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Original article

LETERMOVIR PROPHYLAXIS FOR CYTOMEGALOVIRUS INFECTION IN HEMATOPOIETIC TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE

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Abstract

Introduction: Post-transplant cyclophosphamide is a widely used platform for graft-versus-host disease prophylaxis in allogeneic hematopoietic cell transplantation (allo-HCT). However, it is associated with a higher incidence of cytomegalovirus (CMV) infection, regardless of donor type. Primary prophylaxis with letermovir has been shown to reduce the rate of CMV infection.

Materials and methods: This multicenter, retrospective cohort study aimed to evaluate the efficacy of letermovir for CMV prophylaxis in CMV seropositive patients undergoing alternative donor allo-HCT, using post-transplantation cyclophosphamide-based graft-versus-host disease prophylaxis compared to those who did not receive primary prophylaxis in a real-world setting in Argentina.

Results: A total of 136 adult patients who underwent allo-HCT between January 2018 and December 2022 were analyzed, of whom 36 received letermovir. Most of the patients underwent haploidentical allo-HCT (82%). The median follow-up time was shorter for the letermovir group, 7.6 months (IQR 2.9-13.7) vs. 13.2 months (IQR: 4.4-27.6), due to the more recent introduction of letermovir in Argentina. The cumulative incidence of CMV infection at day +100 was significantly lower in patients treated with letermovir: 14% (CI 5-27) vs. 56% (CI 46-65), p=0.0003, and this benefit persisted at one year: 37% (CI 21-53) vs. 56% (CI 46-65), p=0.0019). The 1-year cumulative incidence of non-relapse mortality was similar between patients with and without letermovir treatment (26% vs. 28%), as was overall survival (62% vs. 62%).

Discussion: In summary, letermovir effectively prevented CMV infection in this high-risk population of allo-HCT recipients.

Key words: letermovir, hematopoietic stem cell transplantation, cytomegalovirus infection, prophylaxis, post-transplant cyclophosphamide

Resumen

Profilaxis con letermovir para infección por citomegalovirus en trasplante hematopoyético con ciclofosfamida post-trasplante

Introducción: La ciclofosfamida post-trasplante es una plataforma ampliamente utilizada para la profilaxis de la enfermedad injerto contra huésped en receptores de trasplante alogénico de células precursoras hematopoyéticas (alo-TCPH). Sin embargo, se asocia con mayor incidencia de infección por citomegalovirus (CMV), independientemente del tipo de donante. La profilaxis primaria con letermovir demostró beneficio disminuyendo la tasa de infección por CMV.

Materiales y métodos: Estudio de cohorte, retrospectivo y multicéntrico para evaluar la eficacia de letermo-

vir como profilaxis primaria de infección por CMV en receptores sero-positivos de alo-TCPH que recibieron ciclofosfamida post-trasplante y comparar con aquellos que no recibieron profilaxis.

Resultados: Analizamos 136 pacientes adultos trasplantados entre enero de 2018 y diciembre de 2022, de los cuales 36 recibieron letermovir. La mayoría realizaron alo-TCPH con donante haploidéntico (82%). La mediana de tiempo de seguimiento fue más corta para el grupo letermovir, 7.6 meses (RIC: 2.9-13.7) vs. 13.2 (RIC: 4.4-27.6), por su reciente aprobación. La incidencia acumulada de infección por CMV al día +100 fue significativamente menor en los pacientes tratados con letermovir: 14% (IC 5-27) vs. 56% (IC 46-65), p=0.0003, manteniéndose este beneficio al año: 37% (IC 21-53) vs. 56% (IC 46-65), p=0.0019. Al año de seguimiento, la incidencia acumulada de mortalidad no relacionada a la recaída fue similar en ambos grupos (26% vs. 28%), así como la sobrevida global (62% vs. 62%).

Discusión: En resumen, el letermovir fue efectivo en la prevención de infección por CMV en esta cohorte de pacientes de alto riesgo.

