Preparation with rhTSH for $^{131}$I remnant ablation is associated with a longer half-life of $^{131}$I in the thyroid remnant while reducing exposure to the rest of the body and the general public.


**SUMMARY**

**BACKGROUND**

Since recombinant human thyrotropin (rhTSH) has been approved for radioactive remnant ablation RRA, several studies have found that patients prepared in this manner receive less whole-body radiation from $^{131}$I, as compared with patients prepared by thyroid hormone withdrawal (THW). The aim of this prospective study was to compare the biokinetics of $^{131}$I in the thyroid remnant, dosimetry, and radiation protection after preparation with rhTSH as compared with THW.

**METHODS**

This is a prospective, randomized controlled, open label single-center study. The rhTSH group was treated with $^{131}$I after two injections of rhTSH, and the hypothyroid control group was prepared by THW, thus treating this group in a hypothyroid state. Patients included in the study were at least 18 years of age. All had newly diagnosed well-differentiated papillary (PTC) or follicular thyroid cancer (FTC) treated with total thyroidectomy in one or two stages. Tumor pTNM staging was done according to the 6th edition AJCC/UICC classification. All patient tumors were staged as pT1 to T3, N0 to N1, and M0 tumors, and all patients had fewer than 5 lymph nodes and none had extracapsular tumor invasion. A 15-day iodine restriction was prescribed for all patients before they were treated with 100 mCi (3.7 MBq) which was administered 6 weeks after surgery to the hypothyroid group and 2 to 3 weeks after surgery to the rhTSH group, after which all were hospitalized for 2 days.

Evaluations were performed before the first rhTSH injection (day 2) in the rhTSH group, and before $^{131}$I therapy (day 0) and at 24 hours (day 1), and 48 hours (day 2), and on day 6 after RRA in both groups. Levothyroxine (L-4) at 2µg/Kg was restarted on day 1, and a whole body scan was performed on days 2 and 6.

Dose rate (DR) measurements were performed at day 1(DR$_{d1}$) day 2, (DR$_{d2}$) and day 6 (DR$_{d6}$). Urine samples were obtained from day 0 after $^{131}$I to day 2 to evaluate radiation exposure to the bladder. Thyroglobulin (Tg) was assessed at day 0 and day 6 by a Tg assay with a lower detection limit of 0.2 µg/L, and was assessed at days 0, 2 and 6. The initial work-up also included evaluation of renal function and urinary iodine excretion. A Tg performed on day 5 above 0.8 µg/L was considered positive. Anti-Tg antibodies (TgAb) less than 20 IU/ml comprised a negative result. In patients with residual TgAb, Tg was determined by recovery tests (reference range 70 to 13% of recovery).

**Evaluation of iodine biokinetics in thyroid remnants**

Three parameters were determined: thyroid remnant uptake, effective half-time in the remnant, and the remnant residence time. Remnant uptake was determined from images obtained at days 2 and 6. A mono-exponential decay function was used to fit the uptake values. Individual dose estimate calculations were performed using residence times obtained from the whole body, thyroid remnant, stomach, large intestine, and bladder.

**RESULTS**

The study group comprised 43 patients in the rhTSH group and 45 in the hypothyroid group. Of the two groups, 79 patients were eligible for the evaluation of iodine biokinetics, residence time in target organs, and total-body effective half-life. Data from 9 patients were incomplete for a full evaluation.

**Dosimetric analysis**

Dosimetric analysis was performed in 61 patients in whom urinary samples were obtained. In the rhTSH group, mean TSH during L-4 therapy was 1 mIU/L. In the hypothyroid group, mean TSH at the time of RRA was 110 mIU/L. Renal function was higher in the rhTSH group (90.3±20.2 ml/min·1.73 m2, than that in the hypothyroid group (67.6±15.4 ml/min·1.73m2); P = 10-3 (1.73 is an adjustment for a standard body surface).
This difference was related to an increase of patients with moderate transient renal function impairment: The hypothyroid group had an estimated GFR from 30 to 59 ml/min·1.73m² (35.1% vs. 2.8% in the rhTSH group). At the 9-month follow-up GFR value returned to normal in the hypothyroid group. There were no significant differences in age, sex, weight, height, body mass index, and urinary iodine excretion 25.8±14.6 µg/dl in the hypothyroid group versus 23.2 ± 12.6 in the rhTSH group. The ablation rate in the two groups was statistically equivalent.

