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Response and remision in depressive patients with anxiety symptoms treated with venlafaxine extended release in primary care

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Introduction. The aim of this observational study was to evaluate the long term effect of treatment with venlafaxine extended release on response and remission in patients with depressive syndrome and associated anxiety symptoms, in primary health care.

Methods. Observational, naturalistic and prospective, open-label study. Inclusion criteria were as follows: age over 18 years, diagnosis of depressive syndrome with anxiety symptoms and minimum scores of 17 and 10 on Hamilton Depression Rating (HAM-D_{17}) and Anxiety Rating (HAM-A) scales, respectively. Daily doses of 75-150 mg of venlafaxine extended release were administered for 24 weeks. Effectiveness on the depressive-anxious symptoms was assessed using the HAM-D_{17} and HAM-A scales. Response and remission criteria were considered.

Results. 6,719 patients were evaluable for effectiveness and safety - intention to treat population. Venlafaxine extended release treatment was associated with significant decreases in the scores in the HAM-D_{17} and HAM-A scales, as well as with significant increases in response and remission rates. At week 24, remission rates were: 74.62% (HAM-$D_{17} \leq 7$), 81.55% (HAM-A ≤ 7) and 72.63% (HAM-$D_{17} \leq 7$/HAM-A ≤ 7). 81.8% of patients completed 24 weeks of treatment. 6.4% of patients reported adverse events, of mild-moderate intensity in 94.9% of cases.

Conclusion. In this study, venlafaxine extended release shows that it is an effective and safe drug in the treatment of the depressive-anxious symptoms of patients with depressive syndrome treated in primary care, both in remission and response rates. It would be of interest to compare data of venlafaxine extended release with that of other antidepressive drugs, such as SSRI.

Key words:
Depression. Anxiety. Remission. Venlafaxine. Extended release. Primary health care. Observational study.

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Respuesta y remisión en pacientes depresivos con síntomas de ansiedad tratados con venlafaxina retard en atención primaria

Introducción. Con este estudio se pretende evaluar el efecto a largo plazo de venlafaxina retard sobre la respuesta y remisión en pacientes con síndrome depresivo y síntomas de ansiedad asociados atendidos en atención primaria.

Métodos. Estudio abierto, observacional, naturalístico y prospectivo. Como criterios de inclusión se consideraron: edad superior 18 años, diagnóstico de síndrome depresivo con síntomas de ansiedad y puntuaciones mínimas de 17 y 10 en las escalas de Hamilton de Depresión (HAM-D17) y de Ansiedad (HAM-A), respectivamente. Venlafaxina retard se administró a dosis diarias de 75-225 mg/día durante 24 sem. La efectividad sobre la sintomatología depresivo-ansiosa se evaluó mediante las escalas HAM-D17 y HAM-A.

Resultados. Los 6.719 pacientes fueron evaluables (intención de tratar) para efectividad y seguridad. Venlafaxina retard se asoció a reducciones significativas en las puntuaciones de las escalas HAM-D_{17} y HAM-A, así como a incrementos significativos en las tasas de respuesta y remisión. En la semana 24 los porcentajes de remisión fueron: 74,62 % (HAM-$D_{17} \leq 7$), 81,55 % (HAM-A ≤ 7) y 72,63 % (HAM-$D_{17} \leq 7$/HAM-A ≤ 7). El 81,8 % de los pacientes completaron las 24 sem de tratamiento. El 6,4 % de los pacientes presentaron efectos adversos, de intensidad «leve o moderada» en el 94,9 % de los casos.

Conclusiones. Venlafaxina retard resulta en este estudio un fármaco efectivo y seguro en el tratamiento de la sintomatología depresivoansiosa de pacientes con síndrome depresivo tratados en atención primaria tanto si se analizan tasas de respuesta como de remisión. Sería interesante comparar los datos de venlafaxina retard en esta población con otros fármacos antidepresivos como los ISRS.

Palabras clave:
Depresión. Ansiedad. Remisión. Venlafaxina retard. Atención primaria. Estudio observacional.

INTRODUCTION

Depressive pictures make up one of the most frequent and incapacitating medical disorders[1]. In the 1980's, the wide use of antidepressive drugs allowed for great optimism in the treatment of depressive disorders. However, lack of clinical efficacy in a relevant percentage of patients and depressive recurrences have recently made it necessary to pose previously marginalized questions.

