EFFICACY, SAFETY AND TOLERABILITY OF ROTIGOTINE TRANSDERMAL PATCHES FOR TREATING EARLY PARKINSON'S DISEASE: A META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

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ABSTRACT

Objective*: Systematically evaluate the clinical efficacy, safety and tolerance of rotigotine transdermal patch in the treatment of patients with early Parkinson's Disease (PD).*

Methods: *The literature of randomized controlled trial (RCT) of the clinical efficacy, safety and tolerance of rotigotine transdermal patch in the treatment of patients with early PD were searched using "Rotigotine;Parkinson Disease","Neupro;Parkinson Disease","Rotigotine;Parkinson Disease(in Chinese)" as keywords in pubmed, FMRS database, CNKI database, wanfang database, weipu database. The references of the selected literature were also screened. The publication time of the literature was from the establishment of the above mentioned database to December 2019. Two researchers independently screened the literature, extracted the data and evaluated the quality. Rev Man 5.3 software was used for m eta analysis. Outcome indicators included unified Parkinson's Disease rating scale (UPDRS) Part II and III scores, rate of adverse events (AEs), number of people who completed the experiment.*

Results: *A total of 880 early PD patients of six studies were included. Compared with placebo group, the total scores of UPDRS part II and III (WMD: -4.72, 95%CI:-6.01, -3.44), the UPDRS part II scores (WMD:-1.31, 95%CI:-1.39, -1.23) and the UPDRS part III scores (WMD: -3.35, 95%CI:-4.48, -2.22) of rotigotine transdermal patch group were decreased. There was no statistically significant difference of the incidence of at least one adverse drug event and serious AEs (RR:1.13, 95%CI:0.99,1.28; RR:1.35, 95%CI:0.74, 2.47). There was also no statistically significant difference of the incidence in the number of people who completed the experiment (RR:0.96,95%CI: 0.91,1.01).*

Conclusion: *Our studies have shown that rotigotine transdermal patches can improve motor and nonmotor symptoms in patients with early PD. Safety and tolerability are acceptable. The optimal formulation and dosage still need to be further confirmed.*

Keywords: *Rotigotin, early, parkinson's disease, meta analysis.*

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Introduction

Parkinson's Disease (PD) is a common degenerative disease of the nervous system in the elderly. Its typical pathological changes are the aggregation of α-synuclein and the loss of dopaminergic neurons, leading to a series of motor and non-motor symptoms. The etiology of this disease is currently unclear, and may be related to factors such as heredity, environment, age, and oxidative stress. The development of PD to late stage can seriously affect the quality of life of patients. Therefore, how to carry out effective treatment in the early stage of PD has become an urgent problem that needs to be solved.

At present, the drugs used to treat PD mainly include dopamine receptor agonists, β-monoamine oxidase inhibitors, etc., but no specific drugs have been found to cure PD. After long-term use of these drugs, most patients will experience fluctuations in

symptoms, leading to aggravation of the disease. Rotigotine is a non-ergot selective dopamine receptor agonist, which mainly exerts anti-PD efficacy by stimulating D3/D2/D1 receptors[1]. In 2006, rotigotine transdermal patch preparations were marketed and used in Europe, and clinical results showed that its safety and tolerability were good, but it is not currently on the market in China and is still in the experimental stage[2].

Therefore, the meta-analysis method is used to comprehensively analyze the efficacy, safety and tolerability of rotigotine transdermal patch in patients with early PD, which can play a certain guiding role in the use of this patch in the treatment of PD in China.

Materials and methods

Inclusion and exclusion criteria

Inclusion criteria:

• The included study is a randomized controlled trial (Randomized controlled trial, RCT) of rotigotine transdermal patch in the treatment of patients with early PD, and the PD course of the patients is not more than 3 years;

• It meets the clear British Parkinson's Disease Society Diagnostic criteria for primary Parkinson's disease in the brain bank[3];

• The test group and the control group were treated with rotigotine transdermal patch and placebo respectively;

• The study included at least one of the following outcome indicators: UPDRS II, III score, Adverse events (AEs), Serious AEs (Serious AEs), the number of people who completed the trial.

