Comparison of Therapeutic Efficacy and Clinical Parameters Between Recombinant Human Thyroid Stimulating Hormone and Thyroid Hormone Withdrawal in High-Dose Radioiodine Treatment with Differentiated Thyroid Cancer

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Abstract

Purpose High-dose radioiodine treatment (HD-RIT) after injection of recombinant human thyroid stimulating hormone (rh-TSH) has become widely used. This study compared the therapeutic efficacy of HD-RIT and clinical parameters between rh-TSH supplement and thyroid hormone withdrawal (THW) after total thyroidectomy in patients with differentiated thyroid cancer.

Methods We retrospectively reviewed 266 patients (47 male and 219 female; age, 49.0 ± 10.9 years) with differentiated thyroid cancer detected from September 2011 to September 2012. Patients comprised THW (217, 81.6 %) and rh-TSH (49, 18.4 %). Inclusion criteria were: first HD-RIT; any TN stage; absence of distant metastasis. To evaluate the complete ablation of the remnant thyroid tissue or metastasis, we reviewed stimulated serum thyroglobulin (sTg), I-123 whole-body scan (RxWBS) on T4 off-state, and thyroid ultrasonography (US) or [F-18]-fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) 6–8 months after HD-RIT. We defined a complete ablation state when all three of the follow-up conditions were satisfied; <2.0 ng/ml of the sTg, I-123 RxWBS (–), and thyroid US or F-18 FDG PET/CT (–). If one of the three was positive, ablation was considered incomplete. We also

compared various clinical biomarkers (body weight, body mass index, liver and kidney function) between THW and rh-TSH groups.

Results The rates of complete ablation were 73.7 % (160/217) for the THW group and 73.5 % (36/49) for the rh-TSH group. There was no significant difference between the two groups ($p=0.970$). The follow-up aspartate transaminase ($p=0.001$) and alanine transaminase ($p=0.001$) were significantly higher in the THW group. The renal function parameters of blood urea nitrogen ($p=0.001$) and creatinine ($p=0.005$) tended to increase in the THW group. The change of body weight was $+ \Delta 0.96 (\pm 1.9)$ kg for the THW group and was decreased by $- \Delta 1.39 (\pm 1.5)$ kg for the rh-TSH group. The change of body mass index was $0.4 (\pm 0.7)$ kg/m² in the THW group and was decreased by $-0.6 (\pm 0.6)$ kg/m² in the rh-TSH group.

Conclusions Consistent with previous studies, the rates of complete ablation between the THW and rh-TSH groups were not significantly different. The clinical parameters, as we mentioned above, were elevated for THW group but were irrelevant for the rh-TSH group. The findings favor HD-RIT after rh-TSH, especially for patients with chronic liver and kidney disease.

Keywords Thyroid cancer · High-dose radioiodine therapy · Recombinant human TSH · Thyroid hormone withdrawal · Complete ablation rate · Liver function · Kidney function

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Introduction

In Korea in 2013, thyroid cancer was predicted to be the most common cancer in females 15–64 years of age and also in males 15–34 years of age. In that year, thyroid cancer was projected to account for 35.4 % (43,973/124,122 cases) of incident cases in females in 2013 [1]. Differentiated thyroid

cancer (papillary, follicular type) predominantly (70–80 %) consists of thyroid cancer and, especially in Korea, papillary microcarcinoma has rapidly increased in the past 5 years.

Total thyroidectomy is the initial treatment for the majority of patients with differentiated thyroid cancer. After near-total or total thyroidectomy, radioiodine ablation of remnant thyroid cancer has become a standard therapeutic procedure in medical centers [2]. High-dose radioiodine therapy (HD-RIT) can ablate normal remnant thyroid tissues and microscopic deposits of thyroid carcinoma [6].

Before HD-RIT, patients must either withdraw from thyroid hormone supplementation for 4–6 weeks or use recombinant human thyrotropin (rh-TSH) and start a low iodine diet for about 2 weeks to increase TSH level, which can enhance therapeutic uptake of I-131 in remnant thyroid tissue or metastatic lesions.