One of these questions refers to the different ways of defining clinical improvement and its related aspects, finally established in psychiatric literature by Frank et al.[2]: response, partial remission, total remission, relapses, etc. Clinical response, objective of all treatment, sometimes does not prevent the existence of the so-called residual symptoms of depression[3], whose presence has been associated to a greater risk of relapses, recurrences, chronicity, suicide rates and worse quality of life[3,4]. There are sufficient data to believe that clinical remission is extremely important because it correlates with a lower risk of relapses and greater psychosocial functioning[5,6]. More and more studies are incorporating response and remission criteria for the evaluation of a treatment.

In controlled clinical trials, efficacy has been defined as a reduction of the baseline score in the psychometric scales used. The same has occurred with effectiveness in open labeled studies. The most common scales in affective disorders have been HAM-D (Hamilton Depressing Rating scale)[7] and MADRS (Montgomery and Asberg Depression Rating scale)[8]. The HAM-D has been interpreted as a measurement of seriousness of depressive symptoms while MADRS was specifically designed to identify changes in patients undergoing treatment. It is increasingly considered that the objective of antidepressive treatment is clinical remission and not only response. Thus, studies in psychiatric population are increasingly aimed at defining these concepts in clinical trials to compare drugs or combination of drugs and psychotherapy[9]. Cut-off of the scales to define remission is still not exempt of debate[10,11].

Even though a growing number of depressive patients have been treated in primary health care, most of the studies with response and remission rates refer to patients receiving psychiatric treatment. A very recent meta-analysis of controlled studies[12] only finds fourteen methodologically adequate studies in which depressive patients are treated in primary health care. Only three of them include single antidepressive drug treatment[13-15]. In five, antidepressive treatment is associated to psychological therapies and in four to specific intervention programs. The remaining study included refers to a psychotherapy without associated pharmacology. The three clinical trials reviewed with antidepressants include patients with major depression and 6 to 8 weeks of treatments, comparing mirtazapine with paroxetine, citalopram with fluoxetine and escitalopram with placebo.

With these backgrounds, we established an observational, naturalistic study of long term response and remission in patients seen in primary health care with depressive pictures and associated anxiety symptoms. The patients have been identified with clinical criteria, validated by a diagnostic interview, in this case PRIME-MD (Primary Care Evaluation of Mental Disorders)[16,17] and treated by their own physicians in Spanish public health site for 24 weeks with venlafaxine extended release. This is a dual action drug whose response and remission rates have been studied in psychiatric patients, comparing them with placebo and selective serotonin reuptake inhibitors[18].

METHOD

Study population

Analysis of effectiveness, tolerability and safety of treatment with venlafaxine extended release administered for 24 weeks in a total of 6,719 adult out-patients with depressive syndrome and associated anxiety symptoms was done. This is an observational, prospective, open-labeled and multicenter study conducted in Spain in the years 2003-2004, in which 2,119 primary health care physicians participated. The study was conducted according to the ethics principles contained in the Declaration of Helsinki and subsequent amendments, Good Clinical Practice (GCP) guidelines and other applicable international guidelines for the conduction of clinical trials in humans. The study was presented to the Spanish Drug Agency. Written informed consent was obtained from the patients prior to their enrolment in the study, guaranteeing data confidentiality.

Out-patients of both genders, over 18 years of age, who fulfilled the following enrolment criteria were included in the study: diagnosis of depressive syndrome susceptible of receiving treatment according to clinical observation; associated anxiety symptoms; and minimum scores of 17 and 10 on the Hamilton Depression Rating scale (HAM-D_{17}) and Anxiety Rating scale (HAM-A), respectively. Among the exclusion criteria, the following were found: known hypersensitivity to venlafaxine, use of psychodrugs or drugs with possible psychoactive effect in the week prior to study onset, electroconvulsive therapy or sumatriptan in the 30 days prior to study onset, use of monoamine-oxidase inhibitors or St. John's Wort in the 14 days prior to enrolment, and presence of serious cardiovascular, hepatic or renal medical disease or pharmacologically uncontrolled arterial hypertension. Use of non-benzodiazepinic hypnotics was permitted during the study as concomitant treatments.