Palabras clave: letermovir, trasplante alogénico de células precursoras hematopoyéticas, infección por citomegalovirus, profilaxis, ciclofosfamida post-trasplante

KEY POINTS

- Post-transplant cyclophosphamide is widely used for graft-versus-host disease prevention in allogeneic hematopoietic cell transplantation; however, it increases the risk of cytomegalovirus (CMV) infection. Primary prophylaxis with letermovir resulted in a decreased incidence of CMV infection, and was approved in Argentina in May 2020; however, insurance coverage restrictions limit its use. We evaluated the efficacy of letermovir in a real-world setting in Argentina, focusing on a high-risk cohort of patients who received post-transplant cyclophosphamide as graft-versus-host disease prophylaxis. Our findings showed that letermovir was highly effective in preventing CMV infection, but this effect did not lead to improved non-relapse mortality or overall survival outcomes.

Despite effective therapies, cytomegalovirus (CMV) reactivation remains a considerable threat after allogeneic hematopoietic transplantation (allo-HCT), with significantly associated morbidity, mortality and costs. It is associated with negative transplant outcomes due to increased risk of coinfections, graft-versus-host disease (GVHD), neutropenia, and poor graft function, all conditions translated into increased transplant-related mortality and direct transplant costs[1-5].

Post-transplant cyclophosphamide is a widely used platform for GVHD prophylaxis in allo-HCT[6-8]. However, a study by the Center for International Blood and Marrow Transplant Research (CIBMTR) demonstrated its association with a higher incidence of CMV infection, irrespective of the donor source[9].

Letermovir, a CMV DNA terminase complex inhibitor, has been approved for the prophylaxis of CMV infection and disease in adult recipients of allo-HCT who are CMV seropositive based on the results of a clinical trial published by Marty et al, in 2017[10]. This randomized, placebo-controlled, phase 3 study showed that letermovir significantly reduced the risk of clinically significant CMV infection (defined as CMV disease or CMV viremia leading to preemptive treatment) by week 24 after transplantation. Because the results were consistent across risk groups, letermovir was considered a universal prophylaxis through day 100 after allo-HCT in the CMV seropositive population. However, although most categories of risk factors for CMV reactivation were represented in the study population, data related to patients who received cyclophosphamide after allo-HCT were not collected systematically.

Multiple real-world studies have replicated the results reported by Marty et al[11]. However, the majority of these studies were conducted in the USA or Europe, leading to a significant gap in data representation from Latin America. In Argentina, letermovir was approved in May 2020; nevertheless, access remains severely restricted due to a lack of insurance coverage.

Therefore, we aimed to evaluate the reproducibility of the efficacy of letermovir for CMV prophylaxis in a real-world setting in Argentina, focusing on a high-risk cohort of patients who

received post-transplant cyclophosphamide as GVHD prophylaxis. The primary endpoint was the cumulative incidence of CMV infection post-allo-HCT between patients who received letermovir for prophylaxis and those who did not, while secondary endpoints included cumulative incidence of acute GVHD and chronic GVHD, cumulative incidence of relapse, cumulative incidence of non-relapse mortality, and overall survival.

Materials and methods

This is a retrospective multicenter cohort study of adult patients undergoing allo-HCT at five GATMO-TC centers in Argentina between January 2018 and December 2022. The inclusion criteria were as follows: (a) age ≥ 18 years; (b) CMV-seropositive recipients; (c) receiving post-transplant cyclophosphamide; and (d) haploidentical, matched unrelated, or mismatched unrelated donor. We excluded patients who (e) used letermovir as secondary prophylaxis for previous CMV infection, (f) had detectable CMV viral load at the initiation of letermovir, and (g) followed up less than 100 days after allo-HCT.

Since there is no standardized cutoff for CMV viral load to initiate treatment, CMV infection was defined based on the concept of clinically significant CMV infection. This includes positive viremia requiring treatment and/or organ damage caused by CMV infection. The same definition was used in the study by Marty et al. and aligns with the definition proposed by the *Consensus Definitions of Cytomegalovirus (CMV) Infection and Disease in Transplant Patients, Including Resistant and Refractory CMV, for Use in Clinical Trials*[10,12].

The use of letermovir was subject to approval by the patient's social health coverage, as it is a high-cost drug. Patients who did not receive primary prophylaxis underwent preemptive treatment with ganciclovir, valganciclovir, or foscarnet at the onset of positive viremia, with treatment selection tailored to patient characteristics and institutional protocols. In both groups, anti-CMV therapy was initiated upon diagnosis of CMV infection, in accordance with the local practices of each center.

