Radioiodine therapy of benign non-toxic goitre. Potential role of recombinant human TSH

Résumé

Cette revue constitue une mise au point sur le traitement radio-isotopique par l’iode 131 (I31I), sous stimulation par TSH recombinante humaine (rh-TSH) et souligne son intérêt potentiel dans le traitement des goitres multinodulaires, symptomatiques, bénins et non toxiques. La faisabilité du traitement par l’iode 131 dépend de la capacité à fixer l’isotope. Se fondant sur un doublement de la fixation thyroïdienne de l’iode 131, des études convaincantes ont démontré que l’accroissement de la dose absorbée d’iode 131 est possible, sans majoration de la dose administrée : une amplification de la réduction du volume du goitre de 35 à 56 % est obtenue un an après l’administration d’iode radioactif, en comparaison du schéma traditionnel (sans administration de rh-TSH). Bien que le confort du patient ne soit pas amélioré après un an, cette approche facilite la décompression trachéale et s’avère particulièremment prometteuse en cas de goitre volumineux. La majorité des patients porteurs de goitre multinodulaire non toxique peuvent ne pas requérir d’amplification de la réduction. Mais la stratégie alternative par rh-TSH permet de délivrer une activité thérapeutique d’iode 131 réduite jusqu’à 80 %, alors même que la diminution du volume du goitre est analogue avec toujours un haut degré de satisfaction des patients. La stratégie de réduction de la dose administrée (à activité équivalente) est séduisante en termes de minoration des restrictions post-thérapeutiques pour le patient, et de réduction des risques potentiels de malignité radio-induite. Les effets indésirables, comme un gonflement transitoire de la thyroïde, et une majoration de l’hormonémie thyroïdienne sont largement dose-dépendants : généralement les doses de 0,1 mg de rh-TSH ou plus basses encore s’avèrent bien tolérées. En se fondant sur les résultats obtenus, nous concluons que le traitement radio-isotopique sous stimulation par rh-TSH constitue un principe thérapeutique nouveau et prometteur, optimisant un traitement sur mesure pour chaque individu.

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Mots clés : Goitre ; Hormone thyroïdienne ; Traitement radio-isotopique ; TSH humaine recombinante ; Rh-TSH ; MRrh-TSH

Abstract

This review provides an update on recombinant human TSH (rh-TSH) augmented radioiodine (131I) therapy and outlines its potential role in the treatment of symptomatic benign multinodular non-toxic goitre. In some countries, 131I has been used for three decades to reduce the size of nodular goitres. The feasibility of 131I therapy depends on an adequate thyroid 131I uptake. Based on a two-fold increase in thyroid 131I uptake, superiority studies have convincingly demonstrated that the absorbed thyroid 131I dose can be increased without increasing the administrated 131I activity, resulting in a 35–56% amplification of goitre reduction at one-year post radioiodine compared to conventional (without rh-TSH) 131I therapy. Although patient satisfaction is not improved at one-year, this approach facilitates tracheal decompression and is particularly promising in large goitres. The majority of multinodular non-toxic goitre patients may not require amplified goitre reduction. But as an alternative strategy, rh-TSH allows up to 80% reduction of the therapeutic 131I activity while still achieving goitre reduction comparable to that of conventional 131I therapy and maintaining high patient satisfaction. The dose-reduction (equality) strategy is attractive in terms of minimizing post-therapeutic restrictions and in reducing the potential risk of radiation-induced malignancy. Adverse effects like temporary thyroid swelling and thyroid hormone excess are to a large extent dose-dependent and generally 0.1 mg rh-TSH or less is well tolerated. Based on these results we conclude that rh-TSH augmented 131I therapy is a promising new therapeutic principle allowing the tailoring of an optimal 131I therapy on the individual level.