Thyroid hormone withdrawal (THW) and use of rh-TSH are quite different concerning symptoms and signs with or without hypothyroidism. Many patients who have undergone HD-RIT with THW suffer from weight gain, constipation, depression, and sialadenitis [3]. Subjective perceptions of quality of life are significantly better in euthyroid patients than hypothyroid patients [4].

For these reasons, rh-TSH has become increasingly used instead of the classic method of THW. A prospective randomized study reported that THW and rh-TSH administration for I-131 remnant ablation was equally effective in the treatment of thyroid cancer [5]. However, in Korea, no previous report of the therapeutic effect between rh-TSH as an adjunct to I-131 therapy of thyroid carcinoma and I-131 therapy after endogenous TSH elevation from THW has been published.

Also, the clinical parameters between the two methods have not been sufficiently investigated and there has been no consensus concerning which method should be needed corresponding to a patient's clinical situation.

The aim of this study was to compare remnant thyroid ablation rates between rh-TSH and THW, and to investigate the changes of clinical parameters of kidney function, liver function, body weight and body mass index.

Material and Methods

Patients

Two hundred and sixty-six patients with differentiated thyroid cancer who had total thyroidectomy with consecutive HD-RIT at Chonbuk National University Hospital from September 2011 to September 2012 were enrolled. Patients who had been treated with previous radioiodine therapy or who had a distant metastasis (lung or bone) confirmed by post-operative [F-18]-fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) were excluded.

The choice of preparation for HD-RIT (THW vs rh-TSH) was not based on uniform criteria because our research was not prospectively designed. However, patients prepared for rh-TSH tended to be older, with chronic heart or pulmonary disease, or a debilitated physical state. Regardless of these conditions, people who wanted to have the rh-TSH injection were also included. Of these, 217 had RIT after THW and 49 after rh-TSH preparation. The clinical characteristics of the two groups are summarized in Table 1. This study was approved by the Institutional Review Board at our institution. Informed consent was waived because of the retrospective design of this study.

In the THW group, levothyroxine was withdrawn for 5 weeks, and switched to triiodothyronine for first 3 weeks and took no thyroid hormones for the last 2 weeks before HD-RIT. Generally, stimulated TSH level is recommended above 30 mIU/L for the radioiodine therapy after THW. For this recommendation, stimulated TSH level was checked a week

Table 1 Clinical characteristics of two groups

Characteristics	THW ^a group (<i>n</i> =217)	rh-TSH ^b group (<i>n</i> =49)	<i>p</i>
Age (years)	48.3±10.8	58.2±12.1	0.02
Sex (M:F)	41:176	6:43	0.25
Histology			
Papillary carcinoma	212	48	0.91
Follicular variant	5	1	—
Pathologic staging			
T3N1	101	26	0.78
T3N0	53	12	—
T1N1	36	6	—
T1N0	28	5	—
Therapeutic dose (GBq)	5.8±0.6	5.7±0.6	0.66
Pre-therapeutic stimulated thyroglobulin (ng/mL)	12.5±44.1	9.5±18.9	0.64

before HD-RIT and at the time of admission. Stimulated thyroglobulin (sTg) level was also checked at the time of admission for the HD-RIT. Patients in the rh-TSH group were also placed on levothyroxine after total thyroidectomy. However, instead of withdrawal of levothyroxine, they received 1.1 mg rh-TSH intramuscularly on 2 consecutive days before HD-RIT. Stimulated TSH level was checked at the time of admission, and sTg levels were estimated at the time of admission and discharge.

Outcome Assessment

The dose of radioactive iodine administration is determined according to pathologic staging of thyroid cancer. If there is lymph node metastasis below 5 in the central neck area, we treated the patient with 5.55 GBq of radioactive iodine; lateral neck lymph node metastasis or central neck lymph node metastasis more than 5 was given 6.66 GBq [6].

Post-therapy scans were performed on day 3 and day 10 after I-131 administration. I-123 whole-body scan (WBS) (dose of 185 MBq) and sTg were also taken at 8 ± 2 months after administration of radioactive iodine. Stimulated TSH level was above 30 mIU after withdrawal of T4 for 5 weeks

or rh-TSH injection. The neck ultrasonography or F-18 FDG PET/CT was assessed 9 ± 3 months after HD-RIT.