In alignment with site-specific guidelines, letermovir was administered at a dose of 480 mg orally once daily (or 240 mg daily for patients taking cyclosporine) starting from either day 0 or post-leukocyte engraftment and continuing until day +100. PCR tests were performed following standardized procedures for patients with and without primary prophylaxis. Typically, CMV blood PCR monitoring began at engraftment and continued weekly until day +100. From months 3 to 6 post-allo-HCT, monitoring was conducted every 1 to 2 weeks.

Data were obtained retrospectively from medical records. The patients were followed up longitudinally until death or last contact. The variables analyzed were donor type, patient age and sex, pre-transplant CMV serological status, type of conditioning regimen (myeloablative vs. reduced intensity or non-myeloablative), type of immunosuppression, and stem cell source. Comorbidities were categorized using the hematopoietic cell transplantation–specific comorbidity index (HCT-CI) published by Sorror et al[13]. Disease status was categorized into three categories: "Early" includes patients with acute lymphoblastic leukemia and acute myeloid leukemia in first complete remission, chronic myeloid leukemia in first chronic phase, myelodysplastic syndromes with less than or equal to 5% blasts, and non-Hodgkin's lymphoma or Hodgkin's lymphoma in remission or partial remission; "Intermediate" comprises individuals with acute lymphoblastic leukemia and acute myeloid leukemia in the second or subsequent complete remission, and chronic myeloid leukemia in the accelerated phase or second chronic phase; and "advanced" category includes patients with acute myeloid leukemia and acute lymphoblastic leukemia without remission, chronic myeloid leukemia in blast phase, myelodysplastic syndromes with excess blasts, and non-Hodgkin's lymphoma or Hodgkin's lymphoma with stable or progressive disease. We also utilized the Disease Risk Index (DRI) to categorize patients based on their risk of disease[14]. Acute and chronic GVHD were graded using MAGIC consortium criteria and NIH classification respectively[15,16].

Continuous variables are expressed as means and ranges according to their distribution, categorical variables are reported as frequencies and percentages. Continuous variables with normal distribution were compared using the t test for independent samples; otherwise, the Mann-Whitney U test was used. Categorical variables were compared using the chi-square test for independent samples and the Fisher exact test. Survival probabilities were calculated using Kaplan-Meier analysis, and the groups were compared using the log-rank test. Cumulative incidence functions were used to calculate the cumulative incidence of CMV infection, acute GVHD, chronic GVHD, relapse, and non-relapse mortality. Relapse and death for any cause was a competing event for CMV infection and GVHD. Relapse was a competing event for non-relapse mortality and vice versa. Gray's test was used to compare cumulative incidence functions. For the analysis, the statistical software IBM SPSS Statistics for Windows, version XX (IBM Corp., Armonk, N.Y., USA) was used.

The study was approved by the Institutional Ethics Committee for Health Research of the Instituto Alexander Fleming. An exemption from obtaining informed consent was requested due to the retrospective nature of the study, ensuring confidentiality in the collection of data from medical records.

Results

A total of 136 patients were analyzed, 36 received primary prophylaxis with letermovir. The baseline characteristics of the study participants in both groups are shown in Table 1. The median age at allo-HCT was 47.5 years, 62.5% were male, and the most frequent diagnoses were acute myeloid leukemia (52%) and acute lymphoblastic leukemia (36%). Most of the patients underwent haploidentical allo-HCT (82.4%) and myeloablative conditioning (61.8%).

In the bivariate analysis between the groups, there were no significant differences in variables such as age, sex, underlying disease, DRI, HCT-CI, donor type, conditioning intensity, source, and acute GVHD ≥ grade II. Differences were observed in the pre-allo-HCT disease status, with a higher number of intermediate-risk patients in the letermovir group (p=0.022), and CMV receptor/donor (R/D) status, with more R positive/D negative patients in the letermovir group (p=0.029). Letermovir recipients had a shorter follow-up than no-letermovir patients, as expected (7.6 months, IQR 2.9-13.7; and 13.2 months, IQR 4.4-27.6, respectively), due to the more recent introduction of letermovir in Argentina.

