THERAPY OF ENDOCRINE DISEASE

Recombinant human TSH and radioactive iodine therapy in the management of benign multinodular goiter

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Abstract

Multinodular goiter (MNG) is a very common thyroid disorder determined by diverse goitrogenic factors, the most important one being iodine deficiency. The clinical presentation of a patient with MNG varies from a completely asymptomatic goiter to a life-threatening disease due to upper airway compression. Patients can develop underlying subclinical or overt hyperthyroidism due to autonomously hyperfunctioning nodules. In the absence of clinical, ultrasonographic, or cytological findings suggestive of malignancy, the best therapeutic approach for a patient with MNG will depend on the size and location of the goiter, the presence and severity of compressive symptoms, and the presence or absence of thyrotoxicosis. There is still no consensus regarding the treatment of atoxic MNGs. Hence, its optimal management remains controversial; possible therapies include levothyroxine (LT_4), surgery, and radioactive iodine (^{131}I). Suppressive treatment with LT_4 is discouraged due to the development of sub-clinical or overt hyperthyroidism and to its low efficacy when compared with surgery or ^{131}I . Total thyroidectomy is effective; however, it is associated with the risk of surgical complications and is often refused by the patient. ^{131}I therapy is an alternative to thyroid surgery to reduce the size of benign MNGs. Based on the ability of recombinant human TSH (rhTSH) to more than double thyroid ^{131}I uptake, this compound has been evaluated as an adjuvant to ^{131}I in the treatment of MNG. Very small doses of rhTSH have been used in patients with MNG and few safety concerns have been observed, but the ideal dose, both effective and safe, is yet to be defined.

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Introduction

Radioactive iodine (^{131}I) was introduced almost three decades ago for the treatment of multinodular goiter (MNG) (1). Since then, studies have demonstrated that ^{131}I is safe and effective (2, 3), leading to significant thyroid volume (TV) reduction, when compared with levothyroxine (LT_4) suppressive therapy. Overall, LT_4 suppressive therapy offers no benefit (4), particularly regarding the improvement in obstructive symptoms (such as dyspnea and dysphagia), to most patients (5, 6). ^{131}I treatment reduces the MNG volume by $\sim 40\%$ after 1 year and by 50–60% after 2–5 years (4, 5, 6, 7, 8, 9). Nonetheless, the

therapeutic efficacy of ^{131}I in patients with MNG depends to some extent on the ^{131}I uptake (RAIU). Frequently, MNGs have a low and heterogeneous RAIU, requiring high ^{131}I activities (10).

The administration of recombinant human thyrotropin (rhTSH) before ^{131}I has been shown to be a potentially valuable therapeutic tool for the management of MNG (11, 12, 13, 14, 15, 16, 17, 18, 19, 20). rhTSH in a low single dose increases ^{131}I uptake by two- to fourfold, and homogenizes RAIU (21, 22). The effect of rhTSH on RAIU allows for the administration of lower ^{131}I activities, with

similar therapeutic effects (in comparison with higher ^{131}I activities without rhTSH prestimulation), and with lower exposure of extrathyroidal tissues to radiation (23). When usual ^{131}I activities are administered after rhTSH, greater TV reduction has been observed; 33–62% TV reduction when rhTSH plus ^{131}I are administered, compared with 13–46% when placebo and the same ^{131}I activities are given (11, 14, 16, 19, 24, 25). Overall, it has been shown that rhTSH doses lower than 0.1 mg do not cause acute increases in TV or thyroid hormone levels (26). When given 24 h before the administration of fixed or calculated ^{131}I activities, rhTSH is a safe and efficacious adjunct therapeutic approach that allows for the administration of lower ^{131}I activities (24).

Approach to the patient with MNG

Surgery

MNG is defined as the enlargement of the thyroid gland, in the absence of autoimmune thyroid disease, malignancy, or inflammation, and associated with more than one nodule identified clinically, ultrasonographically, or surgically. Factors that favor surgery as the treatment of choice include presence of symptoms or signs of compression within the neck, concern for co-existing thyroid cancer, substernal or retrosternal extension, or need for rapid correction of the thyrotoxic state (27). Factors weighing against the choice of surgery include significant comorbidity such as cardiopulmonary disease, or other debilitating disorders. In other cases, the patient or patient's family refuse surgery.

