REVIEW

Time to reconsider nonsurgical therapy of benign non-toxic multinodular goitre: focus on recombinant human TSH augmented radioiodine therapy

Søren Fast, Viveque Egsgaard Nielsen, Steen Joop Bonnema and Laszlo Hegedüs

Department of Endocrinology and Metabolism, Odense University Hospital, DK-5000 Odense C, Denmark

(Correspondence should be addressed to S Fast; Email: soeren.fast@ouh.regionyddanmark.dk)

Abstract

The treatment of benign multinodular goitre (MNG) is controversial, but surgery is recommended in large compressive goitres. While some patients decline surgery others may have contraindications due to comorbidity, since MNG is prevalent in the elderly. Therefore, non-surgical treatment alternatives are needed. Until recently, levothyroxine therapy was the preferred non-surgical alternative, but due to low efficacy and potential side-effects, it is not recommended for routine use in recent international guidelines. Conventional radioiodine (^{131}I) therapy has been used for two decades as an effective and safe alternative to surgery in the treatment of symptomatic non-toxic MNG. Since much higher activities of ^{131}I are employed when treating non-toxic rather than toxic MNG, there has been reluctance in many countries to use this treatment modality. Frequently, the ^{131}I -uptake in a non-toxic MNG is low, which makes ^{131}I therapy less feasible. Another challenge is the negative correlation between the initial goitre size and goitre volume reduction (GVR). With its ability to more than double the thyroid ^{131}I -uptake, recombinant human TSH (rhTSH) increases the absorbed radiation dose and thus enhances the GVR by 35–56% at the expense of up to fivefold higher rate of permanent hypothyroidism. An alternative strategy is to reduce the administered ^{131}I -activity with a factor corresponding to the rhTSH induced increase in ^{131}I -uptake. Hereby, the extrathyroidal irradiation can be reduced without compromising efficacy. Thus, although in its infancy, and still experimental, rhTSH-augmented ^{131}I therapy may profoundly alter the non-surgical treatment of benign non-toxic MNG.

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Introduction

Despite iodization programmes, simple goitre – defined as a euthyroid goitre that is not associated with thyroid autoimmunity or malignancy – still constitutes a major diagnostic and therapeutic challenge. Such goitres can be diffuse, uni- or multinodular (1). When applying ultrasound (US), most goitres have a nodular structure, particularly in the elderly (1). According to current thinking, they are caused by an interaction between genetic susceptibility and environmental triggers, iodine deficiency being the most important. There is no ideal treatment for benign multinodular goitre (MNG), as reflected by the lack of consensus in questionnaire surveys (2–5). Surgery is recommended when facing a large goitre or when malignancy cannot be ruled out (6, 7). However, it is important to recognise that a considerable proportion of patients refuse surgery, even in the context of a large symptomatic goitre, which underlines the need for non-surgical alternatives. The non-surgical treatment options are: iodine supplementation, levothyroxine (LT_4) therapy and radioiodine (^{131}I) therapy. In theory, percutaneous interventional

therapy (laser photocoagulation or ethanol injection) is also an option in MNG, but so far it is only experimental and no controlled studies exist. At best, LT_4 therapy has a minor effect on the appearance of new nodules but does not shrink the existing nodules (8). Due to low efficacy and accumulating evidence of cardiovascular and skeletal side-effects, it is not recommended for routine use in recent guidelines (6, 9) and reviews (7, 10). Iodine supplementation therapy is not superior to LT_4 therapy and a major hindrance is the potential induction of hyperthyroidism (11). Conventional (without rhTSH) ^{131}I therapy has been used for more than a decade in symptomatic non-toxic MNG, resulting in a mean thyroid volume reduction of ~40% 1 year after treatment (12) and 50–60% after 3–5 years (13). Generally, patient satisfaction is high and symptoms are considerably improved (14). A major drawback of this therapy is the need for relatively high activities of radioiodine when treating large goitres. Furthermore, the effect is attenuated with increasing goitre size (15). Another challenge is the frequent finding of a low (below 20%) thyroid radioiodine uptake (RAIU), caused mainly

by a high dietary iodine intake and/or by extensive degenerative changes within the thyroid gland.

The recent advent of recombinant human TSH (rhTSH) has opened new avenues for ^{131}I therapy of MNG since it can double the thyroid RAIU even using minute quantities (16). In combination with ^{131}I therapy rhTSH enhances the goitre volume reduction (GVR) by 35–56% (17–19) at the expense of up to fivefold higher rate of permanent hypothyroidism (18). Alternatively, the administered ^{131}I -activity can be reduced by a factor corresponding to the rhTSH induced ^{131}I -uptake increase, without compromising efficacy (20). The latter strategy of ^{131}I therapy with reduced administered ^{131}I -activity is intriguing, both in terms of minimizing the long-term risk of extrathyroidal malignancy and in reducing the cost and inconvenience of inpatient treatment. Here, we focus on non-surgical therapeutic aspects of simple MNG, including an update on rhTSH-augmented ^{131}I therapy.