The cumulative incidence of CMV infection on day +100 was significantly lower in patients receiving letermovir: 14% (95% CI, 5-27) vs. 56% (95% CI, 46-65), p=0.0003, and this benefit persisted at one year: 37% (95% CI, 21-53) vs. 56% (95% CI, 46-65), p=0.0019 (Fig. 1). Regarding patients under letermovir, five developed CMV infection, four with viremia, one with organ damage, and those without prophylaxis: 60 patients developed CMV infection, 55 with viremia, and five with end organ damage. The median time to CMV infection post-allo-HCT was 120 days (IQR 56.2-142.5) in the letermovir group vs. 38 days (IQR 29-43) in the control group.

The 100-day cumulative incidence of grade 2 to 4 and 3 to 4 acute GVHD was comparable in the 2 cohorts, as was the 1-year cumulative incidence of chronic GVHD and moderate-severe chronic GVHD. The 1-year cumulative incidence of relapse was comparable between patients receiving letermovir prophylaxis and those who did not: 17% (95% CI, 6-33%) vs. 18% (95% CI, 11-27%), p=0.74. Similarly, non-relapse mortality rates showed no significant difference between the two groups: 26% (95% CI, 12-44%) vs. 28% (95% CI, 19-37%), p=0.66. Overall survival was also equivalent between the two cohorts: 62% (95% CI, 41-78%) vs. 62% (95% CI, 51-70%), p=0.72. Table 2 presents the results.

Discussion

In our cohort of high-risk patients, letermovir prophylaxis administered until 100 days post-transplant proved to be highly effective in preventing CMV infection, consistent with existing literature. However, this effectiveness did not correlate with reduced non-relapse mortality or improved overall survival outcomes.

Findings regarding non-relapse mortality associated with the use of letermovir are inconclusive. Further examination of the phase 3 dataset revealed that individuals who received letermovir had a lower overall mortality rate at week 24 (10.2% vs. 15.9%, p=.03) but a numerically lower mortality rate at week 48 (23.8% vs. 27.6%, p>.05) than those who received a placebo[17]. A 2022 systematic literature review and meta-analysis of 48 unique observational studies, most of which were single-center and where the duration of letermovir prophylaxis ranged between 79 and 191 days, concluded that primary prophylaxis with letermovir resulted in a significant decline in CMV infection at day +100 and day +200 compared to any control group and that letermovir primary prophylaxis significantly reduced the odds of all-cause and non-relapse mortality beyond day +200 compared to historical controls[11].

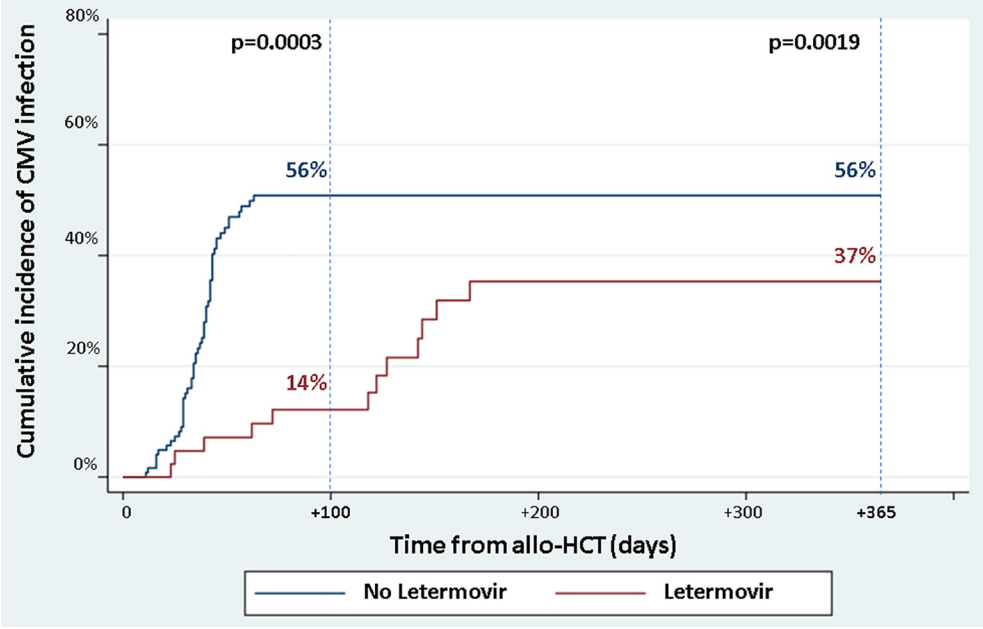
Questions remain regarding the benefits of extending the duration of prophylaxis in the subpopulation of allo-HCT recipients at risk of CMV infection beyond 100 days. In our study, we determined that the benefits of letermovir persisted even after its discontinuation; however, a higher incidence of CMV infection was observed between 100- and 200-days post-discontinuation. Some researchers have suggested that this can be explained by the fact that letermovir may delay CMV-specific cellular reconstitution, which may be attributed to a decreased expo-