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Keywords: Goitre; Thyroid hormones; Radioiodine therapy; Recombinant human thyrotropin; Rh-TSH; MRrh-TSH
1. Introduction

Radioactive iodine ($^{131}$I) has been used in the treatment of hyperthyroidism for more than 60 years. In the last three decades, the use has been expanded to include symptomatic benign multinodular non-toxic goitre (MNG), resulting in a mean goitre volume reduction (GVR) of approximately 40% one year after treatment [1–4], and 50–60% at 3–5 years [2,3]. In large goitres (i.e. above 100 mL), GVR tends to be slightly lower [5–7] and has been demonstrated to be inversely correlated to the initial goitre size [3,5]. Importantly, the feasibility of $^{131}$I therapy depends on an acceptable (at least 20%) thyroid $^{131}$I uptake (RAIU), particularly in large goitres, where relative high $^{131}$I activities are required. The dietary iodine intake is a major determinant of thyroid RAIU and in fact, iodine fortification programs may result in reduced thyroid RAIU [8,9], and thereby decrease the efficacy or even hinder the use of $^{131}$I therapy.

In 2000, Huysmans et al. demonstrated that the RAIU in nodular goitres could be increased by approximately 100% by stimulating with recombinant human thyrotropin (rh-TSH) [10]. Based on this observation, and the above-mentioned challenges, stimulation with rh-TSH before $^{131}$I therapy has been evaluated (off-label) during the last decade. The aim has been to improve the efficacy of $^{131}$I therapy for MNG. Here, we provide an update on rh-TSH augmented $^{131}$I therapy with focus on potential strategies, eligibility criteria and directions for future research.

2. Impact of rh-TSH on thyroid $^{131}$I kinetics

2.1. Radioiodine uptake

The feasibility of $^{131}$I therapy to reduce the size of a MNG depends on an acceptable thyroid RAIU. Previously the only strategy, although not demonstrated in MNG patients, to optimize RAIU was to restrict dietary iodine intake, which is cumbersome. The thyroid RAIU can be increased safely by around 100% using rh-TSH doses between 0.03 and 0.1 mg [10–14], preferably administered 24–48 hours before $^{131}$I therapy [12] (Fig. 1). In this dose range, the dose-response curve in terms of enhancing thyroid RAIU is relatively flat [11], while side effects are mild and uncommon [13–15]. Data with rh-TSH doses below 0.03 mg are conflicting [10,14,16], but the effect seems to decline. Importantly, the increase in RAIU is most pronounced in subjects with a low initial RAIU [12] (Fig. 2). Repetitive injections of rh-TSH have been evaluated in two uncontrolled trials [17,18], with conflicting results. Theoretically, a second dose of rh-TSH could result in an even better retention of $^{131}$I within the thyroid gland. To clarify whether repetitive rh-TSH injections are beneficial in terms of improving the overall $^{131}$I kinetics during $^{131}$I therapy, well-controlled comparative studies, also focusing on alterations in the $^{131}$I half-life, are needed.

It cannot be overemphasized that comparing the effect of rh-TSH on thyroid RAIU between studies is very difficult, especially owing to differences in the baseline RAIU and iodine intake/load. As a consequence of these limitations, we recommend that physicians who consider rh-TSH-augmented $^{131}$I therapy should evaluate the effect of rh-TSH in a patient sample representative of the potential treatment population. This approach is essential if a fixed dose regimen is considered and importantly it allows the physician to estimate whether a low iodine diet should also be instituted. The threshold level of iodine intake/excretion that attenuates the effect of rh-TSH on thyroid RAIU has not been established [19].

2.2. Retained thyroid dose

The absorbed thyroid $^{131}$I dose depends not only on the RAIU but also on the wash-out/release of $^{131}$I from the thyroid gland. Reassuringly, rh-TSH does not reduce $^{131}$I half-life to any greater extent [10,12,20,21]. It should however be kept in mind, that thyroid iodine kinetics are complex and may differ markedly after a therapeutic $^{131}$I activity compared to when evaluating
a tracer $^{131}$I activity [20,22]. Although evidence is limited, it seems that a somewhat lower RAIU following a therapeutic $^{131}$I activity compared to a tracer activity is the rule [20,21], indicating that the absorbed thyroid dose may be lower than expected. Importantly, this is observed both with and without use of rh-TSH [20,21].

