Rating incidence of adverse effects after using recombinant TSH (rhTSH)

Ocena częstości występowania działań niepożądanych po zastosowaniu rekombinowanego TSH (rhTSH)

Agnieszka Suligowska[1], Aldona Kowalska[1,2], Małgorzata Nowalska[3]

[1]Department of Endocrinology, Holy Cross Cancer Center, Kielce, Poland
Head of the Department: Prof. JKU Aldona Kowalska MD, PhD
[2]Department of Cancer Prevention and Epidemiology, Institute of Public Health, Faculty of Medicine and Health Sciences, Jan Kochanowski University, Kielce, Poland
Head of the Department: Prof. JKU Stanisław Góźdź MD, PhD
[3]ZOZ Puls, Masłow, Poland

Medical Studies/Studia Medyczne 2018; 34 (2): 103–106
DOI: https://doi.org/10.5114/ms.2018.76868

Key words: adverse effects, differentiated thyroid cancer, recombinant TSH, rhTSH.

Słowa kluczowe: działania niepożądane, zróżnicowany rak tarczycy, rekombinowane TSH, rhTSH.

Abstract

Introduction: The recombinant TSH (rhTSH) is used in patients with well-differentiated thyroid carcinoma (DTC), who have undergone a thyroidectomy in the process of hormone suppression therapy, in order to stimulate the synthesis of thyroglobulin (Tg) and increased uptake of ^{131}I.
Aim of the research: To assess the type and frequency of adverse reactions with the use of rhTSH.
Material and methods: The survey covered a group of 113 patients, including 95 (84%) women and 18 (16%) men. The research tool was an original questionnaire containing questions concerning patients' particular adverse side effects after the administration of rhTSH, and a comparison of TSH endogenous tolerance stimulation with the use of rhTSH.
Results: The most frequently reported symptoms were hot flushes, 32 (28.3%) patients; headache, 30 (26.5%) patients; and asthaenia, 19 (16.8%) patients. The severity of the symptoms in all cases was small and no medical intervention was required. Among the respondents, 27 (24%) had a follow-up diagnosis, carried out in conditions of thyroid hormone withdrawal. Comparing these two methods, the majority of them (21 patients (78%)) indicated rhTSH stimulation as a more tolerable form.
Conclusions: In the study group, the distribution and frequency of the most common adverse side effects differ from the data presented in the summary of the product characteristics. Reported symptoms, although appearing quite often, were not troublesome to patients. In comparison with TSH endogenous stimulation, rhTSH was preferred and better tolerated by the respondents

Streszczenie

Wprowadzenie: Rekombinowane TSH (rhTSH) jest stosowane u pacjentów z dobrze zróżnicowanym rakiem tarczycy (ZRT), po przebytej tyreoidektomii, będących w trakcie supresji hormonalnej w celu stymulacji syntezy tyreoglobuliny (Tg) oraz zwiększenia wychwytu ^{131}I. Może być wykorzystane zarówno przed leczeniem ^{131}I, jak i podczas badań monitorujących stan remisji choroby.
Cel pracy: Ocena rodzaju i częstości występowania działań niepożądanych po zastosowaniu rhTSH.
Materiał i metody: Badaniem ankietowym objęto 113 pacjentów, w tym 95 (84%) kobiet i 18 (16%) mężczyzn. Narzędzie badawcze stanowił samodzielnie przygotowany kwestionariusz zawierający pytania dotyczące wystąpienia u pacjentów poszczególnych działań niepożądanych i ich nasilenia po podaniu rhTSH oraz prośbę o porównanie tolerancji stymulacji endogennym TSH z zastosowaniem rhTSH.
Wyniki: Objawy niepożądane zgłosiło 75 (66,4%) ankietowanych pacjentów. Najczęściej zgłaszanymi objawami były: uczucie gorąca u 32 (28,3%) osób, ból głowy u 30 (26,5%) osób, osłabienie u 19 (16,8%) osób oraz kołatanie serca u 13 (11,5%) osób. Nasilenie objawów we wszystkich przypadkach oceniono jako niewielkie i krótkotrwałe, żadna z osób nie wymagała interwencji lekarskiej. Żadnego objawu niepożądanego nie zgłosiło 38 (33,6%) osób. Spośród badanych 27 (24%) osób miało w przeszłości przeprowadzoną diagnostykę kontrolną podczas odstawienia hormonów tarczycy. Większość z nich, 21 (78%) osób, porównując te dwie metody, wskazała stymulację za pomocą rhTSH jako lepiej tolerowaną formę leczenia.
Wnioski: W badanej grupie rozkład i częstość występowania najczęstszych działań niepożądanych różnią się od danych przedstawionych w charakterystyce produktu. Odczuwane dolegliwości, mimo że pojawiają się dość często, nie są jednak uciążliwe dla pacjentów. W porównaniu ze stymulacją endogennym TSH stosowanie rhTSH było preferowane i znacznie lepiej tolerowane przez ankietowanych.

