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ORIGINAL ARTICLE

Therapy for Gastroenteropancreatic Neuroendocrine Tumors: drug evaluation reports review in Spain

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Abstract

OBJECTIVES: In Spain it is necessary to conduct additional studies to determine place in therapy and cost-effectiveness of a drug. The main objective of this study is to identify all drug assessments and health technology assessment reports of the drugs for gastroenteropancreatic (GEP) neuroendocrine tumors (NET) at a national, regional and hospital level and to summarize the efficacy in terms of outcome measures, adverse events, economic impact and final recommendations.
METHODS: A search was made on the GENESIS website for drug evaluation reports regarding GwEP NET, including gastrointestinal and bronchopulmonary, to identify the drug assessments at a regional and hospital level. 8 reviews at regional and hospital level were considered. Two clinical guidelines have been reviewed to determine the current management and available treatments.
RESULTS: Surgery is the main treatment for NETs in different phases of their evolution. If there is recurrence there are other possible treatments as chemotherapy, somatostatin analogues and new biological agents, also called "targeted treatments", that currently have a palliative and symptom control role, since they rarely achieve the elimination of the disease themselves.
CONCLUSIONS: Everolimus and sunitinib are new drugs available for the treatment of GEP NET patients reported to have promising effects in advanced diseases. However, the reports are limited and thus new clinical studies on the impact of these drugs on clinical outcome, prognosis, financial burden and feasibility are necessary to support further recommendations.

Abbreaviations:

PTCs	- Pharmacy and Therapeutics committees	ENETS	- European Neuroendocrine Tumor Society
GEP	- gastroenteropancreatic	GETNE	- Spanish Group of NET
NET	- neuroendocrine tumors	pNET	- pancreatic neuroendocrine tumors
AEMPS	- Spanish Agency of Medicines and Health Products	PFS	- progression-free survival
WHO	- World Health Organization	OS	- overall survival

INTRODUCTION

In European countries during the sales authorization process it is not necessary to demonstrate cost-effectiveness or place in therapy of a new drug (Pignati *et al.* 2011); it is only necessary to show a favorable risk-benefit balance of the new drug to obtain sales authorization (Directive 2004/27/EC).

Hence, it is necessary to conduct further studies to determine the place in therapy and cost-effectiveness, especially since most drugs available in Spain are financed by the public health service. In the UK is the NICE, a national government agency, which carries out centralized evaluations and makes decision on funding (Soto Alvarez, 2009).

Additionally, due to the decentralized structure of the Spanish National Health Service (NHS) the centers that evaluate new medications simply provide recommendations that hospitals and prescribers are not required to follow.

Therefore, there is no institution, national or regional, that establishes common guidelines for the rationalized drug use in the Spanish health system based on the criteria of efficiency, effectiveness and appropriate use. Consequently, drugs are evaluated and selected at a regional level. Regional governments have recently published new regional legislation regarding rational drug use implementing initial assessment for their regions, and have created Pharmacy and Therapeutics committees (PTCs), regional committees that take mandatory decisions for the entire region.

Concretely, drugs used in hospitals, including those administered to inpatients and outpatients attending the hospital for drug administration, and drugs that can only be dispensed by the hospital pharmacy service, are assessed by PTCs. The PTCs select the drugs to be used, generally considering pharmacoeconomic criteria and the relative efficiency of drugs compared with the alternatives available. Then the selected drugs are added to the formulary for each hospital (Fullerton & Atherly, 2004).

Once the drug has been selected, the PTC may set recommendations and conditions for its use, in the case of a drug only used in a specific subgroup or subgroups of patients, for its application to entitle clinical benefits, and it may state whether the costs have been considered. In that case, the use of the drug should be controlled to ensure it meets the established criteria.

Therefore, the main objective of this study is to identify all drug assessments and health technology assessment reports of the drugs used for gastroenteropancreatic (GEP) neuroendocrine tumors (NET) at a national, regional and hospital level and to summarize the efficacy in terms of outcome measures, adverse events, economic impact and final recommendations. The secondary objective is to determine the current management and available treatments for GEP NET.

METHODS

A search was made on the GENESIS website (GENESIS website) for drug evaluation reports regarding GEP NET, including gastrointestinal and bronchopulmonary, to identify the drug assessments at a regional and hospital level. There were no health technology assessment reports for GEP NET at national level.