Clinical manifestations and natural history of benign non-toxic MNG

The aetiology, natural history and diagnostic evaluation of MNG has been thoroughly reviewed recently (7). In brief, the natural history of a nodular goitre is that of gradually increasing size with development of multiple nodules. However, the natural history with respect to growth and function varies and is difficult to predict in a given patient because no specific growth parameters exist. The annual growth rate is in the range of 0–20% and the 5-year incidence of hyperthyroidism is ~10% (7). Clinical manifestations of nodular goitre are related to those of growth or functional autonomy. Symptoms are typically those of local pressure (dysphagia, globulus sensation, cough or dyspnoea) or cosmetic complaints and are difficult to evaluate objectively. It is mandatory to rule out malignancy, for which purpose fine-needle aspiration biopsy is the golden standard (6). There is no simple relationship between goitre size and symptoms (14), which often makes the decision whether to treat or not difficult. In fact, one-third of clinicians would refrain from treatment facing a patient with moderate discomfort due to a multinodular non-toxic goitre of 50–80 g in which malignancy has been ruled out (2, 3). In asymptomatic subjects with relatively small goitres observation is acceptable, although many have a growth potential.

Non-surgical treatment of benign non-toxic MNG

Levothyroxine therapy

LT₄ therapy may have a role in the treatment of diffuse goitre, where clinically relevant goitre size reduction (15–40% after 3 months of therapy) has been

documented in controlled trials (21–24). In uninodular goitre, results are conflicting, but there is a trend toward a positive effect in reducing nodule volume after 6–12 months of therapy (25). However, clinically relevant (more than 50%) nodule or goitre shrinkage occurs only in a minority of patients (10–20%). Even in the case of a modest effect, a matter of concern is the fact that studies (26, 27) have shown re-growth of nodules to baseline levels within 1 year of therapy cessation. Consequently, LT₄ therapy has to be continued for many years to benefit the patient. Little is known about long-term outcome and implications on quality of life (QoL). The only available controlled long-term study (28) showed no significant nodule size reduction after 5 years of continuous LT₄ therapy. In non-toxic MNG only three controlled trials exist, in which US was used for objective size monitoring (8, 26, 29). These studies have shown that the effect is at best very modest. Additionally, disqualifying LT₄ therapy, there is accumulating evidence of adverse effects on the skeleton and cardiovascular system. In a recent study, we have furthermore demonstrated that the vast majority (91%) of unselected consecutive Danish MNG patients are ineligible for LT₄ therapy, when applying the 2006 guidelines from the Endocrinologists and Associazione Medici Endocrinologi (30). Accordingly, LT₄ therapy is not recommended for routine use in recent guidelines and reviews (6, 7, 9, 10).

Iodine supplementation

Iodine supplementation can effectively reduce a diffuse goitre. In a controlled trial, performed in an iodine-deficient area, a daily dose of 400 µg iodine during 8 months was as effective as 150 µg LT₄ in reducing the size of endemic goitre (22). The majority of patients in that study had diffuse goitre and iodine supplementation has only been very scarcely evaluated in MNG patients, but it seems no better than LT₄ therapy (31). A major hindrance in the use of iodine supplementation is the fact that a sudden increase of the iodine intake may induce thyrotoxicosis in predisposed individuals (11). Furthermore, it is of concern that iodine supplementation appears to increase the incidence of papillary thyroid cancers and lymphocytic thyroiditis (32). Due to these major drawbacks it is disregarded as a therapeutic option in Europe (2) (except in Germany), as well as in North America (3).

Conventional (without rhTSH) radioiodine therapy for non-toxic MNG

Radioiodine has been used in the treatment of hyperthyroidism for over 60 years. In the last two decades the use has been widened to include symptomatic benign non-toxic goitre, resulting in a mean thyroid volume reduction of ~40% 1 year after

treatment (8,12, 13, 33) and 50–60% after 3–5 years (13). Approximately half of the effect is obtained within the first 3 months (13). A second ^{131}I -dose may cause additional thyroid volume reduction (13). Considerable variation in GVR (15–70%) is obtained and for incompletely clarified reasons up to 20% of patients do not respond to ^{131}I therapy (33). The superiority of ^{131}I -treatment over LT_4 therapy has been demonstrated in a randomized study by Wesche *et al.* (8). Only a few studies have investigated the effect of ^{131}I -treatment in large goitres above 100 ml. In three studies in which a sensitive goitre monitoring was applied (i.e. computed tomography (CT) or magnetic resonance (MR) imaging the mean GVR was 30–40%, with considerable individual variation (15, 34, 35). Interestingly, these studies demonstrated that the GVR is inversely correlated to the initial goitre size (33). Another drawback when treating large goitres is the need for relative high ^{131}I activities, thus requiring expensive and inconvenient inpatient treatment. Fractioned ^{131}I therapy is an option in such patients (36), but due to potential thyroid stunning the doses should probably be given with wide intervals, thus rendering this treatment modality cumbersome.

Theoretically, the efficacy of ^{131}I therapy depends mainly on the dose of absorbed radioactivity in the thyroid. When evaluating the outcome of different trials it should be remembered that results are difficult to compare due to variation in both the dose calculation method and in the method for determination of outcome (palpation, US, CT-scan or MRI) in terms of GVR. The issue concerning the optimal dose and dose planning for non-toxic MNG is controversial and much of the literature concerning dose selection deals with hyperthyroid patients (7). Generally, ^{131}I -activities have been adjusted to RAIU, aiming at an absorbed thyroid dose of ~ 100 Gy (13, 15, 33), but others question whether this is worthwhile and instead use fixed-dose regimens, only taking thyroid size into consideration (7).