Study design

In the baseline visit (visit 1), the depression module of the Spanish validation of Primary Care Evolution of Men-

tal Disorders (PRIME-MD)[16,17] was administered to determine the different diagnostic categories included in the depressive disorder in each one of the patients. Treatment with venlafaxine extend release (VXR) was initiated at recommended doses of 75 mg/day. Given the observational design of the study and according to the clinical response and tolerability, the VXR dose could be increased up to 225 mg/day according to the clinical criteria. Treatment with venlafaxine extended release was continued for 24 weeks.

Evaluations

Follow-up visits were made at weeks 4, 12 and 24 (visits 2, 3 and 4, respectively). Effectiveness, safety and treatment tolerability with venlafaxine extended release were evaluated in these visits.

Intensity of the symptoms and their course were evaluated by the Hamilton Depression rating scale (HAM-D_{17})[7,19,20] and Anxiety rating scale (HAM-A)[21,22]. Primary variables of effectiveness were considered to be response rates and remission rates both for depression and associated anxiety. In agreement with definitions commonly accepted and used in different studies, response[23,24] was defined as a reduction of at least 50 % from baseline in the Hamilton Depression rating scale scores (HAM-D) and Anxiety rating scale (HAM-A), while remission was defined as a score less than or equal to 7 on the HAM-D_{17} and HAM-A[25]. Percentage of patients who scored «0» on the grouped items of these scales was also determined.

As secondary variable of effectiveness, baseline seriousness of the clinical picture and its course over time was evaluated. To do so, the Clinical Global Impression scales of Seriousness (CGI-S) and Improvement (CGI-I)[26] were administered according to the investigator's and patient's evaluations. Measurements of tolerability and safety included collection and assessment of adverse events reported, reasons for withdrawal and drop-out and effect exerted by treatment on variables of physical examination such as weight, systolic and diastolic blood pressure and heart rate.

Statistical analysis

All patients who fulfilled the enrolment/exclusion criteria had signed the informed consent and had received at least one study drug dose were included in the statistical analysis by intention to treat and were evaluated for effectiveness, safety and tolerability. Numeric variables were described using mean and standard deviations and upper and lower ranges. For the categorical variables (nominal or ordinal), absolute and relative frequencies in percentage were used. Evolution during the study in the HAM-D_{17} and HAM-A scales (global scores for associated and individual items) was evaluated by an analysis of the variance (ANOVA) for repeated measurements, using the Student's *t* test for comparison of subgroups. Comparisons between groups for categorical variables were made with the chi square test, Fisher's exact test or McNemar test, as considered appropriate. The WHODRUG v.2003 and MedDra v.5.0 systems were used for coding adverse events and concomitant diseases. All the comparisons were bilateral, considering $p \leq 0.05$ values as significant. The statistical program SAS v.6.12 (SAS Institute Inc., Cary, NC, USA) was used.

RESULTS

Demographic and baseline characteristics

Analysis of effectiveness, tolerability and safety was done on a sample of 6,719 adult out-patients diagnosed of depressive syndrome and associated anxiety, who fulfilled enrolment/exclusion criteria. Mean age of the patients was 50 ± 14.2 years. A total of 73.5 % of all the patients included were women; 49.2 % of the patients had concomitant diseases, the most frequent being those affecting the musculoskeletal (24.48 %), cardiovascular (15.17 %) and gastrointestinal (12.25 %) systems. Most frequently administered concomitant drugs on enrolment in the study were anti-hypertensive (14.60 % of the cases), analgesics (9.68 %) and anticoagulants (0.93 % of the cases) agents.

A total of 4,512 patients (67 % of the sample) were classified according to the PRIME-D scale in the baseline visit into one of the following diagnostic groups: major depression, 2,725 patients (60,4 %); dysthymia, 1,523 patients (33.8 %); minor depression, 191 patients (4.2 %), and recurrence of major depression, 73 patients (1.6 %). A total of 87.5 % of the patients initiated treatment with doses of 75 mg/day of venlafaxine extended release, 12.30 % received a 150 mg/day dose and the remaining 0.20 % required another dose. The mean, median and mode doses were 84.53, 75 and 75 mg/d, respectively. At the end of the study, most of the patients (72.9 %) continued receiving 75 mg of VXR as daily dose, while 25.9 % required a 150 mg/day dose and 1.2 % received another dose. The mean, median and mode doses were 96.24, 75 and 75 mg/day, respectively.

