Title: Recombinant human TSH-assisted radioactive iodine remnant ablation achieves short-term clinical recurrence rates similar to those of traditional thyroid hormone withdrawal.

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SUMMARY

Background: Recent studies have confirmed that radioactive iodine therapy after recombinant human TSH (rhTSH) stimulation effectively ablates the normal thyroid remnant. However, no published study has determined the effectiveness of rhTSH preparations on the important endpoint of disease recurrence.

Methods: Disease recurrence was retrospectively assessed a median of 2.5 years after radioiodine remnant ablation (RRA) in 394 consecutive thyroid cancer patients: 93% papillary; 71% female; 47 ± 15 yrs old; median RI$^{131}$ dose of 4 MBq [108 milliCi].

Results:

1. Similar rates of clinically evident disease recurrence (4% with rhTSH versus 7% with thyroid hormone withdrawal [THW], P=NS) and residual thyroid bed uptake without other evidence of persistent disease (4% with rhTSH versus 7% with THW, P=NS) were seen in the 320 patients undergoing rhTSH-assisted RRA and the 74 patients prepared for RRA by THW.

2. When the definition of no clinical evidence disease included a suppressed Tg level of < 1 ng/ml, and a stimulated Tg level of < 2 ng/ml, rhTSH-assisted RRA was associated with significantly higher rates of no clinical evidence of disease (74% with rhTSH versus 55% with THW; P=0.02) and significantly lower rates of persistent disease (19% with rhTSH versus 32% with THW; P=0.02) than was RRA after THW.

3. Patients selected for rhTSH were older (48 ± 15 versus 44 ± 15; P=0.03) and received a slightly higher administered activity of RI$^{131}$ (median 4.033 MBq [109 milliCi] versus 3.811 MBq [103 milliCi]; P=0.01) but did not differ with respect to sex, histology, disease stage, or mean time to recurrence (19 ± 9 months for rhTSH versus 20 ± 16 for THW).

Conclusions: rhTSH-assisted RRA is associated with rates of clinically evident disease recurrence and persistent uptake in the thyroid bed that are similar to those for traditional THW.

COMMENT

After total thyroidectomy for differentiated thyroid carcinoma (DTC), radioiodine (RI$^{131}$) is given with the following objectives: a) ablate normal thyroid remnants; b) destroy possible residual disease (microscopic foci of tumor); c) decrease the risk of clinical tumor recurrence; and d) facilitate long-term follow-up testing by periodic Tg measurements under l-T4 replacement therapy. The RI$^{131}$ doses vary, but postsurgical administration of 75-150 milliCi RI$^{131}$ results in successful ablation of thyroid remnants in over 85% of patients. Traditionally, remnant ablation is carried out after l-T4 withdrawal (or withholding the initiation of l-T4 administration after surgery for > 4 weeks) in order to increase
endogenous TSH (to ≥ 30 mU/L) production and optimize RI^{131} uptake & retention in thyrocytes. The introduction of rhTSH (since about 10 years now) has profoundly modified our diagnostic strategies for the follow-up of patients with DTC. More recently, rhTSH has been approved as an adjunct, not only for diagnostic purposes, but also for radioiodine remnant ablation (RRA). The present important article is the first study to have assessed in a large series of patients the efficacy of RRA after rhTSH preparation. To this aim, the authors have compared the outcome in two groups of patients, using either rhTSH or thyroid hormone withdrawal (THW) for preparation to RI^{131} administration. This study presents the results obtained in a large and impressive series of consecutive patients with DTC, followed at Sloan Kettering between 1997 and 2005. Obviously, the study was not randomized and the 2 groups differed in size: 320/394 patients (i.e. >80%) using rhTSH preparation compared to 72/394 patients using the traditional THW preparation. The choice of RRA preparation was a clinical decision made by the patient and the treating physician. The administered RI^{131} activity was, in general, 75-100 milliCi for intrathyroidal papillary carcinomas, 100-150 milliCi if cervical nodes were involved, and more than 150 milliCi if disease was considered locally aggressive or known metastases present. The results demonstrated clearly that there was no significant difference in short-term recurrence rates after RRA with either method of preparation. Furthermore, when no clinical evidence of disease (NCED) was defined as a suppressed serum Tg of less than 2 ng/ml and a rhTSH-stimulated serum Tg of less than 2 ng/ml 2.5 years after initial ablation, the results showed that rhTSH-assisted RRA was superior to RRA after THW.

Limitations of the study: a) non randomized; b) retrospective review of medical charts; c) the two groups are not strictly comparable (although it seems difficult to have done better); d) a relatively short follow-up period and, hence, one cannot rule out differences in later recurrences; and finally e) potential bias of selection of the patients toward RRA after withdrawal for those considered to be more ‘at risk’.

Another comment concerns the patients with a ‘bad’ clinical outcome, namely those with clinical recurrence (3.8% & 6.8%, respectively for rhTSH versus THW), persistent disease (15.9% & 24.3%), and RI^{131} uptake in the thyroid bed at follow-up (4.1% & 6.8%). These percentages were obtained using a suppressed serum Tg of less than 2 ng/ml and a rhTSH-stimulated serum Tg of less than 10 ng/ml to define NCED, thus indicating that in the non NCED patients (i.e. those with a bad prognosis), the later outcome is still unknown and much longer follow-up studies are required to assess possible outcome differences that might eventually be linked to the decision of using rhTSH or THW preparation for radioiodine remnant ablation. This being said, if it is shown that RRA using rhTSH is indeed as effective as THW, this would considerably facilitate the post-surgical management of patients with DTC. Patients could receive l-T4 replacement therapy immediately after the initial surgery and the work up for ablation carried out a few months later, hence avoiding the additional stress of becoming hypothyroid after a tumor has been discovered and removed.

(Daniel Glinoer, M.D.; Ph.D.)

See Figure and Table below
FIGURE 2. Kaplan–Meier curve showing time to recurrence in both rhTSH cohort and THW cohort. Longer time of follow-up for THW did not result in higher recurrence rates, because most recurrences in both groups were detected in first 24–36 mo after ablation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NCED</th>
<th>Clinical recurrence</th>
<th>Persistent disease</th>
<th>TB uptake Only</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>THW (n = 74)</td>
<td>62.2% (46)</td>
<td>6.6% (5)</td>
<td>24.3% (18)</td>
<td>6.8% (5)</td>
<td>0.10</td>
</tr>
<tr>
<td>rhTSH (n = 320)</td>
<td>76.3% (244)</td>
<td>3.8% (12)</td>
<td>15.9% (51)</td>
<td>4.1% (13)</td>
<td></td>
</tr>
<tr>
<td>Total (n = 394)</td>
<td>73.6% (290)</td>
<td>4.3% (17)</td>
<td>17.5% (69)</td>
<td>4.6% (18)</td>
<td></td>
</tr>
</tbody>
</table>

TB = thyroid bed.