The adverse effects of conventional ^{131}I therapy are well documented and described in detail elsewhere (7). Early adverse effects are in most cases mild and transient and include radiation induced thyroiditis (3%), transient hyperthyroidism (5%), Grave's-like hyperthyroidism (5%) and occasionally a 15–25% increase of thyroid size. A late adverse effect of ^{131}I therapy is the development of hypothyroidism, ranging from 22 to 58% within 5–8 years post ^{131}I therapy. The long-term risk of extrathyroidal malignancy following ^{131}I therapy for non-toxic MNG is unknown. In theory, this risk is higher in euthyroid MNG patients than in hyperthyroid patients, since higher activities of ^{131}I are employed. Thus, a novel strategy using lower activities of ^{131}I is desirable. It is however, reassuring that in a large survey in 35 593 hyperthyroid patients, mainly from the USA, followed up for a mean of 21 years, radioiodine therapy was not linked to total cancer

deaths or any specific cancer, except for an increase in the standardized mortality ratio for cancer of the thyroid (37). The risk of thyroidal malignancy was assessed in a study of 5000 hyperthyroid patients during 27 years of follow-up (38). In that study, the risk of subsequent thyroid cancer was not significantly increased and bearing in mind that toxic MNG is a different stage of non-toxic MNG, this report is reassuring. But as indicated by the study of Metso *et al.* the issue is not finally laid to rest (39).

A major hindrance in the use of conventional ^{131}I therapy in MNG is the frequent finding of a low (below 20%) thyroid RAIU. In this situation, ^{131}I therapy is not feasible since high activities of radioiodine are needed to obtain an acceptable GVR. In such cases, the extra-thyroidal irradiation increases and as a consequence the theoretical risk of long-term extrathyroidal malignancy. The thyroid RAIU is dependent on the dietary iodine intake and the extent of nodular autonomy (7). As a consequence of the widespread iodine enrichment programs a low thyroid RAIU is more often encountered.

RhTSH has been documented to increase the thyroid RAIU by more than twofold (20). With regard to the above-mentioned limitations of conventional ^{131}I therapy, rhTSH has the potential to improve GVR – when using standard ^{131}I activities (18) – or allow treatment with reduced ^{131}I activities, without compromising efficacy. In the following we will explore these options.

Radioiodine therapy with rhTSH pre-stimulation

Optimal rhTSH dose for enhancement of thyroid RAIU

Since the initial reports on the effects of rhTSH on thyroid RAIU (40), efforts have focused on determining the optimal dose and timing for rhTSH administration. In the following, we present the current knowledge on the dose and timing of rhTSH (Table 1).

The optimal dose of rhTSH for stimulation of thyroid RAIU remains to be established. Defining a lower dose limit that increases RAIU sufficiently is paramount, since adverse effects, especially the induction of transient thyrotoxicosis, are dose dependent (40–42). The changes in thyroid RAIU following rhTSH doses between 0.01 and 0.9 mg have been investigated in both healthy individuals and patients with MNG (Table 1). In our opinion, data from studies conducted in healthy individuals should not uncritically be applied to MNG patients, since the morphological changes in MNG may indicate an altered and/or delayed physiological response. Generally, studies are difficult to compare due to considerable variations in dietary iodine intake, baseline RAIU and goitre size. The lack of a control group in many studies also complicates the

Table 1 The effect of recombinant human TSH (rhTSH) on thyroid radioiodine uptake (RAIU) and retained thyroid ¹³¹I-dose.

Author	n	Study design	Dose rhTSH (mg)	Time interval between rhTSH and I-tracer	Baseline mean RAIU	Relative increase in mean RAIU
Huysmans <i>et al.</i> ^a (2000), (40)	15	Open, non-controlled	0.01 0.01 0.03	2 h 24 h 24 h	24 h: 30% 24 h: 29% 24 h: 33%	24 h: 50% (median) 24 h: 90% (median) 24 h: 100% (median)
Nieuwlaat <i>et al.</i> ^a (2003), (20)	12 10	Open, non-controlled	0.01 0.03	24 h 24 h	24 h: 27% 24 h: 22%	24 h: 87% 24 h: 145%
Duick <i>et al.</i> ^a (2004), (45)	21 9	Open, non-controlled	0.1 0.3	0 h 0 h	— —	48 h: 76% 48 h: 77%
Silva <i>et al.</i> ^a (2004), (19)	17	Open, non-controlled	0.45	24 h	24 h: 18%	24 h: 151%
Albino <i>et al.</i> ^a (2005), (43)	18	Open, non-controlled	2 × 0.1	24 h/0 h	24 h: 12%	24 h: 335%
Cohen <i>et al.</i> ^a (2006), (44)	17	Open, non-controlled	0.03	24 h	24 h: 26%	24 h: 68%
Paz-Filho <i>et al.</i> ^a (2007), (46)	17	Open, non-controlled	0.1	24 h	24 h: 18%	24 h: 174%
Torres <i>et al.</i> ^b (2001), (42)	6	Open, non-controlled	0.9	24 h	24 h: 23%	24 h: 75%
Pena <i>et al.</i> ^b (2006), (41)	5 10 10	Open, non-controlled	0.1 0.1 0.1	24 h 48 h 72 h	24 h: 25% 24 h: 30% 24 h: 30%	24 h: 88% 24 h: 36% 24 h: 0%
Lawrence <i>et al.</i> ^c (2001), (47)	4 5	Open, non-controlled	0.9 0.9	8 h 32 h	16 h: 3.4% 16 h: 3.2%	16 h: 64% 16 h: 100%
Nielsen <i>et al.</i> (2005), (48)	35	Randomized placebo-controlled	0.3 placebo	24 h before therapy	24 h: 33%	24 h: 43%
	28			24 h before therapy	24 h: 36%	24 h: —8%