Table 1 | Patient characteristics

	All patients (N= 136), n (%)	Letermovir (N=36), n (%)	No letermovir (N=100), n (%)	p
Age, median (IQR)	47.5 (30.2-60.0)	47 (32.7-63.2)	47.5 (29.2-58.7)	0.56
Gender, male	85 (62.5)	24 (66.7)	61 (61)	0.35
Disease				0.10
AML	52 (38.2)	12 (33.3)	40 (40)	
ALL	36 (26.5)	8 (22.2)	28 (28)	
NHL	18 (13.2)	4 (11.1)	14 (14)	
MDS/MPN	17 (12.5)	7 (19.5)	11 (11)	
Other	13 (9.6)	5 (13.9)	7 (17)	
Disease status				0.02
Early	80 (58.8)	15 (41.7)	65 (65)	
Intermediate	40 (29.4)	17 (47.2)	23 (23)	
Advanced	16 (11.8)	4 (11.1)	12 (12)	
DRI				0.22
Low	13 (9.6)	6 (16.7)	7 (7)	
Intermediate	57 (41.9)	12 (33.3)	45 (45)	
High	55 (40.4)	15 (41.7)	40 (40)	
Very high	10 (7.3)	3 (8.3)	7 (7)	
HCT-CI				0.15
Low	74 (54.4)	21 (58.3)	53 (53)	
Intermediate	21 (15.4)	8 (22.2)	13 (13)	
High	42 (17.6)	6 (16.7)	18 (18)	
Donor				0.65
MUR	10 (7.4)	4 (11.1)	6 (6)	
MMUR	14 (10.3)	4 (11.1)	10 (10)	
Haploidentical	112 (82.4)	28 (77.8)	84 (84)	
R/D CMV serostatus				0.03
positive/positive	111 (81.6)	25 (69.4)	86 (86)	
positive/negative	25 (18.4)	11 (30.6)	14 (14)	
Conditioning				0.31
MAC	84 (61.8)	25 (69.4)	59 (59)	
RIC/NMA	52 (38.2)	11 (30.6)	41 (41)	
Stem cell source, PB	131 (96.3)	35 (97.2)	96 (96)	0.19
GVHD prophylaxis				<0.001
PTCy + MMF + TAC	132 (97.1)	32 (88.9)	100 (100)	
PTCy + MMF + CsA	4 (2.9)	4 (11.1)	0 (0)	
aGVHD ≥ GII	47 (34.6)	14 (38.9)	33 (33)	0.33
Time to follow up, median (IQR)	10.8 (4.1-24.5)	7.6 (2.9-13.7)	13.2 (4.4-27.6)	0.03

AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; NHL: non Hodgkin lymphoma; MDS/MPN: myelodysplastic/myeloproliferative neoplasms; DRI: disease risk index; MUR: matched related donor; MMUD: mismatched unrelated donor; R/D CMV: serostatus, receptor/donor cytomegalovirus serostatus; MAC: myeloablative conditioning; RIC/NMA: reduced intensity conditioning/nonmyeloablative conditioning; PB: peripheral blood; PTCy: post-transplant cyclophosphamide; MMF: mycophenolate mofetil; TAC: tacrolimus; CsA: cyclosporin A; aGVHD: acute graft-versus-host disease

Figure 1 | Cumulative incidence of cytomegalovirus infection



CMV: cytomegalovirus; allo-HCT: allogeneic hematopoietic cell transplantation

Table 2 | Secondary endpoints between patients with and without primary prophylaxis with letermovir

