International Journal of Infectious Diseases 85 (2019) 74–79

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Linezolid interruption in patients with fluoroquinolone-resistant tuberculosis receiving a bedaquiline-based treatment regimen

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ARTICLE INFO

Article history:
Received 21 March 2019
Received in revised form 25 April 2019
Accepted 26 April 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Drug-resistant tuberculosis
Linezolid
Bedaquiline
Outcome
Treatment interruption

ABSTRACT

Background: Treatment outcomes of patients with extensively drug-resistant tuberculosis (XDR-TB) are suboptimal and treatment options remain limited. Linezolid is associated with improved outcomes but also substantial toxicity, and details about the relationship between these are lacking from resource-poor HIV-endemic settings.

Methods: This was a prospective follow-up study of 63 South African XDR-TB patients (58.7% HIV-infected; median CD4 131 cells/μl) between 2014 and 2018. The frequency and severity of linezolid-associated adverse events and the impact on treatment outcomes were compared between linezolid interrupters and non-interrupters.

Results: Twenty-two patients (34.9%) discontinued or underwent dose reduction due to presumed linezolid-associated toxicity. Anaemia (77.3% vs. 7.3%; $p < 0.001$), peripheral neuropathy (63.6% vs. 14.6%; $p = 0.003$), and optic neuritis (18.2% vs. 9.8%; $p = 0.34$) occurred more frequently in linezolid interrupters than in non-interrupters. Anaemia, peripheral neuropathy, and optic neuritis occurred at a median of 5, 18, and 23 weeks, respectively, after treatment initiation. Linezolid interruption was not associated with unfavourable outcomes but was strongly associated with HIV co-infection (adjusted hazard ratio 4.831, 95% confidence interval 1.526–15.297; $p = 0.007$) and bacterial load (culture days to positivity; adjusted hazard ratio 0.824, 95% confidence interval 0.732– 0.927; $p = 0.001$).

Conclusions: Linezolid-related treatment interruption is common, is strongly associated with HIV co-infection, and system-specific toxicity occurs within predictable time frames. These data inform the clinical management of patients with drug-resistant TB.

Introduction

The increasing prevalence of multidrug-resistant tuberculosis (MDR-TB) has become a serious public health problem (Dheda et al., 2017). MDR-TB is defined as *Mycobacterium tuberculosis* with resistance to isoniazid and rifampicin, the two most important TB drugs. Treatment outcomes for MDR-TB are poor and treatment options are limited. Extensively drug-resistant tuberculosis (XDR-TB) is defined as MDR-TB with further resistance to a fluoroquinolone and a second-line injectable drug. Although injectables are no longer frontline treatment for MDR-TB, the term XDR-TB has been retained in this article and it was the definition used for the duration of the study. Linezolid, usually together with bedaquiline, is now widely used to treat XDR-TB and fluoroquinolone-resistant TB and is associated with improved culture conversion and survival (Borisov et al., 2017; Guglielmetti et al., 2017; Lee et al., 2012; Olayanju et al., 2018; Sotgiu et al., 2012; Tang et al., 2015). However, linezolid has substantial toxicity and is associated with significant myelosuppression, peripheral neuropathy, and optic neuropathy (Cox and Ford, 2012; Lee et al., 2012; Sotgiu et al., 2012). Thus, toxicity often leads to interruption of linezolid (stopping the drug for a variable period of time or reducing the dose) in 30–60% of patients (Cox and Ford, 2012; Lee et al., 2012).

Details about the specific relationship between the duration of linezolid treatment and system-specific toxicity, the impact of treatment interruption on outcomes, and the effect of HIV co-infection are lacking. Moreover, there are very limited data about linezolid toxicity from TB and HIV endemic settings. To address this knowledge gap, the frequency of linezolid-associated toxicity, the temporal relationship between linezolid initiation

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https://doi.org/10.1016/j.ijid.2019.04.028

and system-specific drug toxicity, and the effect of linezolid interruption (dose reduction or discontinuation) on treatment outcomes of XDR-TB patients receiving a bedaquiline-based regimen were determined in this study.

