Research Paper

Pharmacovigilance Analysis of Adverse Psychiatric Events and Suicidality Reported for Roflumilast, an Add-On COPD Therapy

ABSTRACT

Aims: Roflumilast is a phosphodiesterase-4-inhibitor used as add-on therapy to long-acting bronchodilators in chronic obstructive pulmonary disease. Although roflumilast is well tolerated, there have been concerns regarding psychiatric problems, including suicide tendencies. This study aims to identify and characterize signals of adverse psychiatric events reported for roflumilast in the US FDA Adverse Event Reporting System (FAERS).

Study design: Retrospective pharmacovigilance analysis.

Place and Duration of Study: Adverse event reports submitted to FAERS from October 1997 through September 2012.

Methodology: Multi-item Gamma Poisson Shrinker data-mining algorithm was applied to adverse psychiatric events (APE) that were submitted to the FAERS (3Q1997-3Q2012). Empirical Bayes Geometric Mean (EBGM) and 95% confidence interval (EB05-EB95) were calculated for roflumilast-associated APE compared to all drugs in FAERS. The following Preferred Terms of the MedDRA terminology were used to define the outcome of interest: “anxiety”, “depressed mood”, “depression”, “insomnia”, “suicide attempt”, and “suicidal ideation”. Signals with EB05$\geq$2 are considered significant disproportional reporting ($\geq$twice that expected) of APE.

Results: 126 reports of APE were identified for roflumilast, corresponding to mutually non-exclusive events of insomnia (n=53), anxiety (n=38), depression (n=36), suicidal ideation (n=30), depressed mood (n=8), and suicide attempt (n=6). EBGM (EB05-EB95) were: APE, 3.55 (3.06-4.11); insomnia, 4.55 (3.62-5.66); anxiety, 2.96 (2.26-3.82); depression, 2.88 (2.19-3.75); suicidal ideation, 5.65 (4.16-7.52); depressed mood, 3.90 (2.20-6.53); and suicide attempt, 1.66 (0.86-2.95).

Conclusion: Roflumilast is associated with higher than expected reporting of APE, including suicidal thoughts, but not suicide attempts. Pharmacoepidemiologic studies are required to test these hypotheses; meanwhile, prescribers should consider alternative add-on therapies to patients with past or present depression or suicidality.

Keywords: Roflumilast; Adverse Event Reporting System; FAERS; Suicide; Psychiatric Events; COPD; Pharmacovigilance.

1. INTRODUCTION

Roflumilast is a novel orally-administered phosphodiesterase-4 inhibitor approved in February 2011 for maintenance therapy in individuals with severe chronic obstructive

pulmonary disease (COPD) who have frequent exacerbations that are not well controlled by long acting bronchodilators alone [1]. Data from clinical trials and unpublished spontaneous reporting sources in the United Kingdom (UK) raised concerns about roflumilast-associated psychiatric problems, including suicidal thoughts, suicide attempts and completed suicides [2-4]. Anxiety, depression, insomnia, and suicidality are the most common psychiatric events observed with roflumilast therapy in clinical trials [4]. The incidence rates from clinical trials are estimated to be 1%-10% for insomnia; 0.1%-1% for anxiety; and 0.01%-0.1% for depression and suicidality [4]. Reports of suicidality prompted the UK Medicines and Healthcare products Regulatory Agency (MHRA) to issue pertinent warnings to healthcare professionals in January 2013. In particular, three cases of completed suicides occurred in men exposed to roflumilast who did not have a known history of depression and two cases of suicidal attempts in women from [2-3].

There is no published pharmacovigilance analysis of roflumilast-associated psychiatric events, and this study evaluates this potential association by signal detection and characterization using spontaneously reported adverse events in the US FDA Adverse Event Reporting System (FAERS).

2. METHODOLOGY

2.1 Data Source

Adverse event reports submitted to the FAERS from October 1, 1997 through September 30, 2012 are used to conduct a retrospective pharmacovigilance analysis of roflumilast-associated adverse psychiatric events. The FAERS is a spontaneous reporting system of adverse events for all medicinal products approved for marketing in the US. It is an important source of postmarketing safety signal detection and assessment for marketed products. The database structure has been described elsewhere [5].