The reports included in this analysis assess the current treatment of GEP NET. These correspond to 8 reviews at regional and hospital (CatSalut website. Everolimus report; CatSalut website. Everolimus opinion; CatSalut website. Sunitinib report; CatSalut website. Sunitinib opinion; GENESIS website. Sunitinib report; ICO website. Everolimus & Sunitinib report; SEOM website. Everolimus report).

The following parameters were considered for each of the reports: country, region and agency or hospital were the report has been written, drug name, active ingredient, presentations, posology and administration form, Spanish Agency of Medicines and Health Products (AEMPS) authorization date, pharmaceutical company that commercializes the drug, price, report initiation date, report publication date, disease area, indication evaluated, ATC code, RTCs methodology, RCTs comparators, primary outcomes measures, secondary outcomes measures, efficacy measures results, adverse events, conclusions (efficacy, safety and costs), recommendations and web link to the report.

Moreover, in order to determine the current management and available treatments for GEP NET, two clinical guidelines have been reviewed (Matos & Capdevilla, 2015; GTNE website).

RESULTS

Current situation of GEP NET in Spain

Description of the disease

GEP NET constitute a heterogeneous group of tumors with their origin in neuroendocrine cells of the embryological gut. Most commonly, the primary lesion is located in the gastric mucosa, the small and large intestine, the rectum and pancreas. Most NETs are sporadic and do not have a known cause or risk factors. However, in some cases aggregates can appear in families, giving rise to hereditary syndromes, when there are certain germ-line mutations that can be transmitted in successive generations. The most currently accepted classification of the GEP NET is based on that established in 2010 by the World Health Organization (WHO) improved by the criteria and guidelines proposed by the European Neuroendocrine Tumor Society (ENETS). It distinguishes in a primary way between well differentiated and poorly differentiated tumors, to then make a more precise classification by means of a system of gradation (G1, G2, G3) in stages, using proliferation markers and anatomopathological criteria (Table 1).

Diagnostic process

Tab. 1. GEP NET classification

Grade of malignanacy	GEP NET ENETS	GEP NET WHO
G1 (low)	<2 mitosis/10 HPF <3% Ki-67	<2 mitosis/10 HPF ≤2% Ki-67
G2 (medium)	2-20 mitosis/10 HPF 3%-20% Ki-67	2-20 mitosis/10 HPF 3%-20% Ki-67
G3 (high)	>20 mitosis/10 HPF >20% Ki-67	>20 mitosis/10 HPF >20% Ki-67

10 HPF: 10 high power fields = 2 mm^2, at least 40 fields (at ×40 magnification) evaluated in areas of highest mitotic density.

The histological diagnosis is mandatory to establish the diagnosis of NET and is usually obtained by surgery, endoscopic biopsy or liver biopsy guided by ultrasound or CT. The diagnostic process must include the following steps: 1) Adequate anatomopathological identification; 2) Hormone characterization of the tumor, clinical and biochemical; 3) Imaging studies to locate the primary tumor, assess its resectability and establish the extent of metastatic disease; 4) MEN1 syndrome identification. The Spanish Group of NET (GETNE) in its clinical guideline has developed an algorithm of diagnosis (Figure 1).

Current management of GEP NET

Surgery is the main treatment of NETs in different phases of their evolution. In early stages, complete tumor resection is performed with curative intent; in more advanced cases, surgery can be carried out with cytoreductive intention or palliation of symptoms. If there is recurrence there are other possible treatments as chemotherapy, somatostatin analogues and new biological agents, also called "targeted treatments", that currently have a palliative and symptom control role, since they rarely achieve the elimination of the disease themselves. In many patients, especially if they have metastases, it will be necessary to use several of these treatments throughout the disease.

Treatment algorithm for GEP NET

The current therapeutic goal in GEP NET is to cure the disease by using surgery and if it is not possible, to palliate the symptoms. Thus, the available drugs are focused on extending survival and maintain a good quality of life.

Depending on the NET type there are two main algorithms of treatment.