Methods

Participants

Sixty-three patients with culture-confirmed XDR-TB were followed up prospectively between April 2014 and April 2018. All patients received a bedaquiline-based treatment regimen containing linezolid as one of the major components. The patients were admitted to Brooklyn Chest Hospital, Cape Town, the XDR-TB treatment centre in the Western Cape Province of South Africa. Patients' treatments were directly observed by trained healthcare workers during hospitalization and after discharge to outpatient treatment centres. Data were captured by a trained researcher; relevant information obtained included demographic characteristics, clinical details, medications received, and adverse events. Patients were classified as linezolid interrupters (dose reduction or discontinuation) or non-interrupters, and a comparative analysis of linezolid interrupters and non-interrupters was performed to expressly interrogate whether this interruption adversely impacts outcomes and to determine its potential association with HIV co-infection. Ethical approval was obtained from the University of Cape Town Human Research Ethics Committee.

Diagnosis and medications received

All patients had culture isolates with *M. tuberculosis* strains resistant to isoniazid, rifampicin, ofloxacin, and a second-line injectable anti-TB drug, and met XDR-TB diagnosis criteria (WHO, 2006). They all received a treatment regimen based on a backbone of linezolid and bedaquiline. Linezolid was administered at 600 mg daily for 1 year and bedaquiline at 400 mg daily for 2 weeks and then 200 mg three times weekly for 22 weeks. The other drugs common to most of the patients were clofazimine, levofloxacin, pyrazinamide, and para-aminosalicylic acid.

Adverse events profiling

Adverse events were actively reported by trained healthcare workers using a standardized case report form and were graded according to the modified American National Institutes of Health Common Terminology of Criteria for Adverse Events. Grade 0 means no adverse events; grade 1 means a mild adverse event, requiring no intervention; grade 2 means a moderate adverse event, requiring a change of dose or frequency of the offending drug, or the prescription of another drug to manage the adverse event; grade 3 means a severe adverse event, enough to stop the offending drug; grade 4 means a life-threatening or disabling adverse event; grade 5 means death resulting from the adverse event (Trotti et al., 2003).

Outcomes

Treatment outcomes were assigned according to an adapted version of the 2013 World Health Organization (WHO) definitions and reporting frameworks for TB and the core research definitions for drug-resistant TB clinical trials recommended by Furin et al. (Furin et al., 2016; WHO, 2013). Patients were said to have achieved a favourable outcome if they were cured or completed treatment; other treatment outcomes were deceased, lost to follow-up, and treatment failure, and these were considered to be unfavourable.

Statistical analysis

The effect of linezolid interruption was determined by comparative analysis of demographic characteristics, clinical characteristics, and treatment outcomes. Qualitative and quantitative variables were reported in percentages and the median with interquartile range (IQR). Quantitative and qualitative variables were compared using the Mann–Whitney *U*-test and Chi-square or Fisher's exact test, respectively. The univariate Cox proportional hazards model was used to estimate the relationship between independent variables (demographic and clinical characteristics) and selected outcome variables (mortality, the development of linezolid-associated adverse events, linezolid interruption, culture conversion, and unfavourable outcome). Multivariate models included variables that were significantly associated with outcomes and pre-selected variables. A p-value of <0.05 was taken as statistically significant. Kaplan–Meier curves for the probability of survival were estimated considering the duration between the day of treatment initiation and follow-up censor date. Comparison between strata (HIV-infected vs. HIV non-infected, linezolid treatment for more than 3 months vs. linezolid treatment for less than 3 months) was made using the log-rank test. The statistical analysis was done using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic and clinical characteristics

Sixty-three patients with XDR-TB met the diagnostic requirements for this study. Demographic and clinical characteristics are reported in Table 1. The median age at admission was 37 years (IQR 30–44 years) and 39 (61.9%) were male. The median weight at admission was 51.8 kg (IQR 46.0–58.6 kg) and patients were on admission for a median of 155 days (IQR 102–214 days). Thirty-seven patients (58.7%) were HIV-infected; the median CD4 count was 131 cells/μl (IQR 56–257 cells/μl) at admission and all patients were on antiretroviral (ARV) therapy. Patients received a median of 8 (IQR 7–8) anti-TB drugs, with linezolid and bedaquiline being the major components. Drugs used in the regimen are outlined in Table 2. Linezolid interruption due to adverse events occurred in 22 patients (34.9%) during the course of treatment, while the remaining 41 patients (65.1%) completed 1 year of uninterrupted linezolid therapy. Of the 22 patients who had linezolid interruption, 10 had a dosage reduction from 600 mg to 300 mg daily, while 12 had linezolid discontinued.