2.2 Exposure and Outcome Definition

Roflumilast was identified by the generic name in the classification system of the World Health Organizations' Anatomical Therapeutic Chemical (ATC, January 2012). Reports with roflumilast's role in APE occurrence defined as concomitant, primary or secondary suspect are included. Psychiatric events were identified by the Preferred Term (PT) hierarchy of the Medical Dictionary for Regulatory Activities (MedDRA 16.0, March 2013). The following PTs were used to reflect adverse psychiatric events (APE) in conformism with the events reported in clinical trials: "anxiety", "depressed mood", "depression", "insomnia", "suicidal ideation" and "suicide attempt".

2.3 Statistical Analysis

Statistical analyses are conducted using Empirica Signal (7.3, November 2011, Oracle USA Inc., Redwood, CA). Multi-item Gamma Poisson Shrinker (MGPS) disproportionality algorithm was applied to test the hypothesis of disproportional reporting of APE for roflumilast compared to other drug-event combinations in FAERS. Empirical Bayes Geometric Mean (EBGM) values and corresponding 95% confidence intervals (EB05-EB95) are reported for roflumilast-associated APE. Roflumilast-APE combinations with EB05$\geq$2 are considered significant disproportional reporting (at least twice that expected) of APE.

In addition, signal sector mapping is applied to describe APE signals relative to other signals detected for roflumilast. In signal sector maps, tile color is controlled by the EB05 value, and PT box size displayed by System Organ Class (SOC) is controlled by whether Public Health

Impact (PHI) score is calculated for individual PT. Tiles with larger size have larger PHI score. PHI score takes into account the distribution of PT regardless of its association with a particular drug, thus, tile size for a particular PT is stable across sector maps for different drugs. The score is the product of the number of times the PT occurred in serious events and the proportion of reports with the PT that are serious. Furthermore, additional analysis was restricted to reporting period of 1 February 2011-30 September 2012 to characterize signals during the period following roflumilast introduction to market (28 February 2011).

3. RESULTS

3.1 Overview of APE Reports

A total of 1,605 adverse event reports were submitted for roflumilast during the reporting period, 7.8% of total reports were for APE (n=126). Each APE report could include >1 psychiatric PT. There were 53 insomnia reports; 38 anxiety reports; 36 depression reports; 30 suicidal ideations; 8 depressed mood reports; and 6 suicide attempts. Figure 1 depicts reporting trend of APE in relation to other events reported for roflumilast. The trend for APE was consistent with overall events and peaked one year after product approval (Q1 2012). Characteristics of APE reports are described in table 1. The majority of roflumilast users who experienced APE were men with a median age of 67 years, in whom the drug had a primary role in APE occurrence with most indications being for COPD. On average, 27% and 19% of reported APE has occurred after 30 days and within 1 day of starting roflumilast, respectively. About 48% of reports indicated patients had 3-10 concomitantly administered medications; however, 27% of occurred APE was reported in patients without concomitant exposure to other medications.

None of patients recovered from the reported events. Vast majority of reported APE were classified as serious events that were reported within 15 days of event happening. One APE report might have >1 serious event, e.g., a report of hospitalization might also include intervention or subsequent disability. Most of serious events were unclassified, followed by requirement for medical or pharmacological intervention and hospitalization. Only 6 APE reports contributed to patient's death, corresponding to about 6% of all reported serious APE. Half of reported APE were domestic (within the US), and half came from overseas (mainly Germany), with approximately 47% of reported events submitted by healthcare professionals. Only about 17% of the events were reported by roflumilast users.

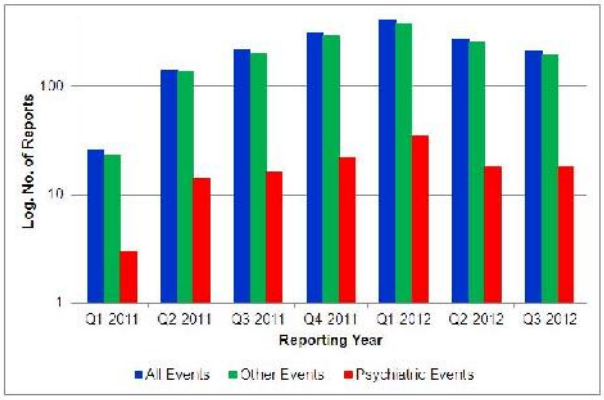

Figure 1. Trend of adverse event reports submitted for roflumilast

112 **Table 1. Characteristics of adverse psychiatric events reported for roflumilast**
113