Effectiveness

Treatment with venlafaxine extended release was associated to significant reductions in the scores on the HAM-D_{17} and HAM-A scales during the 24 weeks of treatment. In the case of the HAM-D_{17} scale, the mean baseline score was 22.53 ± 4.63 (upper and lower range of 17 and 48, respectively; median 22). In week 24, the score decreased to 5.52 ± 4.43 (upper and lower ranges of 0 and 34, respectively, median 5) (p=0.001; visits 2, 3 and 4 vs baseline). Similarly, mean score on the HAM-A scale decreased from 22.36 ± 6.85 in the baseline visit (lower and upper ranges of 10 and 52, respectively; median 22) to 4.78 ± 4.39 in week

24 (lower and upper ranges of 0 and 44, respectively; median 4) (p=0.001; visits 2, 3 and 4 vs baseline) (table 1).

Response

Response rate (HAM-D_{17}/HAM-A) significantly increased during treatment. Response percentages were 19.52 %, 66.43 % and 88.28 % (visits 2, 3 and 4, respectively) (p= 0.001; visits 3 and 4 vs visit 2). At the end of the study and in the case of the anxiety/somatization symptoms associated with depression (items 10, 11, 12, 13, 14 and 17 of the HAM-D_{17} scale), the response rate was 85.76 % (p=0.001; visits 3 and 4 vs visit 2).

Remission

Considering the remission of the associated depressive and anxiety symptoms, treatment with venlafaxine extended release was associated to a significant increase in the number of patients who remitted. At the end of the study, remission percentages were 74.62% (HAM-D_{17}), 81.55 % (HAM-A) and 72.63 % (HAM-D_{17}/HAM-A) (p=0.001 visits 3 and 4 vs visit 2, in all the measurements). Table 2 shows the percentage of patients who reached remission for the associated depression and anxiety symptoms during the study. At the end of the study, complete resolution of the symptoms was 20.78 % in the case of anxiety/somatization factor (items 10, 11, 12, 13, 14 and 17 of the HAM-D_{17} scale), 28.5 % in the case of the energy subscale (items 1, 7, 8 and 14 of the HAM-D_{17} scale), 15.89 % on the psychic anxiety subscale (items 1-6 and 14 of the HAM-A scale) and 30.11 % on the somatic anxiety subscale (items 7-13 of the HAM-A scale) (fig. 1).

Table 1 Scores on the HAM-D_{17} and HAM-A scales: baseline and follow-up visits

Measurements	Mean (SD)[c]	Range	p value[d]
Scores HAM-D_{17} scale[a]			
Baseline	22.53 (4.63)	17-48	
Visit 2 (week 4)	14.79 (5.73)	0-44	0.001
Visit 3 (week 12)	0.95 (5.28)	0-35	0.001
Visit 4 (week 24)	5.52 (4.43)	0-34	0.001
Scores HAM-A scale[b]			
Baseline	22.36 (6.85)	10-52	
Visit 2 (week 4)	13.95 (6.66)	0-47	0.001
Visit 3 (week 12)	8.11 (5.52)	0-42	0.001
Visit 4 (week 24)	4.78 (4.39)	0-44	0.001

[a] HAM-D_{17}: Hamilton Depression rating scale. [b] HAM-A: Hamilton Anxiety rating scale. [c] DE: standard deviation. [d] The mean values are significantly decreased from baseline (p=0.001; visits 2. 3 and 4 vs baseline, in all the measurements); Student's t test.