Adverse events

A total of 208 adverse events were reported by 57 (90.5%) patients; a median of 3 (IQR 2–5) adverse events were reported in the whole cohort. Thirty-three (52.4%), 45 (71.4%), and 36 (57.1%) patients reported grade 1, grade 2, and grade 3 adverse events, respectively. No patient had life-threatening adverse events or died from them. Anaemia (31.7%), peripheral neuropathy (31.7%), and body pains (27%) were the most commonly reported adverse events in the whole cohort. Comparison of adverse events between linezolid interrupters and non-interrupters are outlined in Table 3. Anaemia, peripheral neuropathy, and optic neuritis developed a median of 5 weeks (IQR 4–10 weeks), 18 weeks (IQR 11–24 weeks), and 23 weeks (IQR 21–26 weeks), after linezolid treatment initiation (**Supplementary Material**, Figure S1). Of the patients who developed anaemia (haemoglobin level <10 g/dl), 62.5% and 87.5% experienced this within 8 weeks and 12 weeks of treatment initiation, respectively, with a median 26.1% (IQR 10.4–36.1%) drop in baseline haemoglobin by 12 weeks of treatment. Table 4 shows

Table 1
Demographic and clinical characteristics, and treatment outcomes of XDR-TB patients treated with a linezolid and bedaquiline-based regimen; data are reported as the number of persons (%) unless stated otherwise.

Variables	Patients without linezolid interruption ($n=41$)	Patients with linezolid interruption (dose reduction or discontinuation; $n=22$)	p-Value
Sex, male	27 (65.9)	12 (54.5)	0.38
Weight (kg), median (IQR)	53.7(46.5–60.8)	48.7 (42.9–54.8)	0.17
Age (years), median (IQR)	36 (29–44)	38 (31.5–46.3)	0.36
Duration of admission (days), median (IQR)	155 (106–222)	155 (107–210)	0.71
Duration of linezolid treatment (days), median (IQR)	365 (181–366)	231.5 (151–366)	<0.001
HIV-infected	22 (53.7)	15 (68.2)	0.27
CD4 count (cells/μl), median (IQR)	169 (55–252)	127 (56–257)	0.37
Patients with previous TB treatment	21 (51.2)	11 (50)	0.93
Number of anti-TB drugs	8 (7–8)	7 (7–8)	0.31
Favourable outcome (cured/completed treatment)	30 (73.2)	15 (68.2)	0.68
Unfavourable outcome	11 (26.8)	7 (31.8)	

XDR-TB, extensively drug-resistant tuberculosis; IQR, interquartile range.

Table 2
Drugs used in the treatment regimens and the number (%) of patients who received them stratified by linezolid interruption.

Drug	Patients without linezolid interruption ($n=41$)	Patients with linezolid interruption (dose reduction or discontinuation; $n=22$)	p-Value
Linezolid	41 (100)	22 (100)	NA
Bedaquiline	41 (100)	22 (100)	NA
Clofazimine	40 (97.6)	22 (100)	0.46
Ethambutol	15 (36.6)	4 (18.2)	0.13
Ethionamide	11 (26.8)	3 (13.6)	0.23
Isoniazid	12 (29.3)	8 (36.4)	0.56
Levofloxacin	40 (97.6)	21 (95.5)	0.65
Para-aminosalicylic acid	39 (95.1)	21 (95.5)	0.95
Pyrazinamide	40 (97.6)	21 (95.5)	0.65
Terizidone	39 (95.1)	20 (90.9)	0.51
Moxifloxacin	8 (19.5)	2 (9.1)	0.28
Delamanid	5 (12.2)	3 (13.6)	0.87