Introduction

In recent years the frequency of differentiated thyroid cancer (DTC) diagnosis has significantly increased. This was influenced by, among other things, widespread access to ultrasound examination of the thyroid and more frequent verification concerning visualised cytological lesions [1, 2]. The majority of new cases of DTC are characterised by a low degree of clinical advancement and a very promising prognosis for a 5-year survival of 97.3% [3]. Applicable recommendations advocating a lifetime of oncology supervision, with the ever-increasing number of new cases, mean that the number of patients for diagnostic control increases significantly every year. Sensitivity check-ups increase significantly if you perform them employing thyroid-stimulating hormone (TSH) stimulation, which until recently could only be achieved through the discontinuation of thyroxine use. However, interruption of the treatment with thyroxine is usually associated with severe hypothyroidism and deterioration in the quality of life, causing exacerbation of comorbid conditions and the inability to maintain employment.

The introduction of recombinant human thyroid stimulating hormone (rhTSH), in 2000, is considered to be a landmark event in the treatment and monitoring of patients with DTC. rhTSH is a glycoprotein consisting of two non-covalently associated sub-units. The α sub-unit is composed by 92 amino acids containing two *N*-glycosylation sites, and the β sub-unit by 118 amino acids containing one *N*-glycosylation site [4]. This structure of rhTSH presents its biochemical properties as comparable to the endogenous TSH. Thyroid-stimulating hormone biological activity is dependent on the degree of saturation of the components of the carbohydrate sialic acid residues. To continue, in the state of over hypothyroidism the degree of saturation is greater than in steady-state hormone conditions; therefore, it results in slower biodegradation of TSH, giving similar chemical characteristics as the ones exhibited by rhTSH. rhTSH when binding to the receptor for TSH on thyroid follicular cells or DTC cells leads to the activation of sodium iodine symporter (NIS), and an increased uptake of ^{131}I as well as production of thyroglobulin.

Aim of the research

The widespread use of rhTSH has significantly improved patients' comfort with DTC during the treatment and diagnostic follow-up. However, parenteral use of the protein formulation can cause various side effects. The aim of the study was the evaluation of the tolerability and adverse side effects associated with the administration of rhTSH in preparation for medical follow-ups for patients with DTC.

Material and methods

The study was conducted at the Department of Endocrinology of Holycross Cancer Centre in Kielce on patients with DTC, after a complete thyroidectomy and adjuvant therapy of ^{131}I, who reported for the planned follow-up diagnostic controls. The study group consisted of 113 patients (average age: 53.7 ±14.8 years), including 95 (84%) women and 18 (16%) men. The test was performed in the period from January to May 2015.

The research tool was an original questionnaire concerning the occurrence of adverse side effects resulting from using rhTSH, such us hot flushes, headache, weakness, palpitations, musculoskeletal pain, rash, discomfort after administration, diarrhoea, dizziness, nausea, vomiting, and others (high blood pressure, swelling of the lower limbs, dry skin, abdominal bloating, and difficulty falling asleep). In addition, the questionnaire contained the request to make a comparison of tolerance regarding endogenous TSH stimulation with the use of rhTSH (for patients who underwent check-ups employing both methods for stimulating TSH). rhTSH was administered according to the recommended schedule, involving two doses of 0.9 mg intramuscularly at 24-hour intervals. An anonymous survey was carried out 24 h after the second injection. Patients were interviewed and examined before rhTSH administration. The study involved patients who, prior to the administration of rhTSH, did not exhibit the symptoms listed in the questionnaire. The study was approved by local Ethics Committee.

Results

Seventy-five (66.4%) patients reported adverse side effects relating to administered treatment (Table 1). Amongst the respondents, the most commonly reported side effects following the use of rhTSH included: hot flushes, 32 (28.3%) patients; headache, 30 (26.5%) patients; weakness, 19 (16.8%) patients; and palpitations, 13 (11.5%) patients. What is more, women most often complained of the following: hot flushes, 28 (29.4%) women; headache, 25 (26.3%) women; and asthenia, 13 (13.7%) women. In contrast, men with the highest frequency enumerated the following: weakness, 6 (33.3%) men; headache, 5 (27.7%) men; and hot flushes, 4 (22.2%) men. Taking into consideration particular surveyed patients, the reported symptoms were summed up: 37 (32.7%) patients reported one side effect, 23 (20.3%) patients reported two side effects, while 15 (13.3%) patients reported three or more. To continue, 38 (33.6%) patients did not list any side effects. The side effects other than those listed in the questionnaire, such as high blood pressure, swelling of the lower limbs, dry skin, abdominal bloating. and difficulty falling asleep, after the use of rhTSH, were noticed by 8 (7.1%) patients.