Table 2 Remision rates. HAM-D_{17} and HAM-A scales: follow-up visits

Measurements	% (No. subjects)	p value[c]
Remission (HAM-D_{17} ≤ 7)[a]		
Visit 2 (week 4)	9.38 (578)	
Visit 3 (week 12)	42.96 (2,485)	0.001
Visit 4 (week 24)	74.62 (4,090)	0.001
Remission (HAM-A ≤ 7)[b]		
Visit 2 (week 4)	16.00 (986)	
Visit 3 (week 12)	54.67 (3,158)	0.001
Visit 4 (week 24)	81.55 (4,469)	0.001
Remission (HAM-D_{17}/HAM-A ≤ 7)		
Visit 2 (week 4)	7.82 (481)	
Visit 3 (week 12)	39.92 (2,302)	0.001
Visit 4 (week 24)	72.63 (3,968)	0.001

[a] HAM-D_{17}: Hamilton Depression rating scale. [b] HAM-A: Hamilton Anxiety rating scale. [c] Remission significantly increased from visit 2 (p=0.001; visits 2, 3 and 4 vs visit 2, in all the measurements); McNemar test.

Clinical global impression

In the baseline visit, 93.2 % of the patients were considered as «markedly or seriously ill» according to the investigator's evaluation (CGI-S). During the study, the patients showed significant improvement in global condition, according to the investigator's and patient's assessments (CGI-I). On visit 2 (week 4), the global condition of the patient was classified as «much/very much better» in 58.05 % of the patients. This percentage was increased to 86.18 % and 93.73 % (visits 3 and 4, respectively) (p=0.001; visits 3 and 4 vs visit 2). Similarly, and according to the patient's opinion,

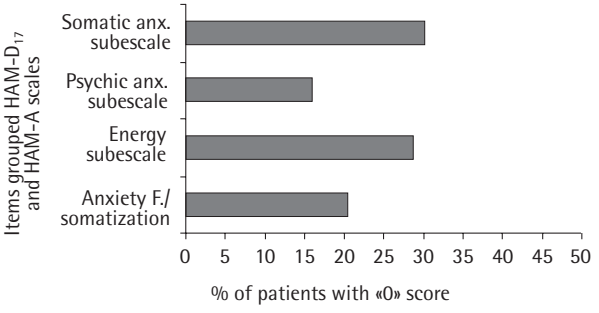

Figure 1 *Patients with «0» scores on HAM-D_{17} and HAM-A subescales: week 24. *Anxiety/somatization factor: items 10, 11, 12, 13, 14 and 17 HAM-D_{17} scale; energy subscale: items 1, 7, 8 and 14 HAM-D_{17} scale; psychic anxiety subscale: items 1-6 y 14 HAM-A scale; somatic anxiety subscale: items 7-13 HAM-A scale.*

89.99% of the patients scored «much/very much better» in week 24 (p=0.001; visits 3 and 4 vs visit 2).

Tolerability and safety

Analysis of withdrawals and drop-outs from the study shows that 18.2% of the patients dropped-out or were withdrawn from the study. A total of 1.8% of the patients were withdrawn/dropped out of the study due to adverse events. Other reasons were: loss to follow-up (12.1%), non-compliance with treatment plan (1.2%), disease or other reason that justified withdrawal (0.7%), inefficacy (0.3%) or other causes (1.9%).

Treatment with venlafaxine extended release for 24 weeks did not produce clinically relevant changes in systolic and diastolic blood pressure and heart rate in comparison with baseline data. In addition, no clinically relevant changes in other variables analyzed in physical check-up, such as weight, were observed. A total of 6.4% of the sample (430 patients) reported adverse events, of «mild or moderate intensity» in 94.9% of the cases and «serious» in the remaining 5.1% (38 cases). There were two cases of serious hypertension during the study. of all the 743 adverse events, 20% were not considered to be related with the treatment and the relationship was considered as «possible» or «probable» in the remaining. One hundred thirty nine patients (2.06%) required temporal or definitive withdrawal from treatment and 1.8% in relationship with the study drug. The 12 most frequent adverse events are shown in table 3.

CONCLUSIONS

Is it a realistic objective to achieve remission in primary health care patients? This question which has been asked by some authors is presently essential to understand the management of depressive pictures; above all, if we consider the importance of remission as a factor that improves the patients' prognosis in regards to relapses, quality of life, complications and even suicide rates. If the objective of the treatment of depression disorders is remission of the symptoms and not only response, we require studies that show the behavior of the different types of drug and non-drug and even combined treatments in primary health care patients which is where more and more of these patients are treated. Most of the existing studies refer to psychiatric patients and it does not seem that we can presently verify that the data can be extrapolated. These patients are fundamentally affected by anxious pictures, dysthymia, mild or mild-moderate depressions. In the recently publication LIDO study, a 9 month follow-up in six european countries[27] is done in patients with depression seen in primary health care, obtaining complete remission rates that varied from 23% to 48% in the different sites. It is observed with a logistic regression model that the only predictors related with the prognosis were: education, quality of life and live events.