The first algorithm corresponds to the treatment algorithm for patients with pancreatic NET (Figure 2). At first, the treatment depends on whether the NET is resectable or not. If it is resectable, a surgical resection is conducted, and, in case of recurrence, a re-resection is recommended. When the NET is not resectable, the treatment depends on whether the tumor is a functioning or a non-functioning tumor. If it is a non-functioning tumor, the treatment depends on the tumor stage and can be treated with targeted therapy, chemotherapy or with radionuclides. If it is a functioning tumor, the first treatment line is symptomatic treatment of hor-

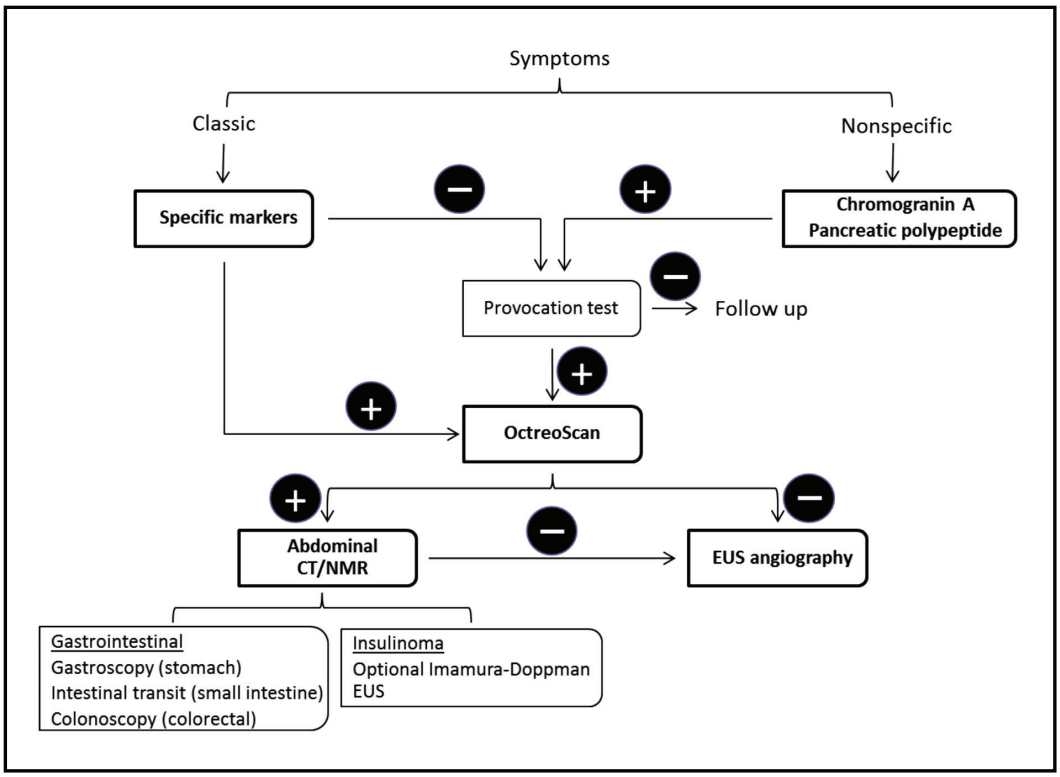

Fig. 1. GEP NET diagnostic algorithm

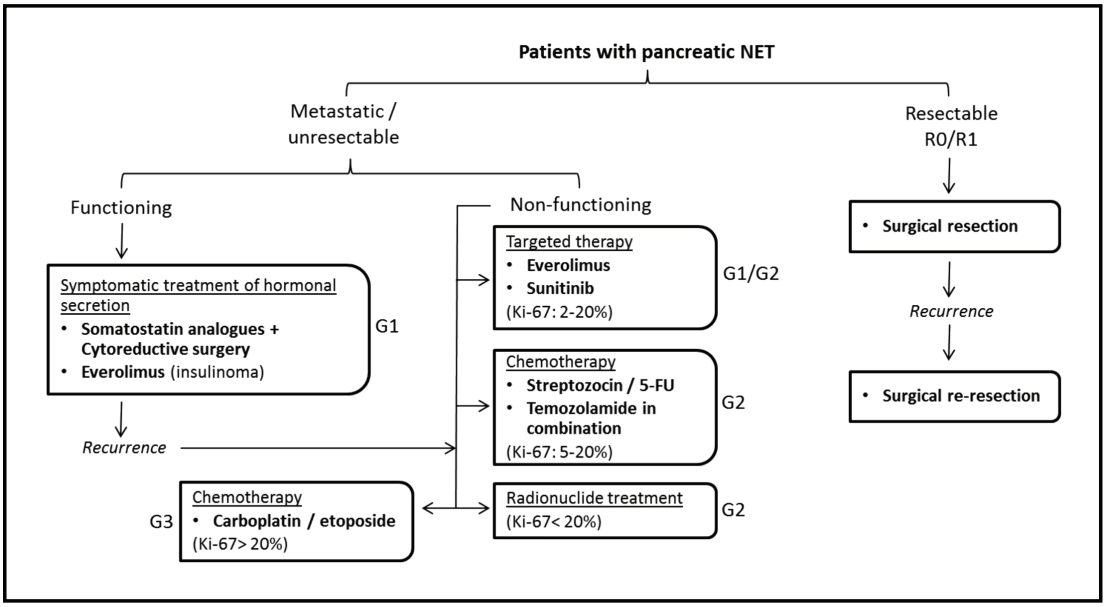

Fig. 2. Treatment algorithm for patients with pancreatic NET

monal secretion, and if there is recurrence, the treatment is the same as if it were a non-functioning tumor.

The second algorithm corresponds to the treatment algorithm for patients with carcinoid NET (Figure 3). At first, the treatment depends on whether the NET is resectable or not. If it is resectable, a surgical resection is conducted, and in case of recurrence a re-resection is recommended. When the NET is not resectable, the treatment depends on whether there is carcinoid syndrome or not. If there is a NET with carcinoid syndrome the first line of treatment is with somatostatin analogues combined with a possible cytoreductive surgery. If there is no carcinoid syndrome the first line of treatment is a treatment with Octreotide LAR. If after these treatments there is tumor recurrence, the treatment depends on the tumor stage and can be treated with targeted therapy, chemotherapy, interferon alpha or with radionuclides.

Drug assessment

The reports included in this analysis assess the current treatment of GEP NET. These correspond to 8 reviews at regional and hospital level (Table 2).

1) Everolimus (afinitor®)

Four reports, one from the SEOM in 2016, two from the CAMHDA in 2012 and one from the ICO in 2011, have evaluated everolimus as treatment for patients with non-functioning, unresectable or metastatic, in progression, WHO grade 1/2 NETs of gastrointestinal