Radioactive iodine

For more than seven decades, ^{131}I therapy has been used to treat thyroid diseases, mainly Graves' disease. ^{131}I not only is effective for curing hyperthyroid states, but also leads to shrinkage of the thyroid gland. Owing to the effect on the gland volume, ^{131}I has been used in the treatment of compressive nontoxic nodular goiters. In 1988, Hegedus *et al.* (1), using ultrasonography, demonstrated that ^{131}I treatment of nontoxic MNG leads to significant goiter volume reduction after 1 year. A number of studies, using ultrasonography, computed tomography, or magnetic resonance imaging, for accurate measurements of TV have shown that ^{131}I therapy in patients with nontoxic nodular goiter results in a mean reduction in the TV by ~40% after 1 year (1, 2, 6), and by 50–60% after 3–5 years (2, 4, 5, 6, 7, 8, 9, 28), with improvement in obstructive

symptoms in the majority of patients (5, 6). The improvement in compressive symptoms is accompanied by significant tracheal widening, as measured by magnetic resonance imaging (6), and improvement in respiratory function (29). The amount of ^{131}I administered depends on thyroid weight and RAIU. Administered doses are ~100 mCi (3.7 MBq) ^{131}I /g thyroid tissue corrected for RAIU at 24 h (28). As patients with nontoxic nodular goiter usually have a rather low and heterogeneous RAIU, they require high doses of ^{131}I activities (10), causing considerable irradiation of extrathyroidal organs and tissues (30), requiring hospitalization and isolation (28) in most cases. Therefore, there was interest to explore strategies to enhance RAIU in these patients.

Recombinant human thyrotropin

The administration of a single, low dose of rhTSH considerably increased RAIU in patients with nodular goiter (21). A dose of 0.01 mg rhTSH given 24 h before ^{131}I increased 24-h RAIU from 29 to 51%, while 0.03 mg rhTSH increased 24-h RAIU from 33 to 63% (21). A single, low dose of rhTSH not only doubled 24-h RAIU, but also determined a more homogeneous distribution of ^{131}I within the thyroid gland in patients with nodular goiter, by stimulating ^{131}I uptake in relatively cold areas, more than in relatively hot areas (22). It has been shown that pretreatment with a single, low dose of rhTSH allows for dose reduction of ^{131}I in patients with nodular goiter (31). ^{131}I therapy after pretreatment with a single, low dose of rhTSH in patients with nodular goiter resulted in TV reduction 1 year after therapy by 35% in the group pretreated with 0.01 mg rhTSH, and by 41% in the group pretreated with 0.03 mg rhTSH. This was accompanied by an increase in the smallest cross-sectional area of the tracheal lumen, by 17 and 44% respectively (31).

rhTSH and ^{131}I for MNG

In patients with toxic MNG (TMNG), medical management before ^{131}I therapy should be tailored based on the severity of the hyperthyroidism, patient's age, and comorbid conditions. Worsening of hyperthyroidism with increased heart rate, and rare cases of supraventricular tachycardia (including atrial fibrillation) have been observed in patients with TMNG or MNG treated with ^{131}I (32, 33). Therefore, the use of β -blockers to prevent post-treatment tachyarrhythmias should be considered in all patients with TMNG who are older than 60 years of age and those with cardiovascular disease or severe

Figure 1

Significant positive correlation between the degree of goiter volume reduction and the effective uCi/g activity of administered ^{131}I ($r=0.676$, $P=0.002$).

hyperthyroidism (34). Pretreatment with methimazole before ^{131}I therapy for TMNG is indicated in patients who are at an increased risk for complications due to worsening of hyperthyroidism, including elderly and those with cardiovascular disease or severe hyperthyroidism (35). rhTSH can at least double thyroid RAIU (12, 18, 36, 37, 38), depending on the baseline RAIU, and it determines a more homogeneous distribution of ^{131}I in MNG (22). During the last decade, and based on the above observations, rhTSH has been evaluated as an adjuvant to ^{131}I therapy, in an attempt to improve the efficacy of this treatment for MNG (18, 39, 40). Different rhTSH doses have been utilized: in some studies 0.2 mg or more (41, 42, 43, 44, 45, 46, 47), while in others 0.1 mg or less (11, 16, 20, 24, 31, 48). Since the introduction of rhTSH as an aid for ^{131}I therapy in MNG, nine randomized controlled trials (RCTs) have been published (11, 14, 15, 16, 19, 24, 25, 44, 45). Despite variations in population characteristics, sample sizes, different rhTSH agents and dosages, radiotherapy methods, outcome analyses, and methodological biases, all RCTs have shown the superiority of rhTSH before ^{131}I therapy over ^{131}I alone to reduce the goiter volume.

Our personal experience with rhTSH and ^{131}I

Following the demonstration that rhTSH was an excellent adjunct therapeutic approach for patients undergoing MNG treatment that allowed for the administration of lower ^{131}I activities (21), we began to use it in different dosages, looking for the safest and still efficacious dose. Our first study employed two consecutive doses of 0.1 mg