Characteristic of report	Distribution (N=126)
Patient's age in years, median (minimum, maximum)	67 (40, 94) n=113
Patient's sex	
Male	68 (54)
Female	57 (45.2)
Unknown	1 (0.8)
Drug role in event occurring	
Primary suspect	114 (90)
Secondary suspect	7 (6.0)
Concomitant	5 (4.0)
Clinical indication	
Chronic obstructive pulmonary disease	100 (79.4)
Unspecified lung disorder	9 (7.1)
Emphysema	6 (4.7)
Asthma	5 (4.0)
Chronic bronchitis	3 (2.4)
Respiratory failure	2 (1.6)
Bronchiectasis	1 (0.8)
Duration of therapy (days)	
0-1	24 (19)
2-7	26 (20.7)
8-14	14 (11.1)
15-30	14 (11.1)
31-180	34 (27)
Unknown	14 (11.1)
Number of concomitant drugs	
None	34 (27)
One	9 (7.1)
Two	8 (6.3)
3-10	60 (47.6)
>10	15 (12)
Serious event	107 (85)
Serious event type (percentage of serious events)[a]	
Unspecified serious event	71(66.3)
Required intervention	41 (38.3)
Hospitalization	34 (31.2)
Life-threatening	8 (7.5)
Disability	7 (6.5)
Death	6 (5.6)
Report type	
Expedited	84 (66.7)
Periodic	28 (22.2)
Direct	14 (11.1)
Report source	
Prescriber	59 (46.8)
Unspecified source	22 (17.5)
Consumer	21 (16.7)
Manufacturer	16 (12.7)
Clinical study	8 (6.3)
Reporting country	
United States	63 (50)

Germany	61 (48.4)
Denmark	1 (0.8)
Brazil	1 (0.8)
Reporting year	
Q1 2011	3 (2.4)
Q2 2011	14 (11.1)
Q3 2011	16 (12.7)
Q4 2011	22 (17.4)
Q1 2012	35 (27.8)
Q2 2012	18 (14.3)
Q3 2012	18 (14.3)

[a] *One report might include more than one serious event*

3.2 Overview of Suicidality Reports

Thirty six suicidality events were reported for roflumilast, corresponding to 30 reports of suicidal ideation and 6 reports of suicide attempts. Consistent with all APE reports, reporting trend for suicidality was the highest during the first quarter of 2012. Table 2 shows the characteristics of these reports. Men experienced most of suicidality events, with relatively older patients reported suicide attempts compared to those with suicidal ideations. Majority of suicidal ideation reports and all of suicide attempt reports indicated roflumilast to be the primary suspect in event occurrence and used for COPD treatment. Approximately fourth of suicidal thoughts occurred after first week of roflumilast exposure, and half of suicide attempts occurred within first day of therapy with roflumilast. About 37% and 50% of suicidal ideation and suicide attempt reports respectively reported concurrent exposure to 3-10 medications at the time of exposure to roflumilast and event occurrence. About 37% of suicidal thoughts and third of suicide attempts did not report concomitant exposure to other drugs.

Almost all of suicidality reports were serious events, the majority however, was unclassified and unlike other APE, none contributed to patient's death; nevertheless, about 13% of suicidal ideation and 33% of attempts were life-threatening. Moreover, majority of suicidal ideations was periodically reported every quarter, compared to suicide attempts which were submitted within 15 days of experiencing the events. About 43% and half of suicidal ideation and suicide attempts were reported by healthcare professionals. Ten percent of suicidal thoughts were reported by consumers. None of suicide attempts were reported by roflumilast users; however, 50% of suicide attempts didn't include reporting source. Preponderance of suicidal ideation reports and half of those for suicide attempt were from the US; the rest was from Germany.