^aStudies in patients with multinodular goitre.
^bStudies in healthy individuals.
^cStudy in iodine loaded healthy men.

interpretation. In addition, measurements of RAIU are extremely prone to variation in the method used. Despite these shortcomings, studies in MNG patients (19, 20, 40, 43–46) and healthy individuals (41, 42, 47) document an approximately twofold increase in RAIU, largely independent of rhTSH dose. In support of this observation, a small comparative trial found that 0.03 mg was not superior to 0.01 mg (40) and another comparative trial observed that 0.3 mg was not superior to 0.1 mg (45). In contrast to these findings, the last comparative trial demonstrated a positive dose response curve, since a relative increase in mean RAIU of 87% was observed using 0.01 mg of rhTSH compared with 145% with 0.03 mg (*p* < 0.05, between rhTSH-dose groups) (20). Favouring the use of rhTSH is the concurrent finding that the increase in RAIU is inversely correlated with the initial RAIU (40).

The importance of the stable iodine load was investigated by Lawrence *et al.* (47), who studied the effect of 0.9 mg of rhTSH in healthy iodine loaded individuals. Although the 16 h thyroid RAIU doubled (from 3 to 6%), it was far from normal by the rhTSH pre-stimulation, suggesting that reducing iodine intake is paramount.

The retained (effective) ¹³¹I-dose depends not only on the RAIU but also on the wash-out/release of ¹³¹I from the gland. So far, one study has investigated changes in the retained thyroid ¹³¹I-dose (48), with and without rhTSH. Following 0.3 mg of rhTSH, the retained thyroid ¹³¹I-dose was increased by 75% compared with placebo (48) (Fig. 1). Interestingly, the

iodine kinetics during conventional (placebo group) ¹³¹I therapy resulted in a lower thyroid dose than the intended 100 Gy. The factors responsible for this phenomenon remain unidentified. A plausible explanation is increased iodine release from the gland during therapy and the possible impact from thyroid stunning (49). Apparently, rhTSH reverses this effect. The relative increase in 24 h RAIU (43%) was considerably less pronounced in this study (48), which may indicate a methodological problem in the RAIU measurements after ¹³¹I therapy. In addition, estimation of the effective half-life from two uptake measurements does not reflect the true iodine kinetics and is very prone to inaccuracies in the uptake measurements.

As for minimizing adverse effects, the optimal rhTSH dose is probably 0.1 mg or lower, since doses down to 0.01 mg have proven effective for enhancing RAIU (20, 40, 41). It is unclear whether large goitres require higher doses of rhTSH for an optimal increase in RAIU.

Timing of rhTSH administration

Although scarcely investigated the optimal time interval between administration of rhTSH and ¹³¹I therapy seems to be 24 h (Table 1). However, this may be heavily influenced by the characteristics of the study/treatment population. One trial, studying 15 MNG patients, documented that an interval of 24 h (relative median increase in 24 h RAIU 90%) was more effective than 2 h (relative median increase in 24 h RAIU 50%) (40). Considering that the sodium–iodide-symporter is

Figure 1 Difference in expected thyroid dose (Gy) and actual absorbed thyroid dose (Gy) after prestimulation with 0.3 mg rhTSH or placebo. (A) Individual values and (B) comparisons of the mean (s.d.) values for each group. The dotted lines denote the intended dose of 100 Gy, Nielsen *et al.* 2005 (48).

stimulated by rhTSH with some time delay (50), this is of no surprise. So far, intervals longer than 24 h have only been studied in healthy individuals, using 0.1 mg of rhTSH (41). This single study points at 24 h being the optimal interval, since it resulted in a mean increase in the 24 h RAIU from 25 to 47% (relative increase 88%) compared with 30–41% (relative increase 36%) using a 48 h interval and 30–31% (no significant increase) using a 72 h interval (41). These findings need to be confirmed in MNG patients, since the morphologic changes in a MNG may very well result in an altered physiological response (51).

Repetitive injections of rhTSH have been investigated in two trials (43, 52). In the first study, 0.1 mg of rhTSH was administered 0 h and 24 h respectively, before the ¹³¹I-tracer, resulting in a fourfold increase in 24 h RAIU (43). The second injection was probably close to the tracer administration to significantly influence the 24 h RAIU. The pronounced increase in RAIU in this study (43) may very likely be due to a low baseline RAIU (12.3%), more than due to repetitive rhTSH administration. From the aforementioned, we conclude that a 24 h interval between rhTSH injection and subsequent

¹³¹I therapy seems to be the optimal interval for obtaining an approximate doubling of RAIU in MNG patients, largely independent of the rhTSH dose.