rhTSH before ^{131}I (12). Owing to the heterogeneity of goiter size and the fact that we used a fixed ^{131}I activity (30 mCi; 1.11 MBq), we calculated the retained thyroid ^{131}I activity and determined correlations with the volume reduction of the goiter. We were able to show a positive correlation between the radiation dose to the thyroid and the decrease in TV at 6 months (Fig. 1) (12). Approximately one-third of our patients receiving 0.2 mg rhTSH developed mild thyrotoxic symptoms controlled easily by the administration of a β -blocking agent (12). In an attempt to lessen the adverse effects, the second study employed a single dose of 0.1 mg rhTSH (20). All patients with low and heterogeneous RAIU developed increased and homogeneous RAIU (Fig. 2) (49). TV was significantly reduced by $46.0 \pm 14.6\%$ after 1 year; after 2 years, TV reduction was sustained in most patients (50). A typical example of goiter shrinkage is shown in Fig. 3 (49). After rhTSH administration, RAIU significantly increased from 18.1 ± 9.7 to $49.6 \pm 13.4\%$. The ratio between post- and pre-rhTSH RAIU (RR) was calculated to indicate the fold increase in uptake in response to rhTSH. The median RR was 2.6 (1.2–9.2). There was an inverse correlation between RR and the pre-rhTSH ^{131}I 24-h uptake ($r=-0.613$, $P=0.009$), indicating that patients with lower basal uptake values achieved higher RR values. Fast *et al.* (51) also demonstrated in a multicentric study that patients with baseline RAIU $<20\%$ achieved a greater reduction in the goiter size using modified-release rhTSH (MRrhTSH, an analog to rhTSH that is equipotent for increasing thyroid RAIU and that determines a lower peak plasma TSH concentration). MRrhTSH has an altered PK with a later T_{max} than aqueous rhTSH. Potentially, MRrhTSH could reduce the side effects due to altered pharmacokinetics, with a delayed time to reach the maximum TSH concentration when compared with aqueous rhTSH (19). Our third study compared two different rhTSH doses

Figure 2

Scintigraphy before (A) and 24 h after the administration of 0.1 mg rhTSH in a single dose (B). Besides making the uptake of ^{131}I more homogeneous, rhTSH increased the 24-h uptake from 4.5 to 39.3%.

Figure 3

An example of goiter reduction. Computerized tomography with multiplanar reconstruction of a patient with multinodular substernal goiter treated with 30 mCi (1.11 MBq) radioactive iodine after 0.1 mg rhTSH. (A1) and (A2): baseline (thyroid volume 147 ml); (B1) and (B2): 1 year after treatment (thyroid volume 42 ml).

(0.005 and 0.1 mg) with one placebo group (16) followed by a fixed 30 mCi (1.11 GBq) activity. We demonstrated that a very low dose of 0.005 mg rhTSH was equally safe and effective as 0.1 mg rhTSH. Both doses increased the efficacy of ^{131}I (12). In a multicentric RCT, we compared two different MRrhTSH doses (0.01 and 0.03 mg) vs placebo (19). The study showed that the threshold for efficacy seems to be ~ 0.03 mg rhTSH, at which dose there are only few minor safety concerns (19).

Side effects of rhTSH use in MNG

Sensation of thyroïdal swelling can occur, but no acute compressive effects have been observed with 0.3 mg rhTSH (45). In a selected group of patients with asymptomatic goiter (median volume of 40.0 ml), a 24% transient goiter volume increase was reported to occur 24 h after the administration of 0.3 mg rhTSH (45). Adjunct therapies with very small doses of rhTSH (0.01–0.03 mg) have been evaluated in both euthyroid and hyperthyroid patients with MNG, and few safety concerns have been observed (19, 20). However, one study showed that hyperthyroid patients had higher increases in thyroid hormone levels after 0.1 mg rhTSH plus ^{131}I , with a higher frequency of side effects (46). Currently, the rhTSH adjunct therapy is not indicated in patients with TMNG (52). In patients with critical tracheal narrowing, prophylactic glucocorticoid therapy should be considered to prevent rhTSH and ^{131}I -related swelling and further respiratory compromise (52).

Painful transient thyroiditis may occur within the first month after treatment. Development of Graves' hyperthyroidism (with high levels of TSH receptor antibodies) in patients with preexisting high thyroid peroxidase antibody concentrations has also been described after treatment of euthyroid MNG with RAI (35). Hypothyroidism development is common and depends on the size of the treated goiter and the administered rhTSH dose and ^{131}I activity (11, 14, 15, 16, 24, 25, 44, 45, 49). It is important to mention that the adjunct therapy of MNG with rhTSH and ^{131}I is not approved by the FDA or EMEA. Moreover, the cost-effectiveness of combined rhTSH has not been demonstrated. As an alternative to rhTSH, two studies showed that, in patients with MNG, methimazole-induced hypothyroidism increases endogenous TSH levels, augmenting RAIU and allowing for the administration of more effective activities of ^{131}I (53, 54). Until now, no studies have compared the efficiency and safety of exogenous TSH vs endogenous TSH.

Concluding remarks

In patients with MNG, ^{131}I therapy preceded by rhTSH further enhances goiter volume shrinkage, compared with ^{131}I treatment alone. This effect has been demonstrated in short- and long-term studies, but it is still unknown as to which patients respond better to rhTSH. Currently, the lowest and most efficacious/effective dose of rhTSH is ~ 0.03 mg. Studies comparing exogenous TSH with endogenous TSH are still required, in order to clarify the benefits and adverse effects of each type of treatment. It should be emphasized that rhTSH-stimulated ^{131}I therapy is still an off-label treatment for MNG.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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