Table 2. Characteristics of suicidality events reported for roflumilast

Characteristic of report	Suicidal ideation (N=30)	Suicide attempt (N=6)
Patient's age in years, median (minimum, maximum)	67 (45, 94) n=26	70 (67, 78) n=5
Patient's sex		
Male	20 (66.7)	5 (83.3)
Female	10 (33.3)	1 (16.7)
Drug role in event occurring		
Primary suspect	24 (80)	6 (100)
Secondary suspect	6 (20)	0

Clinical indication		
Chronic obstructive pulmonary disease	28 (93.4)	6 (100)
Chronic bronchitis	1 (3.3)	0
Respiratory failure	1 (3.3)	0
Duration of therapy (days)		
0-1	2 (6.6)	3 (50)
2-7	7 (23.3)	0
8-14	8 (26.7)	2 (33.3)
15-30	3 (10)	0
31-180	5 (16.7)	1 (16.7)
Unknown	5 (16.7)	0
Number of concomitant drugs		
None	11 (36.7)	2 (33.3)
One	3 (10)	1 (16.7)
Two	2 (6.6)	0
3-10	11 (36.7)	3 (50)
>10	3 (10)	0
Serious event	29 (96.7)	6 (100)
Serious event type (percentage of serious events)[a]		
Unspecified serious event	24 (80)	4 (66.6)
Required intervention	18 (60)	2 (33.3)
Hospitalization	4 (13.3)	2 (33.3)
Life-threatening	4 (13.3)	2 (33.3)
Disability	1 (3.3)	2 (33.3)
Report type		
Expedited	13 (43.3)	4 (66.6)
Periodic	14 (46.7)	1 (16.7)
Direct	3 (10)	1 (16.7)
Report source		
Prescriber	13 (43.3)	3 (50)
Unspecified source	0	3 (50)
Consumer	3 (10)	0
Manufacturer	12 (40)	0
Clinical study	2 (6.7)	0
Reporting country		
United States	19 (63.3)	3 (50)
Germany	11 (36.7)	3 (50)
Reporting year		
Q2 2011	5 (16.7)	0
Q3 2011	1 (3.3)	1 (16.7)
Q4 2011	7 (23.3)	2 (33.3)
Q1 2012	12 (40)	3 (50)
Q2 2012	2 (6.7)	0
Q3 2012	3 (10)	0

[a] *One report might include more than one serious event*

3.3 MGPS Disproportionality Analysis Results

Disproportionality analysis results are described in table 3 and figure 2. Roflumilast is significantly associated with 3.55 times more likely reporting of APE than expected compared to all drug-event combinations in FAERS between 1997-2012 (EBGM, 3.55; EB05-EB95, 3.06-4.11). Among APE reports, significant signals were detected for insomnia (EBGM, 4.55; EB05-EB95, 3.62-5.66), anxiety (EBGM, 2.96; EB05-EB95, 2.26-3.82),

depression (EBGM, 2.88; EB05-EB95, 2.19-3.75) and depressed mood (EBGM, 3.90; EB05-EB95, 2.20-6.53). Among suicidality reports, Roflumilast was significantly associated with disproportional reporting of suicidal ideation (EBGM, 5.65; EB05-EB95, 4.16-7.52), but not with suicide attempt (EBGM, 1.66; EB05-EB95, 0.86-2.95).

Table 3. Disproportionality analysis of APE and suicidality reported for roflumilast

Event MedDRA PT	No. of reports	EBGM (EB05-EB95)	
		1997-2012	2011-2012
All adverse psychiatric events	126[a]	3.55 (3.06-4.11)	1.00 (0.86-1.16)
Insomnia	53	4.55 (3.62-5.66)	0.95 (0.83-1.09)
Anxiety	38	2.96 (2.26-3.82)	0.95 (0.82-1.09)
Depression	36	2.88 (2.19-3.75)	0.95 (0.82-1.09)
Suicidal ideation	30	5.65 (4.16-7.52)	0.94 (0.81-1.09)
Depressed mood	8	3.90 (2.20-6.53)	0.93 (0.79-1.09)
Suicide attempt	6	1.66 (0.86-2.95)	0.93 (0.79-1.09)

[a] *One report might have more than one psychiatric event.*
APE= Adverse psychiatric events
EBGM= Empirical Bayes Geometric Mean
MedDRA PT= Medical dictionary for regulatory activities, preferred term