2.3. Qualitative $^{131}$I uptake

It has often been stated that a low-normal or below-normal serum TSH is related to a high thyroid RAIU. However, in a large series of MNG patients, thyroid RAIU was not determined by goitre size and serum TSH, but rather the age of the patient and the serum T4 level [23]. Nonetheless, a low serum TSH may have important implications for the qualitative RAIU, implying that RAIU is heterogeneous and confined to a few hot spots. Interestingly, rh-TSH appears to reverse this effect, since the increase in RAIU in relatively cold areas has been observed to be significantly higher in patients with a low s-TSH level (i.e. < 0.5 mU/L) [24]. In addition, thyroid scintigrams have shown that some “cold” areas containing down-regulated TSH-level (i.e. < 0.5 mU/L) are taken up by rh-TSH [20,21]. In line with this, we have observed a trend that patients with subclinical hyperthyroidism at baseline obtain a more pronounced increase in 24 hours RAIU than euthyroid patients [12,15]. Taken together, these findings indicate that patients with subclinical hyperthyroidism could be obvious candidates for rh-TSH stimulation before $^{131}$I therapy.

3. Strategies with rh-TSH augmented radioiodine therapy

Based on the marked increase in thyroid RAIU, the potential benefits of rh-TSH, when combined with $^{131}$I therapy, are those of increased absorbed thyroid dose without increasing the administered $^{131}$I activity (superiority strategy) or reduction of the administered activity with a maintained thyroid dose (dose-reduction or equality strategy).

3.1. Superiority strategy

Declining efficacy with increasing goitre size is one of the major challenges in conventional (without rh-TSH) $^{131}$I therapy [5]. Considering that the efficacy of $^{131}$I therapy as regards GVR, to some extent is dependent on the absorbed thyroid radiation dose [3,5,6,25,26], this problem could be overcome by increasing the administered $^{131}$I activity and thereby the delivered thyroid dose. However, particularly in large goitres, increasing the administered $^{131}$I activity is not feasible since the extrathyroidal radiation is already high compared to when treating hyperthyroidism [27]. Facing these challenges rh-TSH was introduced as a method to increase the absorbed thyroid dose without increasing the administered $^{131}$I activity. The marked increase in thyroid RAIU induced by rh-TSH, together with the observation of a more homogeneous RAIU on thyroid scintigrams hold promise that increased GVR could be achieved by stimulation with rh-TSH before $^{131}$I therapy.

In terms of GVR the superiority of rh-TSH, and recently also modified-release rh-TSH (MRrh-TSH), augmented $^{131}$I therapy over $^{131}$I alone has been demonstrated in eight trials which have included a control group [16,18,25,26,28–31]. Of these trials, four were randomized and placebo-controlled [25,26,30,31], two of which were double-blinded [25,26]. On average, GVR is enhanced by 35–56% one-year after therapy. Interestingly, the gain is most pronounced in large goitres (Fig. 3) [25] as also evidenced by the attenuation of the negative correlation between initial goitre size and GVR, when rh-TSH is used [15,26].

Although rh-TSH amplifies the GVR considerably, three RCTs have failed to demonstrate a positive impact on patient satisfaction and quality of life. One study did not address this issue at all [31], whereas the other two studies [25,26] relied on a visual analogue scale (VAS). Lacking a subjective benefit of rh-TSH-augmented $^{131}$I therapy, objective measures to demonstrate the superiority of rh-TSH-augmented $^{131}$I therapy over conventional $^{131}$I therapy are important. Tracheal compression and impaired airflow is often encountered in MNG patients [32], but is easily overlooked since many do not have respiratory complaints [32], which makes the subjective report of improvement less likely. Monitoring alterations in pulmonary function and smallest cross-sectional area of the trachea (SCAT) are obvious methods to demonstrate a positive effect of $^{131}$I therapy. We have previously shown [33] that rh-TSH-augmented $^{131}$I therapy is more effective in relieving tracheal compression. In fact, a 31% increase in SCAT and a 25% increase in the inspiratory flow were observed one-year after rh-TSH-augmented $^{131}$I therapy, whereas no change was found in either parameter in the control group treated with $^{131}$I alone.