	Letermovir (n=36) %(95%CI)	No letermovir (n=100) %(95%CI)	P
100-d CI of grade 2-4 aGVHD	33 (19-49)	28 (20-37)	0.57
180-d CI of grade 2-4 aGVHD	40 (24-55)	31 (22-40)	0.46
100-d CI of grade 3-4 aGVHD	14 (5-27)	10 (5-17)	0.52
180-d CI of grade 3-4 aGVHD	17 (7-31)	10 (5-17)	0.30
1-y CI of cGVHD	17 (6-33)	18 (11-27)	0.96
1-y CI of moderate-severe cGVHD	12 (3-27)	13 (7-21)	0.84
1-y CI of relapse	17 (6-33)	18 (11-27)	0.74
1-y CI of NRM	26 (12-44)	28 (19-37)	0.66
1-y OS	62 (41-78)	62 (51-70)	0.72

D: days; CI: cumulative incidence; aGVHD: acute graft-versus-host disease; y: year; cGVHD: chronic graft-versus-host disease; NRM: non-relapse mortality; OS: overall survival

sure to CMV antigens[18]. Another explanation could be the delayed immune reconstitution due to the use of post-transplant cyclophosphamide, which was more pronounced in the study conducted by Mehta et al, with the use of haploidentical donors[19,20].

Recently, the results of the NCT03930615 trial support extending the duration of letermovir prophylaxis for up to 200 days in patients who remain at risk of late CMV infection, defined as meeting one or more of the following criteria: having a related donor or unrelated donor with at least one mismatch; a haploidentical donor; umbilical cord blood as the stem cell source; recipients of ex vivo grafts depleted of T cells, anti-thymocyte globulin, or alemtuzumab; or having GVHD or other conditions requiring the use of systemic corticosteroids[21]. However, in connection with the previous observation, they could not demonstrate that the extension of prophylaxis improved all-cause mortality, which was similar

between both treatment groups from baseline to week 28 and from baseline to week 48.

Finally, in our country, access to primary prophylaxis is severely limited because of a lack of coverage, primarily due to its high cost. Pharmacoeconomic studies evaluating letermovir as primary prophylaxis compared to preemptive therapy have demonstrated its cost-effectiveness in Italy, Hong Kong, and the USA[22-24]. A significant factor contributing to additional healthcare costs associated with preemptive therapy is the development of antiviral-related toxicities and the frequent need for re-hospitalization. For instance, valganciclovir, ganciclovir, and foscarnet are known to cause dose-dependent adverse effects such as myelosuppression and nephrotoxicity. These complications have been frequently reported in studies involving allo-HCT recipients, highlighting the challenges and added burden of managing these toxicities during preemptive treatment[25-27]. Conducting a cost-effectiveness study in our country is an urgent priority. Such an evaluation should include a prospective analysis of the duration and costs of CMV antiviral treatments, hospital resource utilization, and adverse events associated with both strategies. This assessment is especially critical in low- and middle-income countries, where healthcare resources are limited and optimized decision-making is essential.

We acknowledge that our research has certain limitations, such as its retrospective design, short follow-up period in patients receiving letermovir, and the absence of evaluation of hospitalizations and adverse events. However, it offers valuable information on the use of letermovir prophylaxis in a high-risk cohort of patients who received post-transplant cyclophosphamide, particularly in Argentina, where such data are limited. By offering insights into the effectiveness and outcomes of letermovir use in this patient population, our research aims to inform efforts targeted at improving access to letermovir in these patients.

Based on the data provided in this study, we demonstrated the efficacy of primary prophylaxis with letermovir in preventing CMV infection in a high-risk cohort of patients, specifically in the context of post-transplant cyclophosphamide, which has become widely used as GVHD prophylaxis. Despite its effectiveness, it did not show a correlation with reduced non-relapse mortality or improved overall survival outcomes.

Ongoing research conducted in real-world settings and accumulation of evidence regarding the extended use of letermovir prophylaxis will offer additional insights into several aspects. These include identifying additional high-risk patient groups that may benefit from extending letermovir prophylaxis and evaluating any potential mortality benefits associated with prophylaxis and its extension beyond the initial 100 days after allo-HCT.

Conflict of interest: None to declare

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