Exclusion criteria:

• Non-RCT studies such as articles, reviews, and case reports;

• No clear research results;

• No data to extract from the research;

• Repeated studies;

• The study patients were patients with Parkinson's syndrome or Parkinson's superimposed syndrome.

Search strategy

Using "Rotigotine; Parkinson Disease", "Neupro; Parkinson Disease", "Rotigotine; Parkinson's disease" as keywords, computer searches for Rotigotine, FMRS database, CNKI database, Wanfang database, and Weipu database For the RCT of the clinical efficacy, safety and tolerability of Gortin transdermal patch for early PD patients, the literature search starts and ends from the establishment of the database to December 2019.

Literature quality evaluation

The quality evaluation of the included literature was completed by two researchers. The simple evaluation method recommended by the Cochrane Collaboration was used to evaluate the quality of the included studies.

The evaluation items include whether the random method is used, whether the hidden grouping method is correct, whether the blind method is used, whether there is loss to follow-up and withdrawal, whether the baseline data is comparable, whether the research results are selectively reported, etc. Two researchers conducted data extraction and quality evaluation independently and in parallel according to the above-mentioned standards. After consultation on inconsistencies, the literature was finally included or excluded.

Data extraction

The extraction of research data includes the first author, the year of publication, the basic information of the research object, the sample size, the duration, the mean and standard deviation of the continuity indicators in the outcome indicators, etc.

Statistical analysis

Rev Man 5.3 statistical software was used for Meta analysis. Test the heterogeneity of the results of the included studies. If $P>0.1$, $I2\leq50\%$, it means that there is no heterogeneity among the studies, and the fixed-effects model is used for analysis; if $P\leq0.1$, $I2>50\%$, it means there is no heterogeneity among the studies For heterogeneity, the random effects model is used for analysis. The combined statistics are Weighted Mean Difference (WMD) and 95% confidence interval (95% CI).

Results

General situation of the included studies

A preliminary screening of 112,918 related literatures, 10488 RCT trials of which were selected, duplicate literatures were removed, and 10465 literatures that did not meet the requirements of the title were removed by reading the title and abstract, and then non-randomized controlled trials and no control group were excluded by reading the full text. There were 17 documents that did not meet

the requirements of the included study, such as the trial and the longer course of disease, and finally 6 RCTs were included[4-9]. The basic information of the included studies is shown in Table 1.

Included study	Number of Researchers (T/C)	Duration (weeks)	Gender ratio of patients (M/F), age (M±SD), Years of illness (M±SD)	Outcome
Mizuno, Y (2013)[4]	176 (88/88)	19	T: 33/55, -, 2.0(1.8) C: 37/51, -, 1.8(1.9)	①②③④
PSG, (2003)[5]	95 (48/47)	11	T: 31/17, 61.3 (10.9), 1.2 (1.0) C: 23/24, 62.3 (10.5), 1.3 (1.4)	①②③④
Giladi, N (2007)[6]	333 (215/118)	37	T: 118/97, 61.1, 1.4 C:68/50, 60.4, 1.2	①②③④
Jankovic, J (2007)[7]	277 (181/96)	24	T:123/58, 62.0 (10.3), 1.3 (1.3) C:58/38, 64.5 (10.7), 1.4 (1.3)	①②④
Antonini, A (2015)[8]	349 (224/125)	12	T:129/95, 68.0 (9.4), 2.8 C:67/58, 66.6 (9.8), 2.2	①②③④
Zhen-Xin, Zhang (2016)[9]	247 (124/123)	24	T:74/50, 59.1 (10.3), 0.94 (1.17) C:76/47, 59.7 (10.1), 1.08 (1.27)	①②④

Table 1: General information of the included studies.
Note: T/C: test group/control group; ①UPDRSII and III partial scores; ②adverse events; ③serious adverse events; ④number of people completing the trial.

Bias risk assessment

The 6 RCTs all adopted the correct random method and adopted allocation concealment. The risk assessment of bias in the included studies is shown in Figure 1.

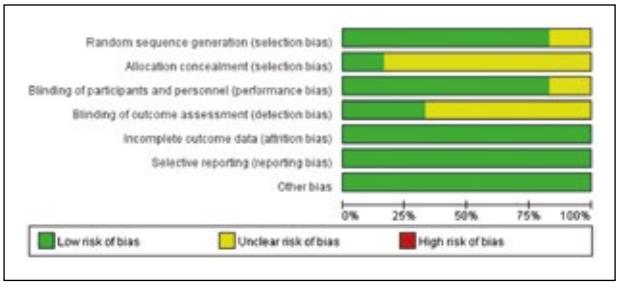

Figure 1: Bias risk assessment (based on Cochrane bias risk assessment tool).