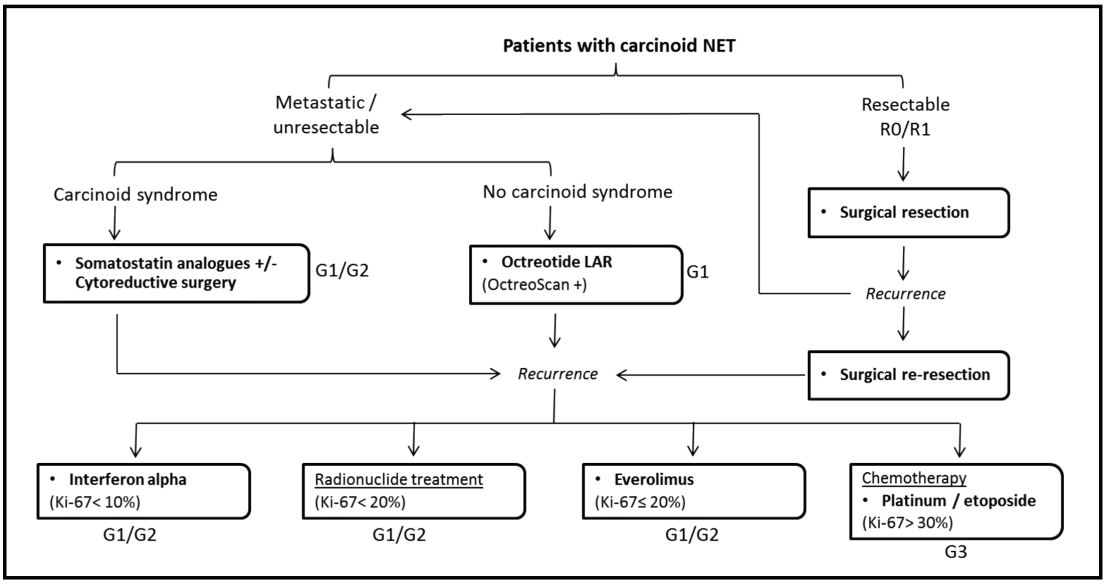

Fig. 3. Treatment algorithm for treatment of patients with carcinoid NET

Tab. 2. Drugs assessed in GEP NET

Name of the drug	Active substance	Pharmaceutical Laboratory	Authorization date	Drug assessment reports
AFINITOR® 1 mg/ml concentrate for solution for infusion	Everolimus	Novartis Europharm Limited	17/09/2009	• 2016 – SEOM • 2012 – CAMHDA (1) • 2012 – CAMHDA (2) • 2011 – ICO
SUTENT® (200;400) u powder for concentrate for solution for infusion	Sunitinib	Pfizer Limited	29/09/2009	• 2013– Genesis Group • 2012 – CAMHDA (1) • 2012 – CAMHDA (2) • 2011 – ICO

and bronchopulmonary origin (Table 3). Considering the efficacy and safety results, and according to the report conclusions, everolimus has demonstrated significant differences in terms of progression-free survival (PFS) in the comparison with placebo. This result was supported by two centralized committees with very similar results. The average overall survival (OS) had not been achieved at the time of the analysis and no significant differences between both treatment groups were observed. No data on the quality of life is available in this study.

The therapeutic positioning recommendations suggest treatment with everolimus in patients with advanced or unresectable NETs of bronchopulmonary and gastrointestinal origin, well-moderately differentiated, WHO grades 1 and 2, non-functioning and progressively documented by RECIST criteria in the last 6 months of follow-up.

2) Sunitinib (sutent®)

Four reports, one from the Genesis Group in 2013, two from the CAMHDA in 2012 and one from the ICO in 2011, have evaluated sunitinib as a treatment for pancreatic neuroendocrine tumors (pNET), well differentiated, non-resectable or metastatic, in adult patients with progressive disease (Table 4). Considering the efficacy and safety results and according to the report conclusions, sunitinib has demonstrated significant

Tab. 3. Everolimus assessment results

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Treatment of patients with non-functioning, unresectable or metastatic, in progression, WHO grade 1/2 neuroendocrine tumors of gastrointestinal and bronchopulmonary origin.	• POSOLOGY - Everolimus: 10 mg once a day, always at the same time. Dose modifications can be applied based on safety and individual tolerability. The recommended modified dose is 5 mg per day. • ADMINISTRATION FORM Oral route	**Efficacy** • Progression-free survival (PFS) • Other variables: Overall survival (OS), Security, Overall response rate (ORR), Disease control rate (DCR), Duration of the response. **Safety** Stomatitis, diarrhea, asthenia, infections, rash, peripheral edema and nausea. **Cost** Global treatment cost	According to the study that evaluated the efficacy of everolimus, this therapy has demonstrated significant differences in terms of PFS in the comparison with placebo. This result was supported by two centralized committees with very similar results. The average OS had not been achieved at the time of the analysis and no significant differences between both treatment groups were observed. No data on the quality of life in this study is available. The global cost per treatment with everolimus is estimated at 40.095,25 €/year, which involves an incremental cost-effectiveness +67.9624 €/year with regards to placebo. In Catalonia, it is estimated that the annual incidence of pNET could be 27 new patients per year. Assuming a 12 month treatment duration, the additional annual budgetary impact of treating 27 patients with everolimus will be 1.082.272 €.	Following the recommendations and approvals of the different regulatory authorities based on the results of the RADIANT-4 prospective and randomized phase III study, everolimus should be recommended for the treatment of patients with advanced or unresectable NETs of bronchopulmonary and gastrointestinal origin, well-moderately differentiated, WHO grades 1 and 2, non-functioning and progressively documented by RECIST criteria in the last 6 months of follow-up.