Table 1. Adverse reactions reported after the administration of rhTSH-frequency, severity, and dependence on gender

Side effect and severity	The frequency of the entire group *N* (%)	The frequency among women *N* (%)	The frequency among men *N* (%)
Hot flushes	32 (28.3)	28 (29.4)	4 (22)
Headache	30 (26.5)	25 (26.3)	5 (27.8)
Weakness	19 (16.8)	13 (13.7)	6 (33.3)
Palpitations	13 (11.5)	11 (11.5)	2 (11.1)
Musculoskeletal pain	11 (9.7)	10 (10.5)	1 (5.5)
Other	8 (7.1)	7 (7.3)	1 (5.5)
Rash	7 (6.2)	6 (6.3)	2 (11.1)
After administration discomfort	7 (6.2)	7 (7.3)	0
Diarrhoea	7 (6.2)	5 (5.2)	2 (11.1)
Dizziness	6 (5.3)	4 (4.2)	2 (11.1)
Nausea	5 (4.4)	2 (2.1)	3 (16.6)
Vomiting	1 (0.88)	0	1 (5.5)

Among the respondents, 27 (24%) patients had previous control diagnosis performed under thyroid hormone withdrawal. As far as those two methods are concerned, the majority of patients (21 (77.8%)) indicated the administration of rhTSH as the preferred method; one patient chose (3.7%) stimulation of endogenous TSH, while 5 (18.5%) patients did not experience any difference between implementing compared methods.

Discussion

In the frequency of adverse side effects described in the Summary of Product Characteristics, Thyrogen [4] differs from the results of a survey conducted among the patients of our Endocrinology Department. The data gathered by the manufacturer came from 481 patients with six prospective studies and the reported cases of adverse reactions after releasing the product. They show that the side effects seen as very common are nausea (12%) and headache (7%). In their study, Menzel *et al.* observed 2 (3.1%) cases of headaches accompanied by nausea [5]. Additionally, Bryan *et al.* described headaches (9.2%), nausea (6.1%), and weakness (3.5%) [6] as the most common side effects. The results of the above-mentioned work, compared to the study of our patients, show a different distribution of reported discomfort and their reduced incidence. Differences may result from individual sensitivity and tolerance of patients undergoing diagnostic controls. Furthermore, perceived symptoms, although appearing often, were usually short term and not harmful to patients. Their severities in all cases were minor and never resulted in the need for medical intervention.

Moreover, 21 of 27 patients (77.8%) who had earlier undergone diagnostic control performed with the endogenous TSH stimulation, comparing the two methods, preferred the administration of rhTSH. Similar results were presented by Dietlein *et al.*, where as much as 97% of respondents chose rhTSH [7].

The benefits of using rhTSH are multidimensional. First of all, it allows avoidance of the symptoms associated with hypothyroidism, such as sluggishness, sleepiness, swelling, weight gain, coldness, and constipation, and therefore it improves the quality of life of the patients, as pointed out in the works of Lee *et al.*, Szymonek *et al.*, and Taïeb *et al.* [8–10]. This is of particular importance for the elderly, with a number of cardiac workload, wherein withdrawal of thyroxine could lead to symptoms of heart failure and ischaemic heart disease. Moreover, in the conditions of hypothyroidism impaired renal function and a reduction in glomerular filtration rate occur, which lead to slower removal of ^{131}I. Therefore, the maintenance of normal creatinine clearance through the use of rhTSH reduces the toxicity of ^{131}I, decreasing the time of its expulsion, as highlighted by Luster *et al.* and Pacini *et al.* [11, 12]. It is worth noting that the use of rhTSH shortens the period of inability to work with patients undergoing diagnostic standard control as well as their relatives [7, 10], positively affecting the socioeconomic status of the society in which the patient functions [13, 14].

There is no doubt that the introduction of rhTSH was a major breakthrough in the treatment of patients with DTC. It allows the same results in ^{131}I treatment and diagnostics control that is obtained during endogenous TSH stimulation [6, 15], without exposing the patients to severe symptoms of hypothyroidism. Although the observed adverse side effects associated with the use of rhTSH were quite common, their severity was minor and short term, which does not detract from the advantages of rhTSH and does not affect the limitation of its usage.