Ablation was considered complete if neck ultrasound or F-18 FDG PET/CT was normal and the stimulated thyroglobulin was <2 ng/mL. Ultrasonographic findings were considered normal if no remnant thyroid gland and no evidence of lymph node metastasis were found. Direct biopsy guided by ultrasonogram was routinely performed for suspicious-looking lymph nodes, and pathologically confirmed to be benign or malignant. In F-18 FDG PET/CT scans, there must be no focal F-18 FDG uptake in the thyroid bed or in lymph node. Furthermore, I-123 WBS displaying no abnormal uptake foci in or outside of the thyroid bed was evaluated as complete ablation. If, one of the three examination approaches (I-123 WBS, thyroid ultrasonography or F-18 FDG PET/CT, Tg), showed evidence of recurred thyroid cancer, it was considered as incomplete ablation. There were some cases that explain incomplete ablation. A 46-year-old man with papillary thyroid cancer, pT3N0, was treated with 5.55 GBq of radioactive iodine after THW (Fig. 1). I-123 WBS after 6 months of radioiodine treatment showed mild uptake in thyroid bed,

Fig. 1 A 46-year-old man who was diagnosed as papillary thyroid cancer, pT3N0, was treated with 5.55 GBq of radioactive iodine after thyroid hormone withdrawal. Post-therapeutic I-131 whole-body scans (WBSs) on 3 days (a) and 10 days (b) showed intense uptake in the thyroid bed, which indicates remnant thyroid tissue. After 6 months, follow-up an I-123 WBS (c) showed focal uptake in the neck area (arrow). The value of stimulated serum thyroglobulin was 0.22 ng/mL. After 7 days, F-18 FDG PET/CT (d) was undertaken, and revealed focal F-18 FDG uptake in the left cervical level IV lymph node (arrow). This could be interpreted as incomplete ablation, and the following lymph node dissection proved metastatic papillary carcinoma

Fig. 2 A 53-year-old woman with papillary thyroid cancer, pT3N1, underwent 6.66 GBq of radioactive iodine treatment after rh-TSH injection. These are images of the I-131 whole-body scans (WBSs) at 3 days (a) and 10 days (b) after radioactive iodine administration. These images showed intense uptake, regarded as remnant thyroid tissue or regional lymph nodes, in the thyroid bed and left lateral neck area. After 6 months, I-123 WBS (c) showed no abnormal uptake in the thyroid bed. At that time, stimulated serum thyroglobulin was 20.7 ng/mL and F-18 FDG PET/CT (d) represented focal F-18 FDG uptake in Lt cervical level III lymph node (arrow), which manifests incomplete ablation. It was pathologically confirmed as a metastatic papillary carcinoma

which suggested incomplete ablation. However, sTg was within the normal range (0.22 ng/mL). F-18 FDG PET/CT represented focal F-18 FDG uptake in left cervical level IV lymph node, which was pathologically confirmed as metastatic papillary thyroid cancer. Another case was a 53-year-old woman, who was diagnosed as having papillary thyroid cancer, pT3N1 (Fig. 2). Subsequent 6.66-GBq radioactive iodine treatment was done. I-123 WBS after 6 months did not show any radioactivity suspicious of remnant thyroid tissue. However, sTg was elevated (20.7 ng/mL), and F-18 FDG PET/CT showed focal F-18 FDG uptake in the left cervical level III lymph node, indicating incomplete ablation. It was proved to be metastatic papillary carcinoma. That might be explained by “de-differentiation,” in which thyroid cancer cells lose their ability to take up iodine. The other case was of a 65-year-old man who was diagnosed as having papillary thyroid cancer, pT3N0, presented only elevated thyroglobulin (9.74 ng/mL) after 6 months of radioactive iodine (5.55 GBq) treatment (Fig. 3). Any other test (I-123 WBS, F-18 FDG PET/CT) had no evidence of remnant thyroid cancer (Fig. 3). This was also considered as incomplete ablation.

F-18 FDG PET/CT scans were undertaken after the intravenous injection of F-18 FDG (3.7–5.5 MBq/Kg) after 6 h of fasting using Biograph Truepoint 40 (Siemens, Berlin, Germany) or Biograph 16 (Siemens, Berlin, Germany). I-123 and I-131 WBSs were obtained by Symbia T16 (Siemens, Berlin, Germany).