Effect on GVR

The potential benefits of rhTSH, when combined with ¹³¹I therapy, are those of increased GVR or reduced administered ¹³¹I-activity and thus reduced extrathyroidal irradiation. Combined with ¹³¹I therapy rhTSH increases the GVR in MNG patients by 35–56%. This effect has been documented in three randomized controlled trials (RCT) depicted in Table 2 (17–19). In small-to-medium sized goitres (median goitre volume 51 ml, range 20–99 ml), we demonstrated that 0.3 mg of rhTSH improved the mean GVR by 33% at 1 year follow-up (Fig. 2) (18). In another study, using 0.3 mg of rhTSH, but in large goitres (median goitre volume 160 ml, range 99–440 ml), the effect of rhTSH was even more pronounced. The average GVR was increased by 56% compared with conventional ¹³¹I therapy (Fig. 2) (17). In consistence with these two studies, Silva *et al.* (19), also treating large goitres (median goitre volume 219 ml, range 82–728) but with a fixed ¹³¹I activity (adjusted to thyroid size), demonstrated a 46% increase in mean GVR after pre-treatment with 0.45 mg rhTSH and a 12 month follow-up. The remaining non-controlled studies (Table 2) have demonstrated considerable GVR between 35 and 53% (20, 43, 44, 46, 52, 53), 6–12 months after rhTSH-augmented ¹³¹I therapy. Although lacking a control group, the results are promising since some of the latter studies (43, 46) were carried out in patients with relatively low baseline RAIU, thus demonstrating the feasibility of ¹³¹I therapy in such patients when employing rhTSH. One study, in 18 MNG patients with a baseline RAIU of 12%, documented a mean GVR of 39% after 6 months and 53% after 2 years (43, 54). Attaining acceptable GVR in patients with a low baseline RAIU is promising, since a high proportion of MNG patients are expected to have low RAIU due to iodization programmes. Before eradicating simple goitre by such programmes, the treatment of patients with existing goitre is in fact impeded.

Another approach is to reduce the administered ¹³¹I activity with a factor corresponding to the increase in RAIU obtained by rhTSH stimulation. This strategy was investigated in 22 MNG patients, using 0.01 or 0.03 mg of rhTSH (20). Pre-treatment with rhTSH allowed a 50% reduction of administered ¹³¹I activity, while still achieving a GVR of 40%, after 1 year. Such a reduced ¹³¹I activity is desirable both in terms of lowering the theoretical risk of late occurring extrathyroidal malignancy and in terms of being able to treat patients on an out-patient basis. Minimizing in-patient treatment reduces the economic burden to society and the inconvenience for the patient.

Table 2 Studies on the effect of rhTSH combined with ¹³¹I therapy, in patients with benign multinodular goitre.

Author (year)	n	Design	rhTSH dose (mg) and time interval	Goitre size estimation	Iodine dose	Mean goitre volume reduction	Myxoedema prevalence at follow-up
Nieuwlaet <i>et al.</i> * (20) (2003)	12 10	Observational/non-controlled	0.01 0.03 24 h	MR-scan	Adjusted Equality study	35%/1 year 41%/1 year	33% 40%
Duick <i>et al.</i> ** (53) (2003)	6 10	Observational/non-controlled	0.3 0.9 24 h	Palpation	Fixed 1110 MBq	30–40%/7 months 30–40%/7 months	50% 60%
Silva <i>et al.</i> ** (19) (2003)	34	Randomized/placebo-controlled	0.45 24 h	CT-scan	Fixed	rhTSH: 58%/1 year placebo: 40%/1 year $P < 0.05$, between groups	rhTSH: 65% placebo: 21%
Albino <i>et al.</i> ** (43) (2005)	18	Observational/non-controlled	2 × 0.1 24/48 h	CT-scan	Fixed	39%/6 months	65%
Cohen <i>et al.</i> ** (44) (2006)	17	Observational/non-controlled	0.03 24 h	CT-scan	1110 MBq Fixed	53%/2 years 34%/6 months	72% 18%
Giusti <i>et al.</i> ** (52) (2006)	12 8	Observational/with matched controls	2 × 0.2 0 24/48 h	CT-scan	Fixed 370–555 MBq	rhTSH: 44%/20 months Controls: 25%/22 months	rhTSH: 17% Controls: 62%
Nielsen <i>et al.</i> ** (18) (2006)	57	Double-blinded/randomized/ placebo-controlled	0.3 24 h	US-scan	100 Gy adjusted	rhTSH: 62%/1 year placebo: 46%/1 year $P = 0.002$, between groups	rhTSH: 61% placebo: 11%
Bonnema <i>et al.</i> ** (17) (2007)	29	Double-blinded/randomized/ placebo-controlled	0.3 24 h	MR-scan	100 Gy adjusted	rhTSH: 53%/1 year placebo: 34%/1 year $P < 0.001$, between groups	rhTSH: 21% placebo: 7%
Paz-Filho <i>et al.</i> ** (46) (2007)	17	Observational/non-controlled	0.1 24 h	CT-scan	Fixed 1110 MBq	46%/1 year 52%/2 years	53% –

*Equality study, reduced ¹³¹I activity, aiming at the same absorbed dose as with conventional ¹³¹I therapy.

