Doses of recombinant human TSH less than 0.3 mg are likely to cause fewer adverse events when given to patients with nontoxic multinodular goiter

Fast S, Nielsen VE, Bonnema SJ, Hegedüs L. Dose-dependent acute effects of recombinant human TSH (rhTSH) on thyroid size and function: comparison of 0.1, 0.3 and 0.9 mg of rhTSH. Clin Endocrinol (Oxf) 2010;72:411-6.

SUMMARY

BACKGROUND

Recombinant human thyrotropin α (rhTSH) is used to increase the effect of radioiodine (^{131}I) therapy for nontoxic multinodular goiter. However, acute thyroid swelling and the induction of hyperthyroidism has been reported with this use of the drug. The object of this study was to determine the effects of various doses of rhTSH on thyroid size and function.

METHODS

Nine healthy men with a mean age of 33 years (range, 22 to 50) volunteered for this study; none of them took drugs known to affect thyroid size or function, and all of them had normal thyroid function without antithyroglobulin antibodies (TgAb), thyroid peroxidase (TPOAb), or TSH receptor antibodies (TSHRAb). The study compared the effects of placebo with 0.01, 0.03, and 0.9 mg of rhTSH in a paired design including four consecutive study rounds. The main outcome measurements were evaluated at baseline; 24, 48, and 96 hours; and 7 and 28 days after injection of rhTSH or placebo. During this time, thyroid volume (TV) was estimated by ultrasound and thyroid function was determined by measurements of serum (TS), free triiodothyronine (FT_3), free thyroxine (FT_4), and serum thyroglobulin (Tg). Thyroid size (range, 10 to 22 ml) and morphology was normal in all volunteers, and all had normal neck ultrasound examinations.

RESULTS

The Effects of rhTSH on Thyroid Volume (Figures 1 to 4)

Ultrasound TV did not change significantly from baseline during the 28-day follow-up. In the 0.3-mg-rhTSH round, the mean (±SEM) TV increased by 37±12.3% (P = 0.03) and 45.3±16.1% (P = 0.05) at 24 and 48 hours, respectively. In the 0.9-mg-rhTSH round, the mean TV increased by 23.3±5.8% (P = 0.008) and 35.5±18.4% (P = 0.02) at 24 and 48 hours. On day 7, the mean TV had returned to the baseline level in all study rounds (Figure 1).

The maximum thyroid enlargement in each study subject occurred between day 1 and day 4, with a significant difference among the four study rounds (P = 0.03) (Figure 2). The mean maximum TV increase was not significantly different in the placebo and 0.1-mg-rhTSH groups as compared with baseline (P = 0.12 and 0.08, respectively), and there were no differences between these two series (P = 0.40). In contrast, the maximum TV increased by 52.7±14.7% (P = 0.01), and 41.5±17.4% (P = 0.008) in the 0.3- and 0.9-mg-rhTSH rounds, respectively (Figure 3). The maximum TV increases after 0.3 and 0.9 mg rhTSH were comparable (P = 0.02 and P = 0.03). However, there was considerable interindividual variation in the maximum relative TV increase from baseline variation, indicating that some of the study subