46.3 – 66.8
Intensive conditioning regimen	50 (53.8)	43.2 – 64.1
Missing data	2	
Haplo-identical donor	31 (32.6)	23.6 – 43.1
Graft-versus-host disease	3 (3.2)	0.8 – 9.7
Missing data	1	
Alemtuzumab use	2 (2.1)	0.4 – 8.1
Cord blood graft	1 (1.1)	0.1 – 6.6
Ex-vivo T-cell-depleted graft	1 (1.1)	0.1 – 6.6
Missing data	1	
Previous CMV infection	16 (16.8)	10.2 – 26.2
Missing data	1	
Time from previous CMV infection, months	1.6	0.8 – 6.1
Missing data	1	
Previous CMV disease	0 (0)	–
Missing data	2	
Intended immunosuppressant treatment**		
Cyclosporine	87 (94.6)	87.2 – 98.0
Tacrolimus	4 (4.3)	1.4 – 11.4
Others	27 (29.3)	20.6 – 39.9
Missing data	4	
Dose of letermovir		
240 mg/day	87 (91.6)	83.6 – 96.0
480 mg/day	8 (8.4)	4.0 – 16.4
Missing data	1	

CMV: cytomegalovirus; GVHD: graft-versus-host disease; IQR: interquartile range.

*One missing data; some patients may have several high risk factors of CMV infection.

**Some patients may have multiple immunosuppressant treatment.

patients because of short follow-up (< 1 month) due to the end of the ATU program (cutoff date) ($n = 11$) or missing data ($n = 7$). At least one follow-up form was completed for 78 patients (Fig. 1).

Baseline characteristics of the primary prophylaxis cohort at the time of treatment access request are shown in Table 1. Median age was 56 years (IQR 40–64), including 40.7% of patients older than 60, and male patients were slightly predominant at 55.2%. Acute myeloid leukemia was the most common cause of transplantation (46.9%). In 60.9% of patients, the donor was CMV seronegative. All patients had a high risk of CMV infection with at least one of the following high-risk criteria: unrelated donor (58.9%); antithymocyte globulin use (56.8%); intensive conditioning regimen (53.8%); haplo-identical donor (32.6%); GVHD (3.2%); alemtuzumab use (2.1%); cord blood graft (1.1%); ex-vivo T-cell-depleted graft (1.1%). History of CMV infection without CMV disease was found in 16.8% of patients with a median time of 1.6 months (IQR 10.2 – 26.2) from previous infection. Nevertheless, these patients were considered as primary prophylaxis since infection had occurred before transplantation. The intended immunosuppressant treatment was

Table 2
Letermovir utilization (n = 78).

	n (%) / median	95% CI / IQR
Time from transplant to letermovir initiation, days*	4	1 – 8
<i>Missing data</i>	11	
Duration of exposure to letermovir, days	78	44 – 101
<i>Missing data</i>	4	
Duration of exposure in patients having completed the treatment, days**	96	84–109
Letermovir exposition > 100 days	18 (23.1)	14.6–34.2
Dose modification of letermovir***	7 (9.0)	4.0 – 18.2
Dose reduction	3 (3.8)	1.0 – 11.5
Dose increase	5 (6.4)	2.4 – 15.0
Change of formulation	0 (0)	–
Time from treatment initiation to the first dose modification, days	13	6 – 28
<i>Missing data</i>	2	
Temporary interruption of letermovir	4 (5.1)	1.6 – 13.3
Reason for treatment interruption		
HHV6 encephalitis	1 (1.3)	0.1 – 7.9
Grade 4 mucositis	1 (1.3)	0.1 – 7.9
Cytokine release syndrome	1 (1.3)	0.1 – 7.9
No treatment release for outpatient	1 (1.3)	0.1 – 7.9
Time from treatment initiation to the first treatment interruption, days	21	7 – 35
<i>Missing data</i>	1	
Duration of treatment interruption, days	10	9 – 162
<i>Missing data</i>	1	
Discontinuation of letermovir during ATU period	39 (50.0)	38.6 – 61.4
Reason for treatment discontinuation		
Planned end of treatment	16 (20.5)	12.5 – 31.4
CMV infection or disease	5 (6.4)	2.4 – 15.0
Patient death	7 (9.0)	4.0 – 18.2
Adverse event suspected to be related to letermovir	1 (1.3)	0.1 – 7.9
Physician's choice (GVHD/disease relapse)	3 (3.8)	1.0 – 11.5
Other reasons	7 (9.0)	4.0 – 18.2

CMV: cytomegalovirus; GVHD: graft-versus-host disease; HHV6: Human herpesvirus 6; IQR: interquartile range.

*Variable calculated from the 85 initiation forms available.

**Median calculated on 15 patients with available data.

***One patient had reduction and increase of letermovir.

cyclosporine (94.6%), tacrolimus (4.3%) and others (29.3%), resulting in a planned dose of letermovir at 240 mg/day (91.6%) or 480 mg/day (8.4%).

Table 2 shows data regarding letermovir use. The median time from transplant to letermovir initiation was 4 days (IQR 1–8), the median duration of letermovir exposure was 78 days (IQR 44–101) across the entire cohort and 96 days (IQR 84–109) in patients who completed all planned treatment. Fifty-seven patients were still considered on treatment at the end date of the ATU program. Eighteen patients (23.1%) received letermovir for more than 100 days. The dose of letermovir was modified in 7 patients (9.0%) with a median time from treatment initiation of 13 days (IQR 6–28). Letermovir was temporarily interrupted in 4 patients (5.1%) with a median time from treatment initiation of 21 days (IQR 7–35) and a median duration of interruption of 10 days (IQR 9–162). The reasons for temporary interruption were: HHV6 encephalitis (n = 1, 1.3%), grade 4 mucositis (n = 1, 1.3%), cytokine release treatment (n = 1, 1.3%), and no treatment delivery for an outpatient (n = 1, 1.3%). Letermovir was discontinued in 39 patients (50.0%) during ATU period, mostly because of a planned end of treatment (n = 16, 20.5%). CMV infection was evidenced in 5 patients (6.4%). The other causes of discontinuation were patient death (n = 7, 9.0%), renal disorder suspected to be related to letermovir (n = 1, 1.3%), GVHD or disease progression (n = 3, 3.8%) and other reasons (n = 7, 9.0%).

Fifteen patients (19.2%) presented, regardless of the threshold, a CMV infection with at least one positive CMV PCR during the follow-up

Table 3
Complications during follow-up (n = 78).

	n (%) / median	95% CI / IQR
CMV infection	15 (19.2)	11.5 – 30.0
Number of positive PCR per patient	2	1 – 3
Time between letermovir initiation and first positive PCR, days	13	7 – 27
Minimum value of PCR, copies/mL	2 045	125–2 269
<i>Missing data</i>	4	
Maximum value of PCR, copies/mL	3 124	125 – 12 660
<i>Missing data</i>	4	
Clinically significant CMV infection	5 (6.4)	2.4 – 15.0
Minimum value of PCR, copies/mL	2 131	2 045–2 379
Maximum value of PCR, copies/mL	5 769	3 529–12 660
CMV disease	0 (0)	–
Any other infection	32 (46.4)	35.2 – 58.0
Suspected to be related to letermovir	0 (0)	–
<i>Missing data</i>	9	
Death	7 (9.0)	4.0 – 18.2
Disease progression	5 (6.4)	2.4 – 15.0
Suspected to be related to letermovir	0 (0)	–
Graft versus host disease	23 (35.9)	25.6 – 47.6
<i>Missing data</i>	14	
Acute GVHD	21 (32.8)	22.8 – 44.5
Grade I-II	14 (21.9)	13.6 – 33.0
Grade III-IV	7 (10.9)	5.3 – 20.5
Chronic GVHD	2 (3.1)	0.7 – 10.6
At least one reported adverse reaction	12 (15.4)	8.6 – 25.7
Immune system disorders	5 (6.4)	2.4 – 15.0
Acute GVHD	4 (5.1)	1.6 – 13.3
Cytokine release syndrome	1 (1.3)	0.1 – 7.9
Gastrointestinal disorders	2 (2.6)	0.5 – 9.9
Diarrhea	1 (1.3)	0.1 – 7.9
Enterocolitis	1 (1.3)	0.1 – 7.9
Transaminitis	2 (2.6)	0.5 – 9.9
Renal and urinary disorders	3 (3.9)	1.0 – 11.7
Acute kidney injury	2 (2.6)	0.5 – 9.9
Toxic nephropathy	1 (1.3)	0.1 – 7.9
Cardiac disorders	3 (3.9)	1.0 – 11.7
Acute cardiac failure	2 (2.6)	0.5 – 9.9
Atrial fibrillation	1 (1.3)	0.1 – 7.9
Central nervous system disorders	1 (1.3)	0.1 – 7.9
Encephalitis	1 (1.3)	0.1 – 7.9
Seizures	1 (1.3)	0.1 – 7.9

CMV: cytomegalovirus; GVHD: graft-versus-host disease; PCR: Polymerase chain reaction; IQR: interquartile range.

with a median number of positive PCR per patient of 2 (IQR 1–3) and a median time from letermovir initiation of 13 days (IQR 7–27) (**Table 3**). The minimum and maximum median values of CMV PCR were 2 045 copies/mL (IQR 125–2 269) and 3124 copies/mL (IQR 125–12 660), respectively. Clinically significant CMV infection was reported in 5 patients (6.4%), representing one third of the patient population with at least one positive CMV PCR. Of these 5 patients, none had CMV infection before transplantation and the median maximum value of CMV PCR was higher (5 769 copies/mL, IQR 3 529–12 660) compared to those without clinically significant CMV infection (419 copies/mL, IQR 125–2 269). No CMV disease was reported during follow-up. Kaplan-Meier analysis for clinically significant CMV infection is shown in **Fig. 2**. Of interest, GVHD was frequent in the 15 patients with positive CMV PCR (n = 11, 73.3%). Non-CMV infections were reported in 32 patients (46.4%) without any suspected infection related to letermovir. Five patients (6.4%) experienced a disease progression. GVHD was reported in 23 patients (35.9%) including grade I-II acute GVHD (n = 14, 21.9%), grade III-IV acute GVHD (n = 7, 10.9%) and chronic GVHD (n = 2, 3.1%). At least one adverse drug reaction was reported for 12 patients (15.4%) (**Table 3**).

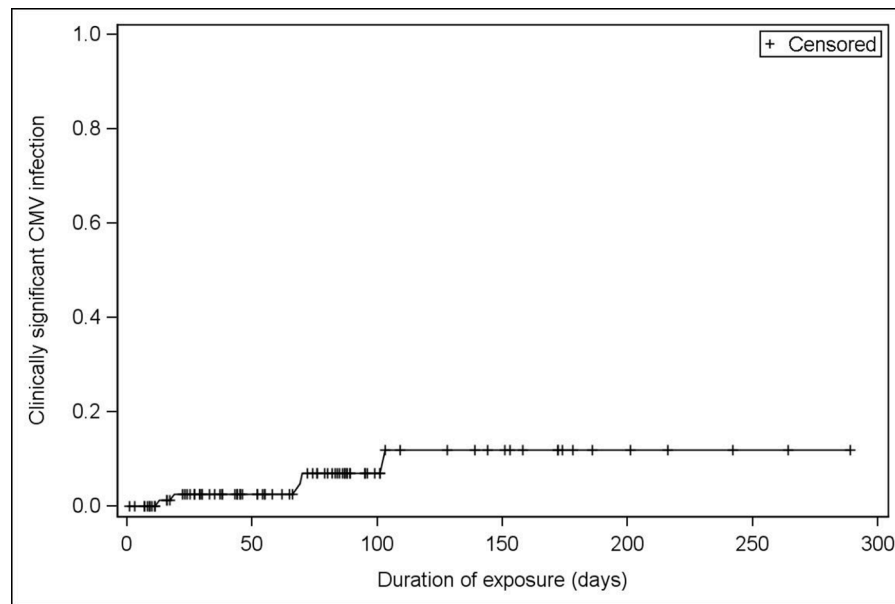


Fig. 2. Kaplan-Meier analysis for clinically significant CMV infection.

4. Discussion

Letermovir efficacy in preventing CMV infection in CMV-seropositive patients after allo-HCT has been demonstrated by Marty et al. in a phase 3 study, and represents a breakthrough in the field of viral complications after allo-HCT [18]. Remarkably, adverse events were not different between the letermovir group and the placebo group. Nevertheless, after approval, making a new drug available to a large number of patients may reveal adverse events not observed during the clinical trial. Indeed, patients in the real world context are selected according to less stringent criteria and may present more comorbidities [22]. Additionally, efficacy may differ due to multiple factors such as non-compliance, malabsorption, drug interaction, and other routine care issues. Real-world studies are therefore essential and form part of the drug's life cycle [23]. The population of the French letermovir ATU program was divided into 3 prophylaxis groups—primary, late primary, and secondary. The results of secondary prophylaxis have already been described [24]. Primary prophylaxis, defined as initiation of letermovir before day 28 post allo-HCT, as in the phase 3 study, accounted for 96 patients. Inclusion in the French ATU compassionate program required CMV-seropositive patients to be at high-risk for CMV infection. The most frequently reported high-risk factors in the compassionate program were receiving a graft from an unrelated donor (58.9%) and antithymocyte globulin use (56.8%), which were not considered as high-risk factors in the study of Marty et al.

The threshold at which CMV infection should be considered clinically significant and preemptive treatment should be initiated has long been debated and varies from center to center [25–27]. The impact of CMV PCR blips has remained uncertain as this may reflect PCR artifact or transient low-level replication [28]. In France, there is a consensus to initiate preemptive therapy with a blood CMV PCR thresholds between 3.0 and 3.5 log UI/mL [29]. The rate of viral load increase must also be considered [30]. Thresholds suggested in the letermovir phase 3 study were lower: 150 copies/mL for low-risk patients and 300 copies/mL for high-risk patients [18]. In the French ATU program, 19.2% of patients had a CMV infection with at least one positive CMV PCR but only 6.4% received preemptive treatment at a minimum viral load median of 2 131 copies/mL (IQR 2 045–2 379). These numbers are comparable to the letermovir group in the Marty et al. study in which 7.7% of patients presented clinically significant infection at week 14. Interestingly, the infection rate increased to 17.5% at week 24 after discontinuation of

letermovir and was probably related to GVHD and corticosteroids use according to the authors. We were not able to study this new period of CMV risk because of a short follow-up of patients whose treatment was discontinued soon after letermovir initiation due to the program ending and due to a limited proportion of patients (23.1%) exposed to letermovir for longer than 100 days. Nonetheless this incidence rate at week 14 is very low compared with studies using similar thresholds but without letermovir, thus strengthening clinical trial results [10,31]. GVHD was frequent (73.3%) in patients with positive CMV PCR, suggesting GVHD as a very high risk factor for CMV infection despite letermovir use [32–34].

Letermovir is a new drug with few known side effects. In the phase 3 study, 17.2% of patients discontinued the trial before week 24 versus 15.9% in the placebo group, mainly because of patient's death without CMV infection [18]. Discontinuation of the trial due to adverse events was reported in 1.8% and 0.6% of patients in the letermovir and placebo groups, respectively. In this compassionate program, only one patient (1.3%) stopped letermovir due to suspected letermovir-related adverse events. No significant specific letermovir complications were reported in the compassionate program. Despite the few adverse effects of letermovir described to date, it should be used carefully because of potential multiple drug interactions. As a CYP3A moderate inhibitor and CYP2C9/19 inducer, therapeutic drug monitoring is recommended where used in combination with cyclosporine and voriconazole [35,36]. In addition, letermovir is eliminated by the hepatic transporter OATP1B1/3 which is inhibited by cyclosporine, leading to a recommendation to reduce the letermovir dose when used in combination with cyclosporine [37]. Other drugs leading to clinically relevant interactions related to transporter inducers (e.g. P-glycoprotein) and/or enzymes (e.g. UDP-glucuronosyltransferase) should not be used with letermovir as it may lead to subtherapeutic letermovir exposure. As letermovir subexposure has been shown to be associated to CMV replication or emergence of resistance [38], monitoring letermovir concentrations could be useful in detecting both under or overexposure to the drug. In view of these issues, real-world studies are particularly important to detect the causes of unexplained adverse events and potential loss of efficacy [39].

The French letermovir ATU compassionate program's results for primary prophylaxis of CMV infection is the first real-world report conducted in multiple transplant centers. Homogeneity was achieved through the French ATU program with strict access criteria. Monitoring

was done prospectively, and data collection was centralized in a dedicated unit. Several limitations can be noted, the main one being that the analysis was not controlled. The decision to discontinue letermovir was made at the discretion of the treating physician and local procedures. No follow-up visit was available for 18 patients, mainly due to the end of the ATU program in January 2019. Finally, due to the very limited data, the effect of letermovir on late CMV infection after day 100 was not evaluable. Because CMV infection appears to increase after discontinuation of letermovir in the phase 3 study, probably related to GVHD and corticosteroids use, extended follow-up should be done in real-world studies. In this way, the results of the clinical trial evaluating the value of prolonging letermovir from day 100 to day 200 will be of great interest (NCT 03930615).

Despite these limitations, this multicenter report in current practice confirms the interest of letermovir, certainly in patients who are high-risk for CMV infection. Because of its high efficacy, letermovir is likely to change practices in hematopoietic transplantation and, in the future, it could be considered in solid organ transplantation where CMV infection also affects numerous patients (phase III ongoing study in kidney transplant recipients, NCT03443869) [40].

5. Authorship statement

AT, SA, NB, CL and IYA designed the study. DB, CR, VC, SDL, AM, PC, AXE, RR, SN, EB, MJ, PT, MTR and PC provided the study materials or patients. DB, NB, CL and IYA assembled and analyzed the data. DB and IYA drafted the manuscript. All authors approved the final version.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: DB received an honorarium from MSD. NB and CL are employees of MSD France. AT and SA have been consultants for MSD France. All other authors declare no commercial or financial relationship that could be construed as a potential conflict of interest.

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Bibliography

- [1] S.A.S. Staras, S.C. Dollard, K.W. Radford, W.D. Flanders, R.F. Pass, M.J. Cannon, Seroprevalence of cytomegalovirus infection in the United States, 1988-1994, *Clin. Infect. Dis.* 43 (2006) 1143-1151.
- [2] S.L. Bate, S.C. Dollard, M.J. Cannon, Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988-2004, *Clin. Infect. Dis.* 50 (2010) 1439-1447.
- [3] P. Ljungman, R. Brandan, Factors influencing cytomegalovirus seropositivity in stem cell transplant patients and donors, *Haematologica* 92 (2007) 1139-1142.
- [4] P. Teira, M. Battiwalla, M. Ramanathan, et al., Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis, *Blood* 127 (2016) 2427-2438.
- [5] Z. Hakimi, S. Ferchichi, S. Aballea, et al., Burden of cytomegalovirus disease in allogeneic hematopoietic cell transplant recipients: a national, matched cohort study in an inpatient setting, *Curr Res Transl Med* 66 (2018) 95-101.
- [6] R. Peffault De Latour, P. Chevallier, D. Blaise, et al., Clinical and economic impact of treated CMV infection in adult CMV-seropositive patients after allogeneic hematopoietic cell transplantation, *J. Med. Virol.* (2020) published online April 16. DOI:10.1002/jmv.25895.
- [7] V. Emery, M. Zuckerman, G. Jackson, et al., Management of cytomegalovirus infection in haemopoietic stem cell transplantation, *Br. J. Haematol.* 162 (2013) 25-39.
- [8] D. Beauvais, E. Drumez, D. Blaise, et al., Scoring system for clinically significant CMV infection in seropositive recipients following allogeneic hematopoietic cell transplant: an SFGM-TC study, *Bone Marrow Transplant.* (2020) 1-11.
- [9] M. Boeckh, P. Ljungman, How we treat cytomegalovirus in hematopoietic cell transplant recipients, *Blood* 113 (2009) 5711-5719.
- [10] M.L. Green, W. Leisenring, H. Xie, et al., Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study, *Lancet Haematol.* 3 (2016) e119-e127.
- [11] P. Ljungman, R. de la Camara, C. Robin, et al., Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7), *Lancet Infect. Dis.* 19 (2019) e260-e272.
- [12] N. Gagelmann, P. Ljungman, J. Styczynski, N. Kröger, Comparative efficacy and safety of different antiviral agents for cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation: a systematic review and meta-analysis, *Biol. Blood Marrow Transplant.* 24 (2018) 2101-2109.
- [13] F.M. Marty, P. Ljungman, G.A. Papanicolaou, et al., Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial, *Lancet Infect. Dis.* 11 (2011) 284-292.
- [14] M. Boeckh, W.G. Nichols, R.F. Chemaly, et al., Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a randomized trial, *Ann. Intern. Med.* 162 (2015) 1-10.
- [15] F.M. Marty, D.J. Winston, R.F. Chemaly, et al., A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Oral Brinciclovir for cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation, *Biol. Blood Marrow Transplant.* 25 (2019) 369-381.
- [16] E.M. Borst, J. Kleine-Albers, I. Gabaev, et al., The Human Cytomegalovirus UL51 Protein Is Essential for Viral Genome Cleavage-Packaging and Interacts with the Terminase Subunits pUL56 and pUL89, *J. Virol.* 87 (2013) 1720-1732.
- [17] R.F. Chemaly, A.J. Ullmann, S. Stoelben, et al., Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation, *N. Engl. J. Med.* 370 (2014) 1781-1789.
- [18] F.M. Marty, P. Ljungman, R.F. Chemaly, et al., Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation, *N. Engl. J. Med.* 377 (2017) 2433-2444.
- [19] P. Ljungman, M. Schmitt, F.M. Marty, et al., A Mortality Analysis of Letermovir Prophylaxis for Cytomegalovirus (CMV) in CMV-Seropositive Recipients of Allogeneic Hematopoietic-Cell Transplantation, *Clin. Infect. Dis.* (2019) published online June 8. DOI:10.1093/cid/ciz490.
- [20] F. Foolad, S.L. Aitken, R.F. Chemaly, Letermovir for the prevention of cytomegalovirus infection in adult cytomegalovirus-seropositive hematopoietic stem cell transplant recipients, *Expert Rev. Clin. Pharmacol.* 11 (2018) 931-941.
- [21] A. Agresti, B.A. Coull, Approximate is Better than "Exact" for Interval Estimation of Binomial Proportions, *Am. Stat.* 52 (1998) 119-126.
- [22] P. Chhabra, X. Chen, S.R. Weiss, Adverse event reporting patterns of newly approved drugs in the USA in 2006: an analysis of FDA Adverse Event Reporting System data, *Drug Saf.* 36 (2013) 1117-1123.
- [23] V. Suvarna, Phase IV of drug development, *Perspect. Clin. Res.* 1 (2010) 57-60.
- [24] C. Robin, A. Thiebaut, S. Alain, et al., Letermovir for secondary prophylaxis of cytomegalovirus infection and disease after allogeneic hematopoietic cell transplantation: results from the French compassionate program, *Biol. Blood Marrow Transplant.* 26 (2020) 978-984.
- [25] G. Gerna, D. Lilleri, D. Caldera, M. Furione, L. Zenone Bragotti, E.P. Alessandrino, Validation of a DNAemia cutoff for preemptive therapy of cytomegalovirus infection in adult hematopoietic stem cell transplant recipients, *Bone Marrow Transplant.* 41 (2008) 873-879.
- [26] F. Mullier, B. Kabamba-Mukadi, M. Bodéus, P. Goubau, Definition of clinical threshold for CMV real-time PCR after comparison with PP65 antigenaemia and clinical data, *Acta Clin. Belg.* 64 (2009) 477-482.
- [27] C. Solano, E. Giménez, J.L. Piñana, et al., Preemptive antiviral therapy for CMV infection in allogeneic stem cell transplant recipients guided by the viral doubling time in the blood, *Bone Marrow Transplant.* 51 (2016) 718-721.
- [28] I.P. Lodding, A. Mocroft, C. da Cunha Bang, et al., Impact of CMV PCR blips in recipients of solid organ and hematopoietic stem cell transplantation, *Transplant. Direct* 4 (2018) e355.
- [29] E. Brissot, T. Alsuliman, B. Gruson, et al., [How to manage EBV reactivation and EBV-PTLD, CMV and human herpesvirus 6 reactivation and infection after allogeneic stem cell transplantation: a report of the SFGM-TC (update)], *Bull. Cancer* 104 (2017) S181-S187.
- [30] V.C. Emery, C.A. Sabin, A.V. Cope, D. Gor, A.F. Hassan-Walker, P.D. Griffiths, Application of viral-load kinetics to identify patients who develop cytomegalovirus disease after transplantation, *Lancet* 355 (2000) 2032-2036.
- [31] R.F. Chemaly, L. El Haddad, D.J. Winston, et al., Cytomegalovirus (CMV) Cell-mediated immunity and CMV infection after allogeneic hematopoietic cell transplantation: the REACT study, *Clin. Infect. Dis.* (2020) published online Feb 20. DOI:10.1093/cid/ciz1210.
- [32] W. Miller, P. Flynn, J. McCullough, et al., Cytomegalovirus infection after bone marrow transplantation: an association with acute graft-v-host disease, *Blood* 67 (1986) 1162-1167.
- [33] L. Cohen, M. Yeshurun, O. Shpilberg, R. Ram, Risk factors and prognostic scale for cytomegalovirus (CMV) infection in CMV-seropositive patients after allogeneic hematopoietic cell transplantation, *Transpl. Infect. Dis.* 17 (2015) 510-517.
- [34] A. Ghobadi, D.R. Milton, L. Gowda, et al., HLA-DP mismatch and CMV reactivation increase risk of aGVHD independently in recipients of allogeneic stem cell transplant, *Curr. Res. Transl. Med.* 67 (2019) 51-55.
- [35] J.B. McCrea, S. Macha, A. Adedoyin, et al., Pharmacokinetic drug-drug interactions between letermovir and the immunosuppressants cyclosporine, tacrolimus, sirolimus, and mycophenolate mofetil, *J. Clin. Pharmacol.* 59 (2019) 1331-1339.
- [36] A. Duong, A. Sweet, R. Jain, et al., Clinically significant drug interaction: letermovir and voriconazole, *J. Antimicrob. Chemother.* 75 (2020) 775-777.

- [37] J. Kobie, Z. Guo, C.R. Cho, et al., Pharmacogenetic Analysis of OATP1B1, UGT1A1, and BCRP variants in relation to the pharmacokinetics of letermovir in previously conducted clinical studies, *J. Clin. Pharmacol.* 59 (2019) 1236–1243.
- [38] S. Alain, L. Feghoul, S. Girault, et al., Letermovir breakthroughs during the French Named Patient Programme: interest of monitoring blood concentration in clinical practice, *J. Antimicrob. Chemother.* 75 (2020) 2253–2257.
- [39] A. Lin, M. Maloy, Y. Su, et al., Letermovir for primary and secondary cytomegalovirus prevention in allogeneic hematopoietic cell transplant recipients: real-world experience, *Transpl. Infect. Dis.* 21 (2019) e13187.
- [40] C. Lumbreras, O. Manuel, O. Len, I.J.M. ten Berge, D. Sgarabotto, H.H. Hirsch, Cytomegalovirus infection in solid organ transplant recipients, *Clin. Microbiol. Infect.* 20 (2014) 19–26.