Iodine biokinetics in remnants and assessment of Tg release (Figure 1)
The values of iodine kinetics in thyroid remnants after rhTSH stimulation and endogenous TSH stimulation were calculated from 79 patients. (Figure1) For iodine biokinetics, three parameters were determined: remnant uptake, effective half-time in the remnant, and the remnant residence time (Figure 1). The effective half-life in thyroid remnant tissue was significantly longer after rhTSH than during hypothyroidism (P = 0.01). The 48-hour $^{131}$I uptake and residence time of $^{131}$I were not statistically significant between the two study groups, although the values were numerically lower in the rhTSH group. (Figure 1)

Dosimetry (Figure 2)
The mean total-body effective half-life was 14.76±2.1 vs. 17.1±2.83 hours in the rhTSH and hypothyroid groups, respectively (P<0.001). Total-body (P < 0.001) and colon (P = 0.037) residence times were shorter in the rhTSH group as compared with the hypothyroid group. Residence time was also shorter in the stomach, but not significantly different in the two study groups. (P = 0.05). Also, for the bladder, residence time was similar between the two study groups (P = 0.29). For patients in the rhTSH group, absorbed doses were lower for total-body (P = 0.005), and other target organs with a statistical significance for the lower intestine (P = 0.011), ovaries (P = 010.5), and bone marrow (P = 0.006) (Figure 2).

Radiation Exposure in $^{131}$I-treated patients
The effective half-life is the time required for deposited radioiodine in tissue divided by 2, from the combined action of physical decay (approximately 8.1 days) and biological disappearance, which is determined by several factors, including renal clearance. To estimate exposure, the effective period after hospital departure was calculated from DRd2 and DRd6.

In this study, exposure was based on a simple model in which only individual effective periods and occupancy factors (OFs) were used as defined by the American Code of Federal Regulations to be the fraction of time that an individual is near the patient. As patients were hospitalized during the initial period, OF was assigned to zero in the first 48 hours after $^{131}$I treatment. Two periods of constraint were defined after hospital: a constraint period including day 3 after hospital departure and an unconstraint period from day to an infinite time. The assumption was that according to the physician’s recommendation, the patient slept in a separate bed.

Assessment of Tg Release
There is a significant relationship between effective half-life and Tg (max peak), $\Delta$ Tg, or $\Delta$Tg to 48-hour uptake ratio. Prior to RRA, the stimulated Tg was not significantly different in the two study groups; however the amplitude of Tg release was significantly higher during hypothyroidism than with rhTSH stimulation. (P = 0.005). Tg release was correlated with radioiodine uptake in the thyroid remnant and the THW group in univariate analysis. Multivariate analysis included gender, study group, age, normalized GFR, 48-hour $^{131}$I uptake, thyroid bed effective half-life and $\Delta$ Tg (Tg day2 to Tg day 6), and remnant half-life was correlated THW group (P = 0.005) and $^{131}$I uptake (P = 0.019).

CONCLUSION
Preparation with rhTSH for $^{131}$I RRA is associated with a longer remnant half-life of $^{131}$I while also reducing exposure to the rest of the body and to the general public who came in contact with patients treated with $^{131}$I.
COMMENTARY

Taieb et al performed an important study that investigated the biokinetics of $^{131}$I in the thyroid remnant, dosimetry, and radiation protection, in patients prepared for $^{131}$I RRA with rhTSH as compared with THW. This is one of several important studies that focus on the effects of whole-body radiation in patients prepared with rhTSH for RRA, which leaves the patient euthyroid, as compared with THW that renders the patient hypothyroid in the process of performing RRA. In these studies, in which patients were treated with 100 mCi, the rates of successful RRA were similar whether patients were prepared with rhTSH or THW. However, the main thrust of these studies concern the effects of whole-body irradiation that occurs with RRA, particularly when patients are prepared with THW. Similar to the studies of Pacini et al (1), Taieb et al found a trend to shorter remnant $^{131}$I uptake in patients treated with rhTSH as compared with those prepared with THW.

Pacini et al (1) first demonstrated that patients treated with rhTSH in preparation for RRA had a statistically significant, one third lower radiation dose to the blood, as compared with that among patients who were rendered hypothyroid with THW. This was an especially important finding, considering the adverse whole-body effects of $^{131}$I that may occur with $^{131}$I therapy (2).