Conflict of interest

The authors declare no conflict of interest.

References

1. Sipos JA, Mazzaferri EL. Thyroid cancer epidemiology and prognostic variables. Clin Oncol 2010; 22: 395-404.
2. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014; 140: 317-322.
3. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S,Hachey M, Kirch R, Jemal A, Ward E. Cancer treatment and survivorship statistics. CA Cancer J Clin 2012; 62: 220-241.
4. Product monograph Thyrogen 2012.
5. Menzel C, Kranert WT, Döbert N, Diehl M, Fietz T, Hamscho N, Berner U, Grünwald F. rhTSH stimulation before radioiodine therapy in thyroid cancer reduces the effective half-life of (131)I. J Nucl Med 2003; 44: 1065-1068.
6. Bryan R, Haugen B, Pacini F, Reiners Ch, Schlumberger M, Ladenson P, Sherman S, Cooper D, Graham K, Braverman L, Skarulis M, Davies T, Degroot L, Mazzaferri E, Daniels G, Ross D, Luster, Samuels M, Becker D, Maxon H, Cavalieri R, Spencer C, Mcellin K, Weintraub B, Ridgway C. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for detection of thyroid remnant or cancer. J Clin Endocrinol Metabol 1999; 84: 3877-3885.
7. Dietlein M, Busemeyer S, Kobe C, Schmidt M, Theissen P, Schicha H. Recombinant human TSH versus hypothyroidism. Cost-minimization-analysis in the follow-up care of differentiated thyroid carcinoma. Nuklearmedizin 2010; 49: 261-224.
8. Lee J, Yun MJ, Nam KH, Chung WY, Soh EY, Park CS. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. Thyroid 2010; 20: 173-179.
9. Szymonek M, Pałyga I, Gąsior-Perczak D, Kowalska A. Assessment of the quality of life in patients with differentiated thyroid carcinoma during a one-month withdrawal of levorotatory thyroxine preparations (L-T4) before a control diagnostics. Endokrynol Pol 2006; 57 Suppl.
10. Taïeb D, Sebag F, Cherenko M, Baumstarck-Barrau K, Fortanier C, Farman-Ara B, De Micco C, Vaillant J, Thomas S, Conte-Devolx B, Loundou A, Auquier P, Henry JF, Mundler O. Quality of life changes and clinical outcomes in thyroid cancer patients undergoing radioiodine remnant ablation (RRA) with recombinant human TSH (rhTSH): a randomized controlled study. Clin Endocrinol (Oxf) 2009; 71: 115-123.
11. Pacini F, Ladenson PW, Schlumberger M, Pacini F, Ladenson PW, Schlumberger M, Driedger A, Luster M, Kloos RT, Sherman S, Haugen B, Corone C, Molinaro E, Elisei R, Ceccarelli C, Pinchera A,Wahl RL, Leboulleux S, Ricard M, Yoo J, Busaidy NL, Delpassand E, Hanscheid H, Felbinger R, Lassmann M, Reiners C. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: result of an international, randomized, controlled study. J Clin Endocrinol Metab 2006; 91: 926-932.
12. Luster M, Lippi F, Jarzab B, Perros P, Lassmann M, Reiners C, Pacini F. rhTSH-aided radioiodine ablation and treatment of differentiated thyroid carcinoma: a comprehensive review. Endocr Relat Cancer 2005; 12: 49-64.
13. Borget I, Corone C, Nocaudie M, Allyn M, Iacobelli S, Schlumberger M, De Pouvourville G. Sick leave for follow-up control in thyroid cancer patients: comparison between stimulation with thyrogen and thyroid hormone withdrawal. Eur J Endocrinol 2007; 156: 531-538.
14. Borget I, Bonastre J, Catargi B. Quality of life and cost-effectiveness assessment of radioiodine ablation strategies in patients with thyroid cancer: result from the randomized phase III ESTIMABL trial. J Clin Oncol 2015; 33: 2885-2892.
15. Pak K, Cheon GJ, Kang KW, Seong-Jang K, In-Joo K, Dong SL, June-Key C. The effectiveness of recombinant human thyroid-stimulating hormone versus thyroid hormone withdrawal prior to radioiodine remnant ablation in thyroid cancer: a meta-analysis of randomized controlled trials. J Korean Med Sci 2014; 29: 811-817.

Address for correspondence:

Agnieszka Suligowska
Department of Endocrinology
Holy Cross Cancer Center
ul. Artwińskiego 3, 25-734 Kielce, Poland
Phone: +48 507 756 268
E-mail: a.suligowska@wp.pl