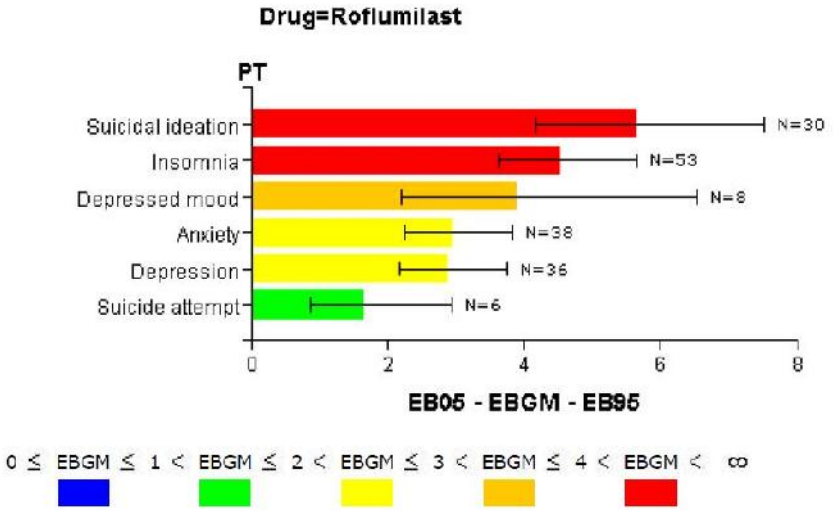

Figure 2. Signals of adverse psychiatric events detected for roflumilast

Figure 3 shows the distribution of top 25 signals detected for roflumilast depicted by SOC, PT, and relative PHI score. Suicidal ideation ranked the fifth detected score, and depression and anxiety had the largest PHI scores among psychological SOC. Strongest signals were found for weight loss and gastrointestinal events.

In addition, restricting analysis to post-approval reporting period of 2011-2012 didn't yield signals of APE (EBGM, 1.00; EB05-EB95, 0.86-1.16), nor other adverse events (Figure 4).