Effectiveness analysis

The 6 included articles all used the UPDRS score to compare the efficacy difference between rotigotine transdermal patch and placebo. Among them, 4 studies [4, 5, 6, 9] (n=468) evaluated the total scores of UPDRS II and III of early PD patients, and there was no statistical heterogeneity among the studies (P=0.98, I2=0%), Using fixed-effects model combined effect size for analysis.

Two studies [7, 9] (n=300) evaluated the partial scores of UPDRSII in patients with early PD, and there was no statistical heterogeneity among the studies (P=0.67, I2=0%), using a fixed-effect model with combined effect size Perform analysis. Three studies [7, 8, 9] (n=506) evaluated the partial scores of UPDRSIII in early PD patients, and there was slight statistical heterogeneity among the studies (P=0.10, I2=57%), using random effects The model combines the effect size for analysis.

Meta analysis results showed that the total scores of UPDRS II and III in the rotigotine transdermal patch group were significantly lower than those in the placebo group (WMD: -4.72, 95%CI: -6.01, -3.44, see Figure 2), single UPDRSIII Partial scores (WMD: -3.35, 95%CI: -4.48, -2.22, see Figure 3) and individual UPDRSII partial scores (WMD: -1.31, 95%CI: -1.39, -1.23, see Figure 4), The difference was statistically significant (P<0.01).

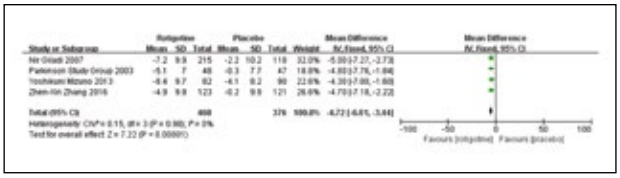

Figure 2: Meta-analysis forest diagram of the difference in total scores of UPDRS II and III between the rotigotine group and the placebo group.

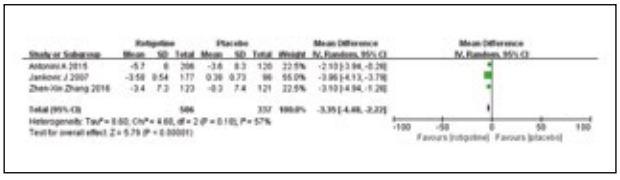

Figure 3: Meta-analysis forest diagram of the difference in UPDRS III score between the rotigotine group and the placebo group.

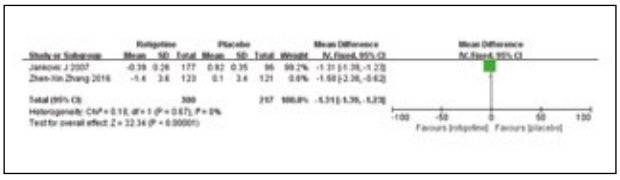

Figure 4: Meta-analysis forest diagram of the difference in UPDRSIIscore between the rotigotine group and the placebo group.

Security analysis

Four of the six included studies [4, 5, 8, 9] evaluated the incidence of at least one adverse event in the experimental group and the control group, and there was slight statistical heterogeneity between the studies (P=0.08), I2=55%), using random effects model combined effect size for analysis.

Three studies [5, 6, 8] evaluated the incidence of serious adverse events in the experimental group and the control group. There was no statistical heterogeneity between the studies (P=0.74, I2=0%), and the fixed-effects model was used to combine The effect size is analyzed. Meta analysis showed that compared with the placebo group, there was no significant difference in the incidence of at least

one adverse event in the rotigotine transdermal patch group (RR: 1.13, 95%CI: 0.99, 1.28, P=0.06, (See Figure 5), there is no statistically significant difference in the incidence of serious adverse events (RR: 1.35, 95%CI: 0.74, 2.47, P=0.32, see Figure 6).