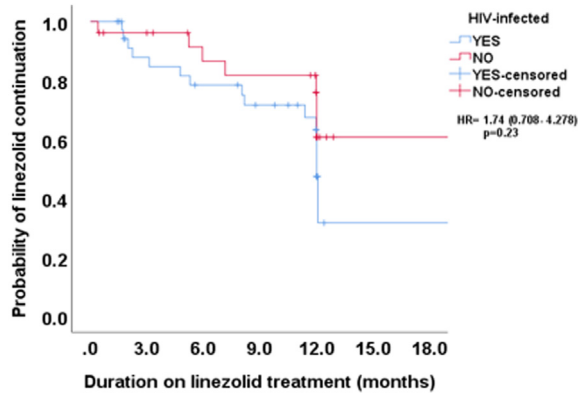
NA, not applicable.

Table 3
Number (%) of patients experiencing adverse events depending on linezolid interruption.

Variables	Patients without linezolid interruption ($n=41$)	Patients with linezolid interruption (dose reduction or discontinuation; $n=22$)	p-Value
Peripheral neuropathy	6 (14.6)	14 (63.6)	0.003
Anaemia	3 (7.3)	17 (77.3)	<0.001
Arthralgia	6 (14.6)	5 (22.7)	0.42
Skin reaction	8 (19.5)	8 (36.4)	0.14
Body pains	11 (26.8)	6 (27.3)	0.97
Optic neuritis	4 (9.8)	4 (18.2)	0.34
Dizziness	5 (12.2)	5 (22.7)	0.28
Dyspepsia	2 (4.9)	1 (4.5)	0.95
Nausea	4 (9.8)	5 (22.7)	0.16
Vomiting	7 (17.1)	5 (22.7)	0.59
Epigastric pain	6 (14.6)	5 (22.7)	0.42
Diarrhoea	4 (9.8)	2 (9.1)	0.93
Thyroid dysfunction	3 (7.3)	4 (18.2)	0.19
Psychosis	3 (7.3)	2 (9.1)	0.81

Table 4
Cumulative number (%) of patients who experienced an adverse event (types) with increased treatment duration.

Treatment duration	Patients who developed any adverse event ($n=22$)	Patients who developed anaemia ($n=16$)	Patients who developed peripheral neuropathy ($n=13$)	Patients who developed optic neuritis ($n=4$)
1 month	5 (22.7)	5 (31.3)	0 (0)	0 (0)
2 months	10 (45.5)	10 (62.5)	2 (15.4)	0 (0)
3 months	15 (68.2)	14 (87.5)	6 (46.2)	0 (0)
4 months	17 (77.3)	16 (100)	6 (46.2)	0 (0)
5 months	18 (81.8)	16 (100)	7 (53.8)	1 (25)
6 months	21 (95.5)	16 (100)	10 (76.9)	3 (75)
9 months	22 (100)	16 (100)	12 (92.3)	4 (100)



Number at risk

YES	15	11	8	6	4	0	0
NO	7	6	4	3	2	0	0

Figure 1. Kaplan-Meier estimate for the probability of linezolid continuation in HIV-infected patients during an 18-month treatment period.

the cumulative number of patients who developed adverse events with treatment progression. Anaemia ($p < 0.001$) and peripheral neuropathy ($p = 0.003$) occurred more frequently in linezolid interrupters. Two of these patients received blood transfusion, and two others had nutritional support.

Although there was no difference in the proportion of HIV-infected patients (89.2%) who reported at least one adverse event compared to the non-infected patients (88.5%), there were more cases of linezolid interruption in HIV-infected patients (40.5%) than in non-infected patients (26.9%). The Kaplan–Meier estimate also suggested that HIV-uninfected patients were more likely to continue linezolid treatment within 18 months of treatment (hazard ratio (HR): 1.74 (0.708–4.278); Figure 1).

Multivariate analysis showed that the duration of linezolid treatment was an independent predictor of linezolid interruption in the whole cohort (hazard ratio (HR) 0.993; $p < 0.001$). It also suggested that HIV-infected patients (HR 4.831; $p = 0.007$) and patients with a higher bacteria load (culture days to positivity; HR 0.824; $p = 0.001$) had a higher probability of linezolid interruption (Table 5). The Kaplan–Meier survival estimate showed no difference in the probability of unfavourable outcome between linezolid interrupters and non-interrupters ($p = 0.59$; **Supplementary Material**, Figure S2) and it also showed that patients who received linezolid for more than 3 months were more likely to survive (HR: 39.949 (4.860–328.37) Figure 2).