Table 2 Therapeutic efficacy between THW and rh-TSH groups

	THW ^a group (n=217)	rh-TSH ^b group (n=49)	<i>p</i>
Complete ablation	160	36	
Incomplete ablation	57	13	
Ratio (CR/total) %	73.7 %	73.5 %	0.97

^a Thyroid hormone withdrawal

^b Recombinant human thyroid-stimulating hormone

Clinical Parameters

We reviewed the clinical parameters of all patients in the two groups. We first compared the body weight change and body mass index (BMI) before the radioiodine therapy and at the first follow-up day after treatment. The time interval was 6 ± 1.6 weeks, which included a 2-week hypothyroid period. Laboratory studies also investigated renal function and liver function. The liver enzymes, aspartate transaminase (AST) and alanine transaminase (ALT), and kidney function in terms of blood urea nitrogen (BUN) and creatinine (Cr) were measured during the admission period for total or completion thyroidectomy; these measurements were regarded as the baseline. Follow-up analysis was performed on the day of admission for HD-RIT. The mean time interval was 5 ± 2 months.

Fig. 3 A 65-year-old man with papillary thyroid cancer, pT3N0, was treated with 5.55 GBq of radioactive iodine after rh-TSH injection. Post-therapeutic I-131 whole-body scans (WBSs) at 3 days (**a**) and 10 days (**b**) indicated remnant thyroid tissue and regional lymph nodes. I-123 WBS (**c**) after 6 months showed no abnormal uptake in thyroid bed. F-18 FDG PET/CT (**d**) after 9 months showed no discernible F-18 FDG uptake suggestive of metastasis. However, stimulated serum thyroglobulin (sTg) was checked as 9.74 ng/mL. This was considered as an incomplete ablation state. Follow-up sTg was 24.1 ng/mL and consecutive 5.55 GBq radioiodine treatment were done

Statistical Analyses

Patients and tumor characteristics between the two groups were compared using the Student *t*-test and Pearson χ^2 test. The therapeutic efficacy between the rh-TSH and THW groups was evaluated by Pearson χ^2 test. The changes of base and follow-up chemistry profiles, including liver and kidney function and body weight and body mass index in both groups, were analyzed using the paired *t*-test. The values are presented as mean $\pm$ SD. Statistical analyses were performed using SPSS software version 20.0. A *p* value <0.05 was considered statistically significant.

Results

The mean age was higher for patients in the rh-TSH group than for those in the THW group (*p*=0.02). This might be predicted result because of our tendency to use rh-TSH in elderly patients. The male-to-female ratio was higher in the rh-TSH group, but was not statistically significant (*p*=0.25). There were no significant differences between the two groups in tumor histology (*p*=0.78). The major tumor histology type was papillary carcinoma (THW, 212/217; rh-TSH, 48/49). The mean values of therapeutic dose in the THW and rh-TSH groups were 5.8 $\pm$ 0.6 and 5.7 $\pm$ 0.6 GBq respectively. The treatment dosage of radioactive iodine between the two groups showed no difference (*p*=0.66). The pre-therapeutic stimulated thyroglobulin levels of the two groups, 12.5 $\pm$ 44.1 ng/mL for the THW group and 9.5 $\pm$ 18.9 ng/mL for the rh-TSH group were not statistically different (*p*=0.64). There was no significant difference between the two groups in pathologic staging (*p*=0.78). The outcomes of treatment between the THW and rh-TSH groups were comparable. Of the 217 patients in the THW group, 160 (73.7 %) displayed a completely ablated state of remnant thyroid cancer. Of the 49 patients in the rh-TSH group, 36 (73.5 %) displayed a complete ablation state. The ratio of complete ablation between the THW and rh-TSH groups was not significantly different (*p*=0.97) (Table 2). We compared the body weight change and body mass index between the rh-TSH and THW groups to investigate the effect of hypothyroidism to body metabolism.