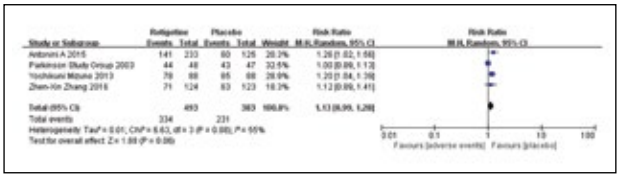

Figure 5: Meta-analysis forest diagram of the difference in the incidence of at least one adverse event between the rotigotine group and the placebo group.

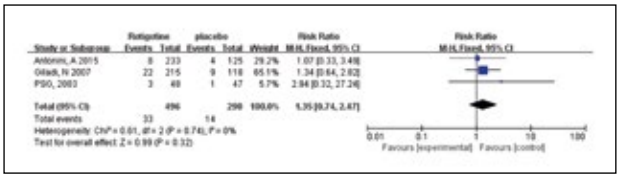

Figure 6: Meta-analysis forest diagram of the difference in the incidence of serious adverse events between the rotigotine group and the placebo group.

Tolerance analysis

The six included studies [4-9] all reported the number of people who completed the experiment during the research process, and there was no statistical heterogeneity among the studies (P=0.21, I2=30%), and the fixed effects model was used to combine the effect size for analysis.

Meta-analysis results showed that there was no significant difference between the rotigotine transdermal patch group and the placebo group (RR: 0.96, 95%CI=0.91, 1.01, P=0.13, see Figure 7), which caused the patient to withdraw midway The main reasons include intolerable adverse reactions, no obvious effect of drugs, poor compliance, and other aspects [4-9].

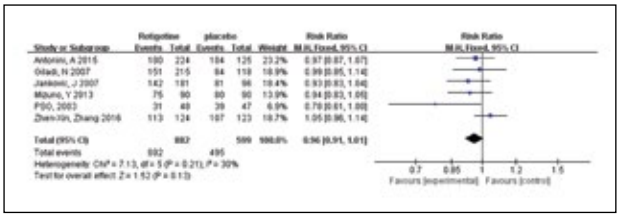

Figure 7: Meta-analysis forest diagram of the difference in the number of people completing the experiment between the rotigotine group and the placebo group.

Assessment of publication bias

Revman5.3 analysis software was used to draw a funnel diagram of the completion of the experiment for the 6 included literatures.

The results of the funnel diagram are shown in Figure 8. The number of points on both sides of the funnel chart is roughly the same, suggesting that the publication bias is small.

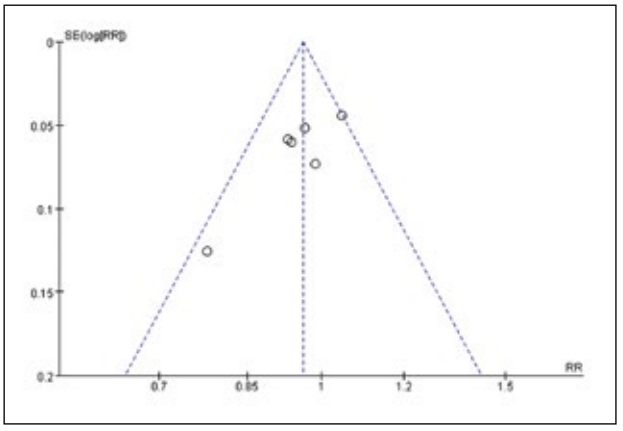

Figure 8: Funnel chart of the difference in the number of people completing the experiment between the rotigotine group and the placebo group.

Discussion

The characteristic pathological changes of PD are the degeneration and necrosis of dopaminergic neurons in the substantia nigra and the deposition of α-synuclein. Therefore, dopamine replacement therapy is currently the most effective and basic method for the treatment of PD. The commonly used drugs are levodopa, but levodopa Dopa has a short half-life and may cause various adverse reactions such as exercise fluctuations after long-term use. Therefore, the new concept of continuous dopamine stimulation for the treatment of PD has gradually attracted attention in recent years. Dopamine receptor stimulants are a class of drugs similar in molecular structure to dopamine, which can directly act on dopamine receptors, independent of endogenous dopamine and dopa decarboxylase, and have a long half-life, gradually becoming the first line of early PD treatment Medication, and often used as an adjuvant drug for levodopa in the late stage of PD[10].