Discussion

This is the first prospective study on probable linezolid-associated adverse events in XDR-TB patients from a TB/HIV endemic country. The major findings were that (1) linezolid interruption is common; (2) the adverse events causing linezolid interruption occur at 'predictable' time-points; (3) HIV co-infection and bacterial burden are associated with linezolid interruption; and (4) linezolid interruption does not affect treatment outcomes.

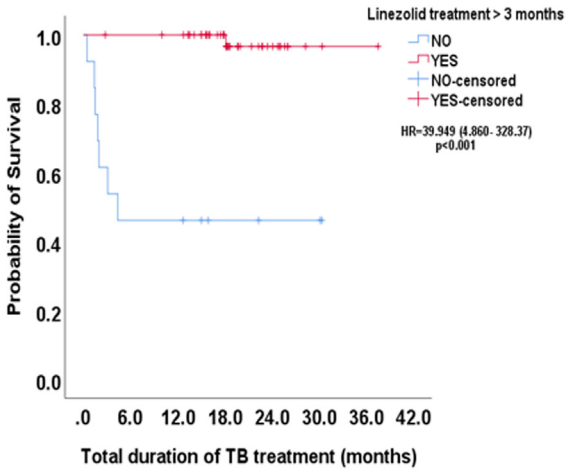
This study established that the use of linezolid in a treatment regimen for XDR-TB, as recommended by the WHO, was associated with several adverse events, especially peripheral neuropathy and anaemia; this is similar to findings from other studies (Agyeman and Ofori-Asenso, 2016; Park et al., 2006; Zhang et al., 2015). Over one third of patients had linezolid interruption in their treatment regimen following the development of an adverse event. Adverse events that were likely due to linezolid toxicity occurred within predictable time frames. The predictability of these events can inform patient care and guide physicians and healthcare workers in patient management, possibly informing dose adjustment at critical time points in a bid to prevent the occurrence or severity of adverse events.

Several methods to reduce linezolid-associated adverse events have been proposed. A deliberate reduction in linezolid dosage at specific times in the course of treatment, when adverse events are known to develop, may mitigate or outrightly prevent the occurrence of such adverse events (Anger et al., 2010; Zhang et al., 2015). A shorter treatment regimen has also been proposed following the preparation of a suitable protocol, approval by

Table 5
Univariate and multivariate Cox proportional hazards model interrogating factors associated with unfavourable outcome and linezolid interruption.

Variable	Unfavourable outcome ($n = 18$)		Linezolid interruption ($n = 22$)	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Univariate analysis				
Weight (kg)	0.977 (0.934–1.023)	0.32	0.973 (0.933–1.013)	0.19
Sex, male	2.655 (1.024–6.889)	0.05	1.790 (0.758–4.229)	0.18
Days hospitalized	0.990 (0.982–0.997)	0.008	0.998(0.994–1.002)	0.38
HIV-infected	1.763 (0.647–4.806)	0.27	1.901 (0.768–4.779)	0.17
Age (years)	1.011 (0.964–1.060)	0.65	1.025 (0.981–1.071)	0.28
Previous TB treatment	1.170 (0.706–2.109)	0.51	1.096 (0.719–1.671)	0.67
Levofloxacin/moxifloxacin treatment	0.045 (0.00–1266)	0.55	1.162 (0.151–8.908)	0.89
PZA treatment	3.715 (0.455–30.357)	0.666	2.143 (0.283–16.261)	0.46
Number of TB drugs	0.975 (0.637–1.492)	0.91	0.898 (0.591–1.366)	0.62
Smear grade (baseline)	2.064 (0.902–4.722)	0.09	1.287 (0.762–2.173)	0.35
Time to culture positivity (days)[a]	0.954 (0.890–1.023)	0.19	0.886 (0.818–0.961)	0.003
Duration on linezolid (days)	0.995 (0.992–0.998)	0.03	0.997 (0.994–1.000)	0.02
Multivariate analysis				
Weight (kg)	1.015 (0.967–1.066)	0.55	0.975 (0.929–1.024)	0.32
Sex, male	1.411 (0.473–4.207)	0.54	1.469 (0.513–4.210)	0.47
Duration on linezolid	0.996 (0.991–1.000)	0.05	0.993 (0.989–0.997)	<0.001
HIV-infected	2.211 (0.645–7.575)	0.21	4.831 (1.526–15.297)	0.007
Days hospitalized	0.996 (0.987–1.005)	0.36	NA	NA
Linezolid interruption	0.981 (0.351–2.744)	0.97	NA	NA
Time to culture positivity (days)[a]	NA	NA	0.824 (0.732–0.927)	0.001
Age (years)	NA	NA	1.093 (1.030–1.160)	0.003