The base body weights of the THW and rh-TSH groups were 63.5 $\pm$ 11.1 and 58.0 $\pm$ 8.8 kg, respectively. There was a significant difference between two groups (*p*=0.03). As most rh-TSH patients were older than THW patients and also tended to be more debilitated people, this could explain this result. However, the baseline body mass index of the rh-TSH and THW groups were 24.6 $\pm$ 4.0 and 23.5 $\pm$ 3.0, and there was no statistical difference between the two groups (*p*=0.09). The THW group gained weight (+1.0 $\pm$ 1.9 kg), while, surprisingly, the rh-TSH group lost weight (−1.4 $\pm$ 1.6 kg). The follow-up BMI in THW and the rh-TSH groups were 25.1 $\pm$ 3.8 and 23.0 $\pm$ 3.1 kg/m². The changes in BMI between two groups were 0.4 $\pm$ 0.7 and −0.6 $\pm$ 0.6 kg/m² respectively, which showed similar tendency to body weight change, as shown above (Table 3). The baseline AST and ALT levels of the THW group was 26.4 $\pm$ 12.7 and 23.1 $\pm$ 15.9 IU/L, respectively, and 22.7 $\pm$ 13.3 and 22.1 $\pm$ 12.1 IU/L, respectively, for the rh-TSH group. The THW group had significantly higher follow-up AST (*p*=0.001) and follow-up ALT levels (*p*=0.001) than did the rh-TSH group (Table 4). Blood urea nitrogen (BUN) and creatinine levels used to evaluate kidney function are summarized in Table 5. The THW group had significantly higher follow-up BUN (*p*=0.001) and follow-up creatinine levels (*p*=0.005).

Discussion

In our study, the remnant ablation rate of rh-TSH was not significantly different to that of THW. The findings are consistent with prior studies, which reported comparable thyroid remnant ablation rates by either administration rh-TSH or THW. In one study, complete ablation of all radioiodine uptake in the thyroid bed was achieved in 34 of 42 in the THW group (80.9 %) and 38 of 45 in the rh-TSH group (84.4 %), with no statistical difference between the groups [7].

Many studies addressing thyroid remnant ablation and iodine kinetics have used THW or rh-TSH before iodine radioablation. In one study, the remnant thyroid tissue uptake and residence time tended to be higher in the hypothyroid than the euthyroid group, whereas the half-life of tissue residence in remnants was lower. Only the difference of the half-lives

Table 3 Comparison of body weight between two groups

	THW ^a group (<i>n</i> =217)	<i>p</i>	rh-TSH ^b group (<i>n</i> =49)	<i>p</i>
Base body mass index (kg/m ²)	24.6 $\pm$ 4.0		23.5 $\pm$ 3.0	0.09
Follow-up body mass index	25.1 $\pm$ 3.8		23.0 $\pm$ 3.1	
ΔBody body mass index	0.4 $\pm$ 0.7	0.002	−0.6 $\pm$ 0.6	0.0001
Base body weight (kg)	63.5 $\pm$ 11.1		58.0 $\pm$ 8.8	0.03
Follow-up body weight	64.5 $\pm$ 11.3		56.6 $\pm$ 8.9	
ΔBody weight	1.0 $\pm$ 1.9	0.005	−1.4 $\pm$ 1.6	0.02

^a Thyroid hormone withdrawal

^b Recombinant human thyroid-stimulating hormone

Table 4 Comparison of the liver enzyme levels between two groups

Liver enzyme	THW ^a group (<i>n</i> =217)	<i>p</i>	rh-TSH ^b group (<i>n</i> =49)	<i>p</i>
Base AST (12–33 IU/L)	26.4±12.7		27.7±13.3	0.5
Follow-up AST (12–33 IU/L)	42.9±21.0		25.0±8.6	
ΔAST	16.5±20.8	0.001	−2.7±14.3	0.216
Base ALT (5–35 IU/L)	23.1±15.9		22.1±12.1	0.6
Follow-up ALT (5–35 IU/L)	42.5±30.4		23.3±12.9	
ΔALT	19.3±31.1	0.001	1.2±13.3	0.573

^a Thyroid hormone withdrawal^b Recombinant human thyroid-stimulating hormone

was statistically significant [4]. In another study, the mean residence time of the radioiodine in the whole body and blood was significantly lower in the rh-TSH group than the THW group. However, the reduced uptake in euthyroid patients was partially compensated for by a significantly increased half-time in the target tissue [8].