3.2. Dose-reduction strategy

The failure to demonstrate a subjective benefit of the superiority strategy within the first year raises the question whether increased GVR is worth pursuing in the majority of patients, with
Moderate-sized oligo-symptomatic goitre. Particularly, since patient satisfaction following conventional 131I therapy is generally high [3,7,34], and the increased GVR when rh-TSH is used is achieved at the expense of an up to five-fold increase in the rate of permanent hypothyroidism [26]. Furthermore, the radiation protection principle As Low As Reasonably Achievable (ALARA) implies that the goal of 131I therapy should be pursued with the lowest possible radiation burden to the patient as well as to the environment. As long as the long-term risk of thyroidal and particularly extrathyroidal malignancy is not clarified, it is obvious that strategies reducing the radiation burden are worth exploring.

In an uncontrolled study, Nieuwlaat et al. were the first to demonstrate that the administered 131I activity could be reduced by a factor corresponding to the increase in RAIU without compromising GVR [14]. Pre-treatment with 0.01 and 0.03 mg rh-TSH allowed a 50% reduction of administered 131I activity, while still achieving a one year GVR of approximately 40%. Importantly, that study also included a dosimetric evaluation, which demonstrated that when the target was a thyroid dose of 100 Gy, prestimulation with rh-TSH resulted in a 2–3-fold lower absorbed dose (i.e. bladder and stomach) compared to controls treated with 131I alone [21]. Recently, we published the results of a large randomized, double-blinded, placebo-controlled trial, demonstrating that the therapeutic 131I activity can be reduced beyond what is accounted for by increased thyroid RAIU [15]. The combination of 0.1 mg rh-TSH and a target thyroid dose of 50 Gy resulted in a GVR (35% at one-year), identical to that of placebo in combination with 100 Gy (Fig. 4). Cervical compression symptoms, as determined by a VAS-score, were effectively and equally reduced in the placebo and the rh-TSH group. The combination of a lower target thyroid dose (50 Gy) and rh-TSH stimulation allowed an up to 80% reduction of the required 131I activity compared to 131I alone (targeting 100 Gy). Consequently, the need for hospitalization and post-therapeutic restrictions were dramatically reduced. Our motivation to evaluate a lower absorbed thyroid dose than what is usually the aim (i.e. 100 Gy) in combination with rh-TSH was based on observations in our superiority studies. In these, it appeared that GVR seemed to be less dependent on the absorbed thyroid dose when rh-TSH was used. Based on these findings we find it likely that rh-TSH preconditions the nodular goitre beyond increasing RAIU, thereby allowing reduction of the absorbed thyroid dose without compromising GVR [15]. The mechanism behind this preconditioning effect may be a qualitative improvement in the RAIU [24], but other yet unidentified factors could be important. While our results demonstrate that considerable GVR can be obtained when rh-TSH is combined with a thyroid dose of 50 Gy, results from our superiority trials [25,26] delivering higher absorbed thyroid doses make it apparent that the absorbed thyroid dose is a major determinant of GVR, also when rh-TSH is used (Fig. 3). Perhaps the preconditioning effect of rh-TSH results in a parallel shift of the dose-response curve.

4. Adverse effects and safety of rh-TSH augmented 131I therapy

All regulatory bodies restrict the use of rh-TSH to thyroid cancer patients who have had a total or near total thyroidectomy [35]. The use of rh-TSH in subjects with an intact thyroid gland is off-label and carries significant risks related to thyroid hyperfunction and acute thyroid swelling. During the last decade, focus has been on establishing whether these side effects are dose-dependent.

4.1. Thyroid hormone response

In both healthy individuals [13,36–38] and subjects with MNG, [10,11,39] the thyroid hormone response shows a positive dose response relation in the rh-TSH dose range between 0.01 and 0.9 mg. Depending on the dose of rh-TSH thyroid hormones peak at 24–48 hours after rh-TSH injection, followed by normalization within three weeks. With rh-TSH doses at or below 0.03 mg most subjects maintain thyroid hormone levels within the normal range and no or only few side effects are seen [10,11].