Rotigotine transdermal patch is a non-ergot dopamine receptor agonist, which has a significant effect on D1 dopamine receptors. It not only has a significant effect on the motor symptoms of PD, but also has a certain effect on non-motor symptoms such as insomnia and pain[11]. As the first transdermal patch for the treatment of early PD, it can maintain a stable blood concentration for up to 24 hours[12], which can reduce sports complications caused by long-term use of levodopa. Compared with the oral mode, the patch administration mode increases

patient compliance and reduces gastrointestinal adverse reactions. However, differences in transdermal absorption can lead to differences in efficacy between individuals, and symptoms such as skin allergies may occur. limitation. Rotigotine transdermal patch is currently not marketed in China, and the early diagnosis and treatment of PD are still to be resolved. The innovation of this study is to evaluate the efficacy and safety of rotigotine transdermal patch for early PD Sex, to provide evidence for the early treatment of PD.

In this study, the meta-analysis method was used to compare the UPDRS score, the incidence of adverse reactions, and the difference in the completion of the experiment between the early PD patients treated with rotigotine transdermal patch and the placebo group. The results found that the difference between the two The differences in the total scores of UPDRSII and Part III, individual UPDRSII part scores, and individual UPDRSIII part scores were statistically significant, indicating that the rotigotine transdermal patch is beneficial to alleviate the motor symptoms and non-motor symptoms of early PD, which is consistent with previous studies. Unanimous. Previous studies by Zhou CQ[13] et al. found that rotigotine transdermal patches are closely related to adverse reactions such as dizziness, headache, and back pain, but do not increase the risk of diarrhea and constipation; Jaime Kulisevsky[14] et al. found Rotigotine transdermal patch can increase the risk of nausea, vomiting, dizziness, drowsiness, insomnia, and hallucinations, but does not increase the risk of headaches and abdominal pain. There was no statistically significant difference between the incidence of at least one adverse reaction and the incidence of serious adverse reactions between the rotigotine transdermal patch group and the placebo group. The severity of the adverse reactions was mild or moderate.

The occurrence of more serious adverse reactions is considered to be not related to the application of rotigotine transdermal patch, and may be related to the patient's own basic state, age and other factors, indicating that the rotigotine transdermal patch is safer. Compared with the control group, the total number of people who completed the experiment was not statistically different between the experimental group and the control group, indicating that the tolerability of the rotigotine transdermal patch is acceptable, which is consistent with the results of previous studies by Fei Chen[15] and others. Research by Sujith OK[16] and others have reported that rotigotine transdermal patches can crystallize, thereby reducing the amount of drug that can be released and changing the efficacy. In recent years, many studies have tried to explore more dosage forms of rotigotine. And prescription optimization, such as long-acting sustained-release microsphere preparations, in order to achieve better bioavailability. At present, the phase I clinical trial of rotigotine sustained-release microspheres for injection has been completed in the United States[17]. Tzeyung AS[18] et al. prepared rotigotine chitosan nanoparticles by ion gel method, and applied nasal-brain administration route to achieve better absorption. Wang A[19] et al. developed the rotigotine sustained-release microsphere preparation LY 03003 as an intramuscular injection that is administered once a week or once a month. If it can be proven to be bioequivalent to transdermal patches Sex, it may become an effective alternative to simplify treatment.

In summary, rotigotine transdermal patch is beneficial to improve the motor symptoms and non-motor symptoms of patients with early PD. It has good efficacy, safety and tolerability, and it can be considered for promotion in early PD. This study also has certain limitations. Subgroup analysis and sensitivity analysis were not performed due to the small number of included literature. There may be reporting bias, and the trial period of the included literature is short, and the dose of rotigotine is different. The optimal dosage form and dosage still need to be further confirmed.

References

1) Aiping Wang, Wanhui Liu, Kaoxiang Sun, et al. Research progress in the preparation of dopamine receptor agonist rotigotine for the treatment of Parkinson's disease[J]. Chinese Journal of New Drugs. 2014. 23(16): 1881-1884+1896.
2) Ke Gao. The pharmacological research of rotigotine and its treatment of Parkinson's disease motor symptoms[J]. Modern Diagnosis and Treatment. 2016. 27(07): 1219-1220, 1372.
3) Postuma RB, Berg D, Stern M, et al. MDS Clinical Diagnostic Criteria for Parkinson's Disease[J]. Mov Disord. 2015. 30(12): 1591-1601.
4) Mizuno Y, Nomoto M, Kondo T, et al. Transdermal Rotigotine in Early Stage Parkinson's Disease: a Randomized, Double-blind, Placebo-controlled Trial[J]. Mov Disord. 2013. 28(10): 1447-1450.