**Superiority study, aiming at increased thyroid irradiation.

Figure 2 Comparison of the relative goitre volume 1 year after conventional (placebo) and rhTSH augmented ^{131}I therapy for non-toxic multinodular goitre, smaller and larger than 100 ml. Bars represent the relative mean goitre volume before therapy and 1 year after therapy. Adapted from Nielsen *et al.* (18) and Bonnema *et al.* (17).

Three studies have published follow-up results on GVR beyond 1 year (19, 43, 46). Two small observational studies (43, 46) found insignificant GVR between 1 and 2 years of observation (54). In a randomized trial (19), further GVR, in both the rhTSH and the placebo group, was reported, between 1 and 4 years of follow-up. The difference between the groups at 1 year was maintained after 4 years, but was not more pronounced (55).

Although rhTSH amplifies the GVR considerably, the three RCTs have failed to demonstrate an effect on patient satisfaction or QoL (16). One study did not address this issue at all (19), whereas the other two studies (17, 18) relied on a visual analogue scale (VAS). Before rhTSH-augmented ^{131}I therapy is implemented this issue deserves further attention. It may very well be due to lack of sensitivity of the VAS for QoL determination. Generally, the patient satisfaction is high with conventional ^{131}I therapy, which also makes the detection of differences difficult (8). Objective measures to document the superiority of rhTSH augmented ^{131}I therapy over conventional ^{131}I therapy are thus important. For this purpose, a newly developed thyroid disease specific QoL questionnaire may prove valuable (56).

Impact on tracheal anatomy and respiratory function of ^{131}I therapy with and without rhTSH

Tracheal compression and impaired airflow is often encountered in MNG patients. In a consecutive population of 153 goitre patients it was documented that one-third had upper airway obstruction detected by lung function tests (57). It is important to recognize that affected individuals do not have an increased frequency of respiratory complaints (57), which makes the

subjective report of improvement less valuable. Monitoring alterations in pulmonary function and the smallest cross-sectional area of the trachea are obvious methods for documenting a positive effect of ^{131}I therapy. So far only one study (58) in patients with a very large goitre has investigated the effect of rhTSH-augmented ^{131}I therapy on these parameters. In that study, we demonstrated that rhTSH-augmented ^{131}I therapy, compared with ^{131}I therapy alone, resulted in a greater improvement of the inspiratory function due to a diminished tracheal compression.

Determinants of GVR

The theoretical foundation of rhTSH augmented ^{131}I therapy is that of increased RAIU leading to increased retained thyroid dose and irradiation. Based on three randomized controlled trials (17–19), pre-treatment with rhTSH beyond doubt improves GVR by 33–56% compared with conventional ^{131}I therapy. But what are the mechanisms behind this enhancement? Employing conventional radioiodine therapy major determinants of GVR are: initial goitre size, retained thyroid dose and as yet unidentified individual susceptibility factors (33). In addition, it has been observed that the presence of dominant nodules (nodule volume > goitre volume) is related to a poorer response to ^{131}I therapy and a higher risk of goitre recurrence (33). This indicates that the degree of morphological and/or functional changes, evidenced by US and thyroid scintigraphy, within the thyroid gland may affect the outcome of ^{131}I therapy.

Initial goitre size and GVR

Using conventional non-rhTSH-stimulated ^{131}I therapy, several studies have reported a negative correlation between initial goitre size and GVR (15, 33), and such a relationship is plausible, because a larger fraction of the gland may become inert and subsequently less susceptible to ^{131}I . With the use of rhTSH this negative correlation seems to be abolished. In our recent controlled randomized study, we demonstrated that GVR was inversely correlated to the initial goitre volume in the placebo group, whereas such a correlation did not exist in the rhTSH group (18). A similar pattern was seen in the large goitre study (17) since only rhTSH stimulation had an impact on GVR, when a regression analysis was performed including rhTSH pre-stimulation, age, gender, use of antithyroid drug pre-treatment, thyroid 24 h ^{131}I uptake at baseline, initial goitre volume and serum TSH before therapy.

Degree of morphological/functional changes

Pre-treatment with rhTSH may improve GVR by causing a more homogeneous distribution of radioiodine within the thyroid, especially increasing the uptake of ^{131}I in

scintigraphically relatively cold areas. In support of this theory, Nieuwlaet *et al.* (59) reported a trend toward a more homogeneous distribution of ^{131}I , judged by scintigraphy and perhaps even an altered regional uptake, evidenced by cold areas becoming warm and vice versa. This observation has been confirmed by Albino *et al.* (43). These findings may very well explain the observation that the gain in GVR was more pronounced in large goitres (above 100 ml), since the degree of both morphological and functional changes within a goitre evolve with increasing goitre size (7).

A highly relevant but unanswered question is whether these rhTSH induced changes in regional RAIU result in a more pronounced nodule reduction, instead of paranodular tissue destruction. The higher prevalence of hypothyroidism with the use of rhTSH suggests that this may not be the case (18).