However, when used in combination with 131I therapy the rise in thyroid hormones caused by rh-TSH per se may not be the only factor determining the increase in thyroid hormones. It is well known [34,40] that the thyroid tissue destruction caused by 131I therapy results in a release of thyroid hormones into the circulation. On average, a 20% increase in thyroid hormones is seen within the first couple of weeks following 131I therapy [40]. When applying the superiority strategy, stimulation with rh-TSH before 131I therapy increases the absorbed thyroid dose [20]. This results in increased thyroid tissue destruction, which in theory could also increase the release of thyroid hormones into the circulation. Consequently, increased efficacy, in terms of GVR, may be inevitably related to a higher risk of thyroid hormone excess, even if using low doses of rh-TSH. Reassuringly, studies using rh-TSH doses at or below 0.1 mg in combination with 131I therapy suggest that this is not a major concern [16,18]. When applying the dose-reduction strategy, 0.1 mg of rh-TSH combined with 50 Gy was not related to an increased frequency of biochemical hyperthyroidism and/or hyperthyroid symptoms.
compared to plain $^{131}$I therapy (targeting 100 Gy) [15]. Interestingly, subjects with subclinical hyperthyroidism at baseline experience a higher increase in thyroid hormones when rh-TSH is combined with $^{131}$I therapy [15]. This observation is in line with the finding by Romao et al. [41], that the prevalence of side effects related to thyroid hyperfunction is higher in subjects with hyperthyroidism (subclinical or overt) at baseline, when stimulating with rh-TSH. Parallel to the finding that subclinical hyperthyroidism is associated with a higher increase in RAIIU with $^{131}$I therapy, while the other randomized placebo-controlled trial [15]. Although radiation regulations may differ between countries, as an additional benefit, patient restrictions are less rigorous with lower $^{131}$I activities. Although cost-effectiveness analyses have not been performed, these results imply that the dose-reduction strategy may also prove cost-effective. Some patients are reluctant to receive $^{131}$I therapy because of fear of developing radiation-induced cancer, a concern also shared by some physicians. The literature estimating the long-term risk of malignancy following $^{131}$I therapy primarily deals with Graves’ disease, whereas data regarding toxic multinodular goitre are sparse, and in the case of MNG nonexistent. Results in hyper-

4.3. Other adverse effects

When applying the superiority principle enhanced GVR is achieved at the expense of an up to five-fold increase in the rate of permanent hypothyroidism [26,31]. It is unclear whether this is solely caused by the increased absorbed thyroid dose or if the use of, and perhaps the dose of, rh-TSH is an independent determinant of hypothyroidism. In the only controlled equality study, 0.1 mg rh-TSH (in combination with 50 Gy) was not associated with an increased prevalence of hypothyroidism compared to $^{131}$I alone (targeting 100 Gy) (i.e. 12 and 7% respectively at one-year) [15]. Thus, it seems that the risk of hypothyroidism is closely related to the GVR obtained.

5. Benefit and future role of rh-TSH augmented $^{131}$I therapy

Based on the existing literature, we may draw some conclusions regarding the benefit and future use of rh-TSH in the context of $^{131}$I therapy for MNG. Clinically immensely important, rh-TSH increases the eligibility for $^{131}$I therapy, since subjects with a low RAIIU may also be treated. Applying the superiority strategy GVR can be enhanced by 35–56% one-year after therapy [25,26,31], the gain being most pronounced in large goitres (Fig. 3) [25]. Consequently, rh-TSH-augmented $^{131}$I therapy more effectively relieves tracheal compression [33]. Although rh-TSH amplifies the GVR considerably, three RCTs have failed to demonstrate a positive impact on patient satisfaction and quality of life [25,26,31]. Before rh-TSH-augmented $^{131}$I therapy is widely implemented, this issue deserves further attention. Long-term results have indicated that the difference in terms of obtained GVR is maintained [44], but only a limited number of patients have been evaluated. In principle, increased GVR could translate into sustained relief of goitre related symptoms and perhaps reduce the need for additional therapy.