5) Parkinson Study Group. A Controlled Trial of Rotigotine Monotherapy in Early Parkinson's Disease[J]. Arch Neurol. 2003. 60(12): 1721-1728.
6) Giladi N, Boroojerdi B, Korczyn AD, et al. Rotigotine T patch in Early Parkinson's Disease: a Randomized, Double-blind, Controlled Study versus Placebo and Ropinirole[J]. Mov Disord. 2007. 22(16): 2398-2404.
7) Jankovic J, Watts RL, Martin W, et al. Transdermal Rotigotine: Double-blind, Placebo-controlled Trial in Parkinson Disease[J]. Arch Neurol. 2007. 64(5): 676-682.
8) Antonini A, Bauer L, Dohin E, et al. Effects of Rotigotine Transdermal Patch in Patients with Parkinson's Disease Presenting with Non-motor Symptoms - Results of a Double-blind, Randomized, Placebo-controlled Trial[J]. Eur J Neurol. 2015. 22(10): 1400-1407.
9) Zhang Z-X, Shang H-F, Hu X, et al. Rotigotine Transdermal Patch in Chinese Patients with Early Parkinson's Disease: A Randomized, Double-blind, Placebo-controlled Pivotal Study[J]. Parkinsonism Relat Disord. 2016. 28: 49-55.
10) Shuli Zhang, Hailong Yang, Yu Tang. Research progress of non-ergot dopamine receptor agonist sustained-release preparations [J]. Modern Medicine and Clinics. 2020, 35 (06): 1279-1283.
11) Rascol O, Zesiewicz T, Chaudhuri KR, et al. A Randomized Controlled Exploratory Pilot Study to Evaluate the Effect of Rotigotine Transdermal Patch on Parkinson's Disease-Associated Chronic Pain[J]. J Clin Pharmacol. 2016. 56(7): 852-861.
12) Yanping Tian, Xiangli Cui. The pharmacological effects and clinical evaluation of rotigotine[J]. Herald of Medicine. 2009. 28(10): 1327-1328.
13) Zhou CQ, Li SS, Chen ZM, et al. Rotigotine Transdermal Patch in Parkinson's Disease: a Systematic Review and Meta-analysis[J]. PLoS One. 2013. 8(7): e69738.
14) Kulisevsky J, Pagonabarraga J. Tolerability and Safety of Ropinirole versus Other Dopamine Agonists and Levodopa in the Treatment of Parkinson's Disease: Meta-analysis of Randomized Controlled Trials[J]. Drug Saf. 2010. 33(2): 147-161.
15) Chen F, Jin L, Nie Z. Safety and Efficacy of Rotigotine for Treating Parkinson's Disease: A Meta-Analysis of Randomised Controlled Trials[J]. J Pharm Pharm Sci. 2017. 20(0): 285-294.
16) Sujith OK, Lane C. Therapeutic Options for Continuous Dopaminergic Stimulation in Parkinson's Disease[J]. Ther Adv Neurol Disord. 2009. 2(2): 105-113.
17) Yi Bai. Rotigotine sustained-release microspheres for injection phase I clinical trials completed in the United States [J]. China Medical News. 2015. DOI: 10.38249/n.cnki.nyiya.2015.000250.
18) Tzeyung AS, Md S, Bhattamisra SK, et al. Fabrication, Optimization, and Evaluation of Rotigotine-Loaded Chitosan Nanoparticles for Nose-To-Brain Delivery[J]. Pharmaceutics. 2019; 11(1). 10.3390/pharmaceutics11010026.
19) Wang A, Liu Y, Liang R, et al. Preparation and Evaluation of Rotigotine-loaded Implant for the Treatment of Parkinson's Disease and Its Evolution Study[J]. Saudi Pharm J. 2016. 24(3): 363-370.

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