Tab. 4. Sunitinib assessment results

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Treatment of pancreatic neuroendocrine tumors (pNET), well differentiated, non- resectable or metastatic, in adult patients with progressive disease	• POSOLOGY - Sunitinib: 37.5 mg orally once daily, with no scheduled rest period. Dose modifications can be applied with variations of 12.5 mg based on safety and individual tolerability. • ADMINISTRATION FORM Oral route	**Efficacy** • Progression-free survival (PFS) • Other variables: Overall survival (OS), Objective response rate (ORR), Duration of the response, Security **Safety** Anorexia, dysgeus la, hypertension, fatigue, gastrointestinal disorders, skin discoloration and palmoplantar erythrodysesthesia syndrome. **Cost** Global treatment cost	According to the study that evaluated the efficacy of sunitinib, this therapy has demonstrated significant differences in terms of PFS and OS in the comparison with placebo. In global, the differences obtained in the variables PFS and OS can be considered clinically relevant results that confirm the superiority in efficacy of sunitinib. The global cost per treatment with sunitinib is estimated at 45.897,6 €, which involves an incremental cost- effectiveness +93.313 €/year with regards to placebo. Taking into account that in a hospital 1 or 2 new patients per year might be candidates to receive treatment with sunitinib, a budget impact between 93.313€ and 186.626€ is estimated assuming a treatment for 12 months.	Because the effective treatment options available to patients with pancreatic neuroendocrine tumors are so limited, sunitinib has become a new option after failure or relapse. Sunitinib is considered a treatment option in adult patients with well differentiated, unresectable or metastatic pancreatic neuroendocrine tumor, with: • Progression of the disease after previous treatment • ECOG ≤1 • Disease progression documented radiographically • Renal, hematological and hepatic normal function

differences in terms of PFS and OS in the comparison with placebo. In global, the differences obtained in the variables PFS and OS can be considered clinically relevant results that confirm the superior efficacy of sunitinib. The therapeutic positioning recommendations that suggest treatment with everolimus in patients with pNETs are limited, and sunitinib has become a new option after failure or relapse. Sunitinib is considered a treatment option in adult patients with well differentiated, unresectable or metastatic pNET tumor, with:
1) Progression of the disease after previous treatment; 2) ECOG ≤ 1; 3) Disease progression documented radiographically; and 4) Renal, hematological and hepatic normal function.

DISCUSSION

Clinical guidelines

The therapeutic objective in gastroenteropancreatic neuroendocrine tumors (GEP NET) is focused in cure by surgery, and if this is not possible, in palliation. This palliation is based on three goals: control of disease, extension of survival and maintenance of quality of life. During the last decade new drugs active in advanced NETs have been found, as a consequence of the more extensive knowledge of the biology of these neoplasms, this advances allow us to be optimistic about the therapeutic options to be used in these patients. Nonetheless, there is still not enough evidence to make strict recommendations.

It remains to be determined whether somatostatin analogues should be used in monotherapy or associated with antiangiogenic agents or mTOR inhibitors. It is also unknown which is the optimal sequence of drugs in NET, if an antiangiogenic and then an mTOR inhibitor should be used first, or vice versa.

Further, it remains unknown which is the most active antiangiogenic agent, and whether biological agents or chemotherapy should be used first, despite all the information provided by clinical guidelines.

Drug assessment

In general, comparators used in the evaluations are considered adequate. However, the combination of streptozocin with doxorubicin or 5-FU would be considered also valid options, with rates of response of 69% vs. 45% achieved according to the randomized trial of Moertel *et al.* (1992).

The use of PFS is considered adequate since it is the recommended variable in efficacy studies where a delay in the progression in absence of radiological tumor responses is expected.

The use of OS is not considered adequate, except in highly refractory cases or when the expected survival is limited.

Follow-up periods of the studies for both treatments (everolimus and sunitinib) appear to be short in continuous treatments. Therefore, it would be necessary to extend the follow-up period in order to obtain long-term efficacy data.

Due to the limited experience on the effectiveness of everolimus and sunitinib in naive patients, it is necessary to conduct a study in order to draw conclusions about this subgroup.

CONCLUSIONS

Everolimus and sunitinib are new drugs available for the treatment of GEP NET patients reported to have promising effects in advanced diseases. However, the reports are limited and thus new randomised, controlled clinical studies on the impact of these drugs on clinical outcome, prognosis, financial burden and feasibility are necessary to support further recommendations.

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