Retained thyroid dose and GVR

The retained thyroid dose is positively correlated to GVR using conventional ^{131}I therapy (17, 18, 33). In our double-blinded, randomized and controlled trial we found in the placebo group a significant positive correlation between the degree of goitre reduction and the retained thyroid dose (17). Such a correlation did not exist in the rhTSH group, implying that the goitre reduction was dependent on not only the thyroid dose but also other factors induced by rhTSH pre-stimulation (Fig. 3). In the study by Nielsen *et al.* (18) a similar pattern was found. By contrast, Albino *et al.* (43) found a positive correlation between the degree of GVR and the effective absorbed ^{131}I -dose preceded by rhTSH-stimulation. As mentioned above, a plausible explanation for this additional rhTSH effect beyond the increase in RAIU could merely be a more homogenous distribution of ^{131}I within the goitre. However, other, yet unidentified mechanisms behind such an effect, should it exist, could be an increased vulnerability to ionizing radiation of the rhTSH stimulated thyrocytes. In support of this theory, the cure rate, when hyperthyroid patients are treated with ^{131}I , is positively correlated to the serum-TSH concentration (60).

Currently, the optimal dose of rhTSH is most likely below 0.1 mg, but it should be noted that the serum concentration of rhTSH may be an independent determinant for outcome in terms of GVR. The results of an ongoing phase 2 trial using 0.01 and 0.03 mg of modified release recombinant human TSH (MRrhTSH) as well as studies using different applied ^{131}I doses to the thyroid will contribute to resolving these interesting issues.

Whether rhTSH influences the long term GVR or goitre recurrence rate is unclear. Follow-up results have only been scarcely reported, but following conventional ^{131}I therapy Le Moli *et al.* found that 8% had recurrent goitre growth 3–5 years after therapy (33).

Although it is early to draw final conclusions, it is worth noting that the study by Bonnema *et al.* (17)

Figure 3 Correlation between the relative goitre volume reduction (GVR) after 12 months and the retained (effective) thyroid ^{131}I -dose. Adapted from Bonnema *et al.* 2007 (17).

documented a 56% GVR in large goitres, as opposed to the 35% in small goitres reported by Nielsen *et al.* (18). If this trend can be confirmed in future studies it indicates that patients with a very large goitre are possibly the best candidates for rhTSH-stimulated ^{131}I therapy, especially if the baseline RAIU is low and surgery is disfavoured by the patient or the surgeon.

Adverse effects of recombinant human TSH

RhTSH has been used in the treatment of differentiated thyroid cancer for more than a decade, and is generally well tolerated, even with repeated doses of 0.9 mg rhTSH. In large-scale clinical studies only a minority of patients had mild adverse reactions, such as nausea and headache (61). In combination with ^{131}I therapy for MNG, acute and long-term alterations in thyroid function and size constitute the main adverse effects in patients with the thyroid gland *in situ*.

Acute adverse-effects

The induction of transient dose dependent hyperthyroidism is the main adverse effect of rhTSH. The effects of rhTSH on thyroid function, both in healthy individuals and in patients with MNG, have been studied by us and others (40–42, 62, 63). Although different doses of rhTSH (0.01, 0.03, 0.3 and 0.9 mg) have been used, the same patterns in the various biochemical markers have been observed. Within 4–8 h of rhTSH injection, a rise in serum levels of thyroxine (T_4) and triiodothyronine (T_3) occurs, peaking at 24–48 h, followed by normalization within 3–4 weeks. A clear dose-response exists, since a more pronounced response in serum levels of T_4 and T_3 and thyroglobulin was observed when administering 0.3 mg rhTSH, compared with lower doses. A maximal stimulatory dose also seems to exist, since

0.9 mg rhTSH did not stimulate thyroid function more than 0.3 mg, when administered to the same subjects (42). With rhTSH doses of 0.01 and 0.03 mg the response is blunted and most patients maintain thyroid hormone levels within the normal range (20). Further reassuring is the observation that pre-treatment with 0.1 mg rhTSH did not affect structural and functional parameters of the heart, despite transient increases in serum levels of thyroid hormones (64). Thus, when limiting rhTSH doses to 0.1 mg or less, the rise in thyroid hormones seems to be of little clinical relevance. Nonetheless, caution is advised, especially when treating the elderly or patients with cardiovascular disease.

Acute swelling of the thyroid gland within the first 48 h following rhTSH injection has been documented in both healthy individuals and MNG patients. Likewise, tumour swelling and pain from metastases, resulting from repeated injections of 0.9 mg rhTSH have been reported in patients with differentiated thyroid carcinoma (65). Thus, 0.9 mg of rhTSH administered to nine healthy individuals resulted in a 35% increase in mean thyroid volume at 48 h (62). One individual developed a very profound and tender thyroid enlargement, from 22 to 90 ml. Similarly, when 0.3 mg of rhTSH was administered to 10 MNG patients, a mean volume increase of 24% was seen after 48 h (63). In susceptible individuals with a large obstructing goitre this may pose a serious threat in terms of respiratory problems. The concern of airway obstruction following rhTSH augmented ^{131}I therapy is enhanced by the observation that conventional ^{131}I -treatment itself may result in an acute increase in thyroid volume. Occasionally, thyroid size increase in the range of 15–25%, following conventional ^{131}I -treatment, is seen (15, 66). If a synergistic effect of rhTSH and ^{131}I on the thyroid swelling exists, combined therapy may pose a serious threat in predisposed individuals. Until now, only one study has evaluated whether rhTSH-augmented ^{131}I therapy results in a significant acute goitre swelling (17). In our trial, using 0.3 mg of rhTSH, the average goitre volume remained unchanged 1 week after ^{131}I therapy, but larger deviations from baseline were observed in patients pre-treated with rhTSH compared with placebo (17). The observations in that study are reassuring, but it should be kept in mind that the most pronounced deviations in thyroid size are seen in the first 48 h after rhTSH administration (62, 63). Although observed in healthy individuals, the acute swelling of MNG tissue is probably dose dependent, since 0.1 mg of rhTSH resulted in a blunted (mean 10%) increase in thyroid volume, when administered to 25 healthy individuals (41).