HR, hazard ratio; CI, confidence interval; TB, tuberculosis; PZA, pyrazinamide; NA, not applicable.
[a] Baseline sputum sample was used.



Number at risk

YES	50	50	50	30	12	2	1	1
NO	13	6	6	3	2	2	0	0

Figure 2. Kaplan-Meier survival estimate for patients who received linezolid treatment for more than 3 months in their treatment regimen.

national ethics committee, and delivery under WHO recommended standards (WHO, 2018). This was corroborated by a study suggesting that the linezolid cumulative dose and days of exposure play an important role in the development of adverse events (Bolhuis et al., 2015). Therapeutic drug monitoring has been suggested for patients on long-term linezolid treatment, but the cost and the rigours involved make it less feasible; a limited sampling strategy that is cheaper, less time-consuming, and more feasible has been proposed to individualize linezolid dosing (Alffenaar et al., 2010; Kamp et al., 2017). Recently, a linezolid-related adverse events predictive score (LAPS) was developed as a tool for clinicians to assess the pre-therapeutic risk of patients developing those adverse events (Buzelé et al., 2015). LAPS entails assigning scores for certain selected clinical risk factors in patients and grading the summation to predict the development of linezolid-associated adverse events.

Yet the effect of linezolid interruption on treatment outcomes remains unclear and has rarely been described in HIV-infected XDR-TB patients from endemic countries. This study explored the relationship between HIV infection and linezolid interruption in patients with drug-resistant TB. It was found that HIV co-infection contributed significantly to the occurrence of linezolid interruption. This is in keeping with numerous studies that have shown higher adverse event rates and consequent drug withdrawal in HIV-infected compared to un-infected patients (Breen et al., 2006; Mehta et al., 2008; Michael et al., 2016). HIV infection also contributed to the development of unfavourable outcome in the present study.

Time to sputum culture positivity in patients has been used over the years as a proxy for disease severity (Dominguez-Castellano et al., 2003; Güler et al., 2007). In this study, it correlated significantly with linezolid interruption and this may be an indication that patients who are sicker at the commencement of therapy are more likely to have treatment interruption. The attending physician may be required to monitor them more closely and make an individualized dosage plan for such patients.

There were a few limitations to this study. All the patients in this study were hospitalized in the designated treatment centre during the course of treatment, thus selection bias might have affected the findings. However, the programmatic policy at the centre requires all patients to be hospitalized at least in the intensive phase of therapy. Given the small sample size, the study may not have been sufficiently powered to detect the differences between patients who had linezolid interruption and those who did not. This, however, is arguably one of the linezolid original studies available with the highest number of participants. This study was conducted in a TB/HIV endemic setting with a very high enrolment on ARV therapy; findings may be different in countries with low HIV prevalence or those with low ARV coverage.

In conclusion, linezolid-associated system-specific toxicity occurs within predictable time frames and is commonly associated with treatment interruption. This prospective study from a TB endemic country demonstrates that linezolid interruption does not negatively impact treatment outcomes, although larger studies are needed to confirm this finding. These data inform the use of linezolid for drug-resistant TB treatment in TB endemic countries.

Conflict of interest

The authors have no conflicts of interest to disclose.

Acknowledgement

K Dheda and the work presented here was supported by the South African MRC (RFA-EMU-02-2017) and the EDCTP (TMA-2015SF-1043 & TMA- 1051-TESAII).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.04.028.

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