As an alternative to the superiority strategy, rh-TSH allows up to 80% reduction of the therapeutic $^{131}$I activity while still achieving a GVR comparable to that of conventional $^{131}$I therapy [15]. Although radiation regulations may differ between countries, an important clinical implication of the equality strategy is that the substantial reduction of the necessary $^{131}$I activity dramatically reduces the need for hospitalization. In most countries, as an additional benefit, patient restrictions are less rigorous with lower $^{131}$I activities. Although cost-effectiveness analyses have not been performed, these results imply that the dose-reduction strategy may also prove cost-effective. Some patients are reluctant to receive $^{131}$I therapy because of fear of developing radiation-induced cancer, a concern also shared by some physicians. The literature estimating the long-term risk of malignancy following $^{131}$I therapy primarily deals with Graves’ disease, whereas data regarding toxic multinodular goitre are sparse, and in the case of MNG nonexistent. Results in hyper-
thyroidism are conflicting [45], but the overall message is that the absolute number of cancers that may be induced by $^{131}\text{I}$ therapy is very small. When rh-TSH is used to enhance GVR (superiority strategy) the absorbed thyroid dose is increased and it is unclear whether this results in a higher or perhaps a lower risk of subsequent thyroid malignancy, as well as whether rh-TSH influences this risk per se. In theory, rh-TSH-augmented $^{131}\text{I}$ therapy reduces the risk of extrathyroidal malignancy [34], since the risk of cancer appears to increase with the administered activity of $^{131}\text{I}$, as reported by Metso et al. [45].

The optimal strategy in a given MNG patient depends on goitre size, the degree of symptoms, the wish to maintain normal thyroid function, the age of the patient, the risks associated with radiation exposure and the therapeutic alternatives. Subjects with a large compressive goitre, in whom the only therapeutic alternative is near total thyroidectomy, are obvious candidates for the superiority strategy. In these patients destroying enough goitre tissue to cause, hypothyroidism may be seen as analogous to near total thyroidectomy, which also leaves the patient with life-long LT4 replacement therapy. On the other hand, patients with small to moderate sized oligo-symptomatic goitres may not require extensive GVR. These patients could possibly benefit from remaining euthyroid, especially considering the increasing awareness that some patients experience a decrease in quality of life on levothyroxine replacement therapy [46]. On the other hand, it may be argued that balancing GVR against the wish to maintain euthyroidism is not worthwhile, since up to 58% of patients eventually become hypothyroid following conventional $^{131}\text{I}$ therapy [3].

6. Unresolved issues and directions for future research

Long-term follow-up studies should establish the outcome of the superiority strategy, focusing on whether the difference in GVR is maintained and whether this reduces the need for addition- al therapy. Furthermore, the superiority strategy should be evaluated in patients with extensive and preferably longstanding compressive symptoms, with the application of the newly developed thyroid disease specific quality of life questionnaire (ThyPRO) [47]. This approach should increase the chance of demonstrating a positive patient outcome. Large well-controlled studies should further explore the strategy of restricting the amount of radioactivity, with focus on cost-benefit and reduction of extrathyroidal radiation [21].

Comparative studies evaluating the dependency of GVR on the retained $^{131}\text{I}$ dose, both with and without rh-TSH stimulation are still lacking, but it may be questioned whether such a study is ethical. Assuming that rh-TSH preconditions the nodular goitre (beyond increasing RAIU) before $^{131}\text{I}$ therapy, this effect, and subsequently the obtained GVR, may be dependent on the dose of rh-TSH per se. It follows that the optimal dose of rh-TSH is still not established and to answer this question we need RCTs comparing the effect of different doses of rh-TSH (between 0.03 and 0.1 mg [30]) in combination with an adjusted thyroid dose.

A more homogeneous RAIU has been observed after rh-TSH administration [24], including increased RAIU of scintigraphically hypoactive (‘cold’) thyroid nodules. This could translate into a more favourable balance between destruction of goitre nodes and normal thyroid tissue. Critics of conventional $^{131}\text{I}$ therapy have argued that most of the GVR observed is caused by the destruction of normal paranodular thyroid tissue. It remains to be demonstrated that rh-TSH results in a better nodule destruction/reduction, which would be another strong argument in favour of using rh-TSH in this context. Finally, large studies should confirm the safety of using rh-TSH in this context and focus on preventing and treating acute thyroid swelling.

Disclosure of interest

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