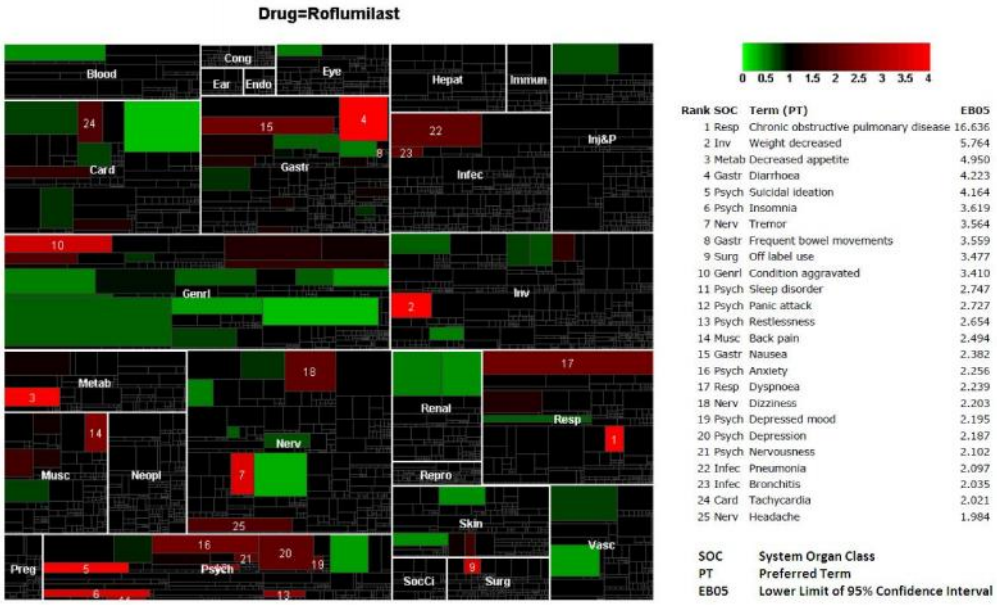

Figure 3. Sector map of top 25 safety signals detected for roflumilast

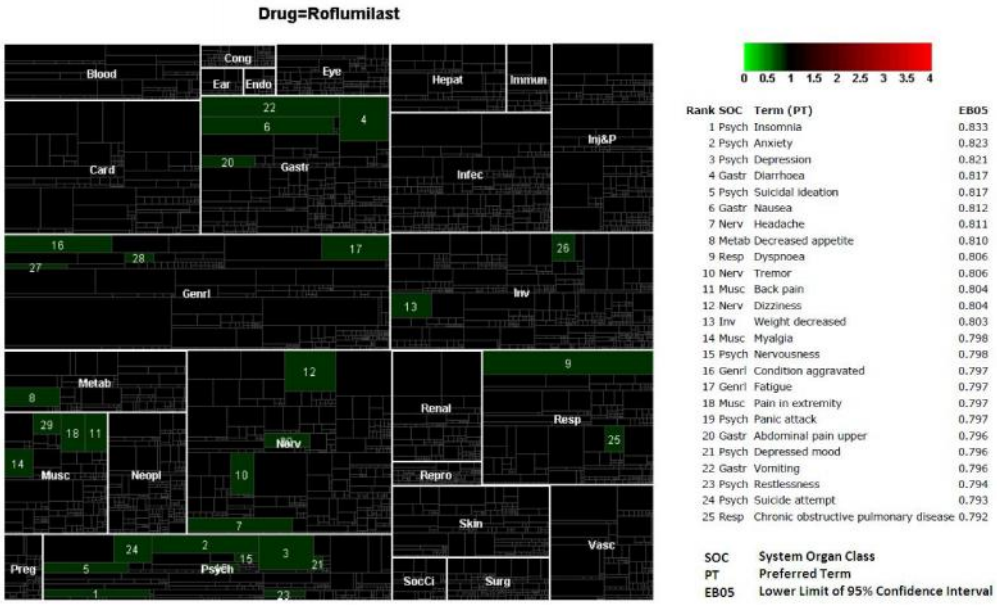

Figure 4. Sector map of top 25 roflumilast-event associations during 2011-2012 period

4. DISCUSSION

The potential association between roflumilast and APE, including suicidality has been an issue with considerable deliberations at regulatory agencies, and there is no known published pharmacovigilance report evaluating this issue. This pharmacovigilance analysis of spontaneously reported APE subsequent to treatment with roflumilast suggests that

roflumilast is associated with APE and suicidal ideation, but not suicide attempts. The findings are consistent with what is known from clinical studies, including signals for adverse events other than APE, e.g., gastrointestinal events and weight loss (Figure 3) [3]. In clinical trials, nausea, diarrhea, headache, and weight loss were the most frequently encountered side effects of treatment with roflumilast, which resulted in drug withdrawal in 9%-16% of patients [6].

Nonetheless, the findings should be carefully interpreted in light of the inherent limitations of spontaneously reported safety data. There is a high likelihood the detected signals are biased estimates because of confounding by indication, where reported events are associated with drug indications; comorbidities; or concomitant medications (73% of reported APE had $\geq$1 drug exposure further to roflumilast). Additionally, reporting of APE events increased within the first year of roflumilast introduction to market, and peaked in the first quarter of 2012, just around the timing of regulatory safety communication by the MHRA, an incident that could contribute to reporting bias and subsequent over-reporting at that time.

Absence of APE signal after restricting analyses to one year after roflumilast introduction to market might be attributed to masking effect, where another drug or group of drugs have a disproportionally large number of APE events, which makes APE appears more common for that drug or group of drugs and less detected in roflumilast. However, this proposition might not be true when no signal was detected for events other than APE (Figure 4). It might be advisable to conduct similar analyses by restricting data after roflumilast approval only after considerable amount of reporting data is available, e.g. 5years.

COPD is a debilitating chronic condition with significant morbidity and poor quality of life burdens. Psychological comorbidities, including depression are increasingly prevalent in individuals with COPD; estimates of coexisting COPD and depression exceed 40% [7]. Further, the severity of depression is correlated with exacerbation frequencies and increased risk of suicidal ideation [8]. Compared to individuals without COPD, those with COPD are significantly associated with suicidal behavior, including suicide attempt [9].

5. CONCLUSION

Roflumilast is an effective novel add-on therapy to long-acting bronchodilators, including long-acting beta-agonists and long-acting muscarinic-antagonists to reduce inflammation and exacerbations [1-3]; and this study should be viewed as a hypothesis generating exercise, and such hypothesis should be tested by more robust pharmacoepidemiologic studies to better characterize the benefit/risk profile of roflumilast. Meanwhile, and in tandem with regulatory recommendations [4], prescribers should consider alternative add-on therapies to patients with past or present depression or suicidality.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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