Other adverse reactions, like cervical pain or tenderness, typically occurring in the first three weeks after treatment, are more frequent with the use of rhTSH (17–19). Most likely, these manifestations are a

consequence of the increased thyroid irradiation, resulting in an increased incidence of radiation induced thyroiditis.

Long-term adverse effects

Of more concern than the acute and transient increase in thyroid hormones, is the up to fivefold increase in the rate of permanent hypothyroidism when rhTSH is used in combination with ^{131}I therapy (18). In the three randomized controlled trials, permanent hypothyroidism was reported in 21% (17), 61% (18) and 65% (19) of rhTSH treated patients, compared with 7% (17), 11% (18) and 21% (51) respectively, in the controls. Life-long LT_4 therapy is needed in these individuals, and since there has been increasing focus on the possibility that hypothyroidism, even if treated with LT_4 , may result in reduced QoL (67), this issue is clearly of importance. Even so, the higher prevalence of hypothyroidism should not withhold clinicians from using rhTSH-augmented ^{131}I therapy in view of the fact that the alternative (surgery) would also lead to hypothyroidism in the majority of cases. Whether the prevalence of hypothyroidism with rhTSH-augmented ^{131}I therapy can be reduced without compromising efficacy (GVR) remains unclear. It is unsettled whether the increased incidence of hypothyroidism is solely caused by the increased absorbed ^{131}I -dose, or if the rhTSH dose is an independent factor (48). As seen with conventional ^{131}I therapy, the incidence of hypothyroidism is positively correlated to the GVR. Appearance of TSH receptor antibodies (TRAb) and/or anti-TPO antibodies has been reported in MNG patients following conventional ^{131}I therapy (68). Apparently, the use of rhTSH does not increase this risk (69).

It is unclear whether rhTSH influences the long-term risk of thyroidal or extrathyroidal malignancy and only long-term follow-up studies can clarify this issue. In theory, this would depend on the strategy adopted. If the administered activity is not adjusted for the rhTSH induced increase in RAIU, the absorbed thyroid dose is increased (48) as is perhaps the long-term risk of thyroidal malignancy. On the other hand, one study has demonstrated that if the administered ^{131}I activity is reduced according to the rhTSH induced increase in RAIU, the absorbed radiation-dose can be reduced in extrathyroidal organs and tissues, especially bladder and stomach (70).

Future role and unresolved issues regarding the use of rhTSH in combination with ^{131}I therapy

Pre-treatment with rhTSH beyond doubt improves GVR by 33–56% compared with conventional ^{131}I therapy. Keeping in mind that rhTSH is used off-label in this setting we suggest that rhTSH may have a future role in ^{131}I -treatment of MNG, especially in

large goitres or in goitres with a low RAIU. Doses of 0.01 and 0.03 mg are effective in increasing the RAIU, but it is too early to offer final recommendations as to the optimal dose of rhTSH. However, there is no evidence to support the use of doses above 0.1 mg. The results of an ongoing phase II trial, testing two low doses of modified release rhTSH in combination with ^{131}I therapy, will help to clarify this issue.

Surgery remains the first line treatment for large compressive goitres, but rhTSH augmented ^{131}I therapy is a promising new strategy in these patients. Another strong argument in favour of rhTSH is the potential to treat with a reduced ^{131}I -activity without compromising efficacy. Considering that the issue of risk of extrathyroidal malignancy is not finally laid to rest, this strategy may be worthwhile. In addition, a reduced ^{131}I -activity also implies that a higher proportion of patients can be treated on an out-patient basis.

Although rhTSH amplifies the GVR, the failure to demonstrate an effect on patient satisfaction or QoL is problematic (16). This issue deserves further attention to clarify whether it is due to lack of sensitivity of the method for QoL determination. Acute swelling of the thyroid gland has been reported with rhTSH doses above 0.1 mg, thus caution should be the rule when treating susceptible individuals with large and/or compressive goitres. This potentially serious side-effect is probably dose dependent, but further studies addressing this and other side-effects, including the long-term effect of the increased hypothyroidism rate, are needed. Most likely, the up to fivefold increase in the rate of permanent hypothyroidism goes hand-in-hand with the improved GVR, but strategies to optimise this imbalance should be explored. In our opinion, the relatively high rate of permanent hypothyroidism does not outweigh the beneficial effect of rhTSH, but points at the importance of identifying the obvious candidates for rhTSH pre-stimulation. Although LT_4 substitution therapy is regarded as a routine treatment without side-effects, there has been increasing focus on potential negative implications on QoL.

Future studies will clarify whether the serum rhTSH concentration is an independent factor for GVR. Also, it should be clarified whether rhTSH leads to a better nodule reduction or if the additional effect is mainly related to increased destruction of the 'normal' paranodular tissue. Finally, the risk of goitre recurrence after ^{131}I therapy with and without rhTSH should be investigated.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this scientific work.

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