In the previously mentioned meta-analysis[12], 3,202 depressive patients included in 14 controlled studies conducted in primary health care were analyzed: 75% were women, with a mean age of 32 years and mean follow-up of 32 weeks. The remission rate ranged from 50% to 67%, with the characteristic that this value is inferior to that reported in the studies that lasted 6 months or less (51.4% remission) and those of duration greater than this period (62.3%). It was observed how the remission rate increases with follow-up duration. In the psychiatric population, remission rates reported are somewhat inferior[18,28,29], between 35% and 46%, although it is very important to state that these were studies with a much shorter duration, from 7 to 10 weeks in the studies with antidepressants and 16 weeks when drugs are compared with psychotherapy interventions.

The prevalence rates in primary health care, when minor depressions or dysthymias are added, grow exponentially[30]. In the population sample of this study, conducted in primary health care setting, almost all of the cases, 95%, corresponded to major depression and dysthymias, with a very low percentage of the category not included in international classifications, minor depression. Remission rates with venlafaxine extended release observed in this study (74.62% in the case of the HAM-D_{17} scale and 81.55% in the case of the HAM-A) scale, are higher than those reported in the psychiatric population, although the 24 week treatment period is longer. Another one of the reasons for these differences could be the greater seriousness of the psychiatric patients. Patients from primary health care are frequently treated for pictures with minor intensity, many times with associated anxiety symptoms, which accounts for the approach of our study. In any event, the mean baseline score of the HAM-D was 22 in this study, as was the baseline score of the HAM-A. The high remission rates obtained offer results on dose and tolerability of venlafaxine extended release that require some comments.

Tabla 3 Summary of 12 most frequently reported adverse events

Description of adverse events	Frequency	% (total population)
Nauseas	97	1.32
Dizziness	57	0.82
Mouth dryness	40	0.60
Tremor	33	0.49
Vomits	32	0.46
Aggitation	31	0.45
Constipation	27	0.39
Headache	24	0.36
Gastric pain	21	0.31
Dyspepsia	19	0.28
Somnolence	19	0.25
Hypertension	18	0.25

Most of the patients receive doses between 75 and 150 mg. These are doses that are somewhat lower compared with the studies in psychiatric populations, which reinforces the hypothesis that we are faced with populations of patients seen who have differential characteristics and that make it difficult to extrapolate the data mentioned.

Do the present methodologies make it possible to differentiate efficacy and effectiveness of the different antidepressant drugs? It would be interesting to compare the data of venlafaxine extended release in this population with other antidepressants such as SSRI (selective serotonin reuptake inhibitors), as has been done in psychiatric patients[28], although retrospectively. The guidelines and clinical protocols bestow similar properties and clinical efficacy to SSRI but many clinicians do not support this statement and, in practice, noticeably differentiate their use according to certain profiles of the patients and drugs, most of the times due to the presence of anxious symptoms. There is still limited data available in the field of primary health care on the systematic objective of the remission concept.

In conclusion, venlafaxine extended release has been shown to be an effective and safe drug in this study in the management of depressive-anxious symptoms of patients with diagnosis of depression seen n primary health care. The main limitations of our study are those characteristic of an open-labeled, non-controlled study. The unquestionable relevance of controlled clinical trials has caused some negligence toward open-labeled or observational studies for some years. However, in recent times, some characteristics of the open-labeled studies are being re-assessed: very large series of patients, identification of each investigator with the most immediate clinical reality, etc. Another limitation is the participation of many clinicians with the same evaluation instruments, which could reduce reliability of results obtained. In any case, we understand that the study, with an effective and well tolerated drug, offers an excellent opportunity to study the different response and remission rates in depressive patients with anxiety, using an instrument especially designed for rapid detection of affective disorders in primary health care. The fundamental clinical implication of the study, in our opinion, is that it contributes to establishing the differences between the psychiatric population and primary health care ones in the field of mood disorders and increases the few experiences up to now on the possibility of converting clinical remission into a realistic objective in this health care framework.

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