In 2006, Hänscheid et al (3) performed a study of the effectiveness of remnant ablation with 100 mCi of $^{131}$I in patients with differentiated thyroid cancer after stimulation with rhTSH or THW. In this study, 63 patients were randomized after thyroidection to either the THW or rhTSH. Starting 48 hours after $^{131}$I administration, scintigraphic neck images were acquired to assess the biokinetics of $^{131}$I in thyroid RRA. The main finding was that the effective $^{131}$I half-time in the remnant thyroid tissue was significantly longer after rhTSH than THW (67.6±48.8 vs. 48.0±52.6 hours, respectively; $P = 0.01$, whereas the observed differences of the mean 48-hour $^{131}$I uptakes, (0.5%±0.7% vs. 0.9% ±1.0% after THW; $P = 0.1$), and residence times of 0.9 ±1.3 vs. 1.4±1.5 hours after THW; $P = 0.1$) between the rhTSH and THW groups were not statistically significant. However the study found that the absorbed radiation dose to the blood was significantly lower ($P <0.0001$) after the administration of rhTSH (mean, 0.109±0.028 mGy/MBq; maximum, 0.18 mGy/MBq) than after THW (mean, 0.167±0.061 mGy/MBq; maximum, 0.35 mGy/MBq), indicating that higher activities of $^{131}$I might be safely administered after exogenous stimulation with rhTSH. The study thus found an influence of the residence time of $^{131}$I in the blood on the fractional uptake of $^{131}$I into thyroid remnant. The authors proposed a novel regimen in which therapeutic $^{131}$I activities to be administered may be determined from the individual specific blood dose.

As $^{131}$I treatment of patients with thyroid cancer may induce adverse side effects, particularly cancer and leukemia (2), Remy et al performed an important study in 2008 on the basis that there were still some uncertainties concerning the parameters that might influence the effective half-life of $^{131}$I and the absorbed doses by organs other than the thyroid. In this study, whole-body $^{131}$I retention was measured in 254 patients, and repeated quantitative whole-body scans and measurements of urinary excretion of $^{131}$I were performed on 30 of these patients. The main finding was that the mean effective half-life (10.5 hours) was shorter by 31%—with little difference between patients—of the 36 patients who received rhTSH as compared with the 218 patients who underwent thyroid hormone withdrawal (15.7 hours). The residence times in the stomach and in the rest of the body were significantly shorter in patients who received rhTSH as compared with patients who underwent THW; however, the residence times were similar in the colon and bladder. The authors concluded that patients who undergo THW, the longer mean effective half-life is mainly due to delayed renal excretion of $^{131}$I and results in dose estimates higher than the data in report 53 of the International Commission on Radiological Protection, which were obtained from healthy, euthyroid subjects.

The study by Taieb et al, which is focused on $^{131}$I biokinetics and dosimetric and radioprotection issues in thyroid cancer patients, is the largest prospective study to compare rhTSH and THW for remnant ablation. As reported in previous studies, Taieb et al found a statistically prolonged remnant effective half-time in patients treated with rhTSH as compared with those who had RRA after preparation with THW. The study found that the residence time, which is dependent on both fractional thyroid uptake and half-time, was not statistically different between the rhTSH and THW groups, but was lower after Taieb et al suggests that the study by Borget et al (4) illustrates that this finding might be used to shorten hospital stay and reduce costs. In the Taieb study, all the patients were discharged 48 hours after $^{131}$I therapy. Using a validated model, the authors found that without any recommendations, radiation exposure in patients prepared with THW could exceed the limits recommended for public safety (1 mSv/year) by the International Commission on Radiological Protection. Taieb et al also found that 2 days of hospitalization and 3 days of confinement to the home is consistent with current legislation and is applicable to most patients treated with 100 mCi of $^{131}$I. The authors point out that the main limitation of dose exposure in this study is that it was not directly measured by dosimeters on contact persons, which is more reliable, although highly dependent upon patient and contact compliance. The main conclusion of this study is that when 100 mCi of $^{131}$I is given, the iodine biokinetics, dosimetry, and radiation protection favor rhTSH rather than THW. Although the $^{131}$I residence times were not significantly different in rhTSH and THW preparation, the remnant effective half-life was significantly longer with rhTSH. Lastly, total-body and organ dosimetry also favored rhTSH rather than THW.

This is an important study that clinicians should consider when performing RRA.

There is, however one major point important point: A number of prospective randomized studies now show that lower $^{131}$I activities, in the range of 30 to 50 mCi (1110 to 1850 MBq), are as effective as 100 mCi for RRA, which can be performed after rhTSH preparation.(5-9)

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References


7. Pilli T, Brianzoni E, Capoccetti F et al. A comparison of 1850 MBq (50 mCi) and 3700 MBq (100 mCi) 131-iodine administered doses for recombinant TSH-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. J Clin Endocrinol Metab 2007;92:3542-6.