The reduced residence time found presently in the rh-TSH group could be explained by the preservation of normal renal function in euthyroidism. For this the same reason, the radiation dose to the blood (a surrogate measure for radiation dose to the bone marrow) was significantly lower in the euthyroid group than in the hypothyroid group. Use of rh-TSH for thyroid remnant ablation reportedly reduces the blood radiation dose and potential risk of radiation-induced malignancies [9, 10]. Furthermore, the significant radiation doses delivered to extrathyroidal tissues may induce side effects such as nausea and vomiting, sialadenitis and xerostomia, loss of taste, and bone marrow insufficiency [11].

Renal function in terms of BUN and creatinine had a tendency to increase in the THW group. Hypothyroidism induces a hypodynamic state of the circulatory system, which would result in impaired renal function and particularly of glomerular filtration rate [12]. Other studies showed that hypothyroidism reduces renal blood flow and renal plasma flow, which may decrease the glomerular filtration rate. Elevation of serum creatinine can occur within as little as 2 weeks after onset of significant hypothyroidism. These levels typically normalize rapidly with thyroid hormone replacement after a short period of hypothyroidism [12, 13]. Other studies monitored multiple renal parameters before and after therapy with thyroid hormone. Especially, BUN and

creatinine had a tendency to increase in patients with hypothyroidism and after therapy BUN and creatinine clearance showed improvement [14–16].

The clinical parameters we analyzed to evaluate liver function showed elevated AST and ALT. Other reports demonstrated that hypothyroidism induces hepatic dysfunction [17, 18]. The liver has an important role in thyroid hormone metabolism and the level of thyroid hormone is also important to normal hepatic function and bilirubin metabolism. Hypothyroidism is also responsible for elevating liver enzymes and for cholestatic jaundice due to decreased bilirubin and bile excretion [19]. These biochemical changes, which are usually mild, are also reversible with adequate thyroid replacement therapy [20].

Thyroid hormones are involved in metabolic regulation that affects body weight and body mass index. Weight gain is expected as a result of a decreased metabolic rate in hypothyroidism [21]. This explains weight gain in the THW patients, who were in the hypothyroid state. However, patients who were in a euthyroid state lost weight in the rh-TSH group. We speculate that a low-iodine diet may be the reason, because most of the Korean foods contain iodized salt. This should be further investigated in other studies.

There are some limitations of this study. The study was an uncontrolled retrospective review. The duration of follow-up between the day of baseline measurements and follow-up biochemistry test varied among patients from 1 to 18 months. In addition, we could not collect the biochemistry data and body weight, which were measured during the exact hypothyroid period.

Table 5 Comparison of the kidney function between two groups

Kidney function	THW ^a group (<i>n</i> =217)	<i>p</i>	rh-TSH ^b group (<i>n</i> =49)	<i>p</i>
Base BUN (8–23 mg/dl)	14.3±3.9		14.7±3.9	0.1
Follow-up BUN (8–23 mg/dl)	18.8±3.8		13.8±4.9	
ΔBUN	3.5±4.2	0.001	−0.9±3.8	0.1
Base Cr (0.7–1.7 mg/dl)	0.7±0.3		0.68±0.2	0.7
Follow-up Cr (0.7–1.7 mg/dl)	0.9±0.3		0.69±0.2	
ΔCr	0.2±0.2	0.005	0.008±0.1	0.68

BUN blood urea nitrogen,
Cr creatinine^a Thyroid hormone withdrawal^b Recombinant human thyroid-stimulating hormone

Conclusion

Concerning therapeutic efficacy, rh-TSH for HD-RIT is compatible with THW. Also, rh-TSH has a lower toxic effect on liver and kidney function than THW. This suggests that rh-TSH can be used effectively and safely, especially for patients with chronic liver and kidney disease.

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Conflict of Interest Sehun Choi, Chang Ju Na, Jeonghun Kim, Yeon-Hee Han, Hee-Kwon Kim, Hwan-Jeong Jeong, Myung-Hee Sohn, and Seok Tae Lim declare that they have no conflict of interest.

Ethics Statement This study was approved by the ethics committee in our institution and was performed in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was waived because of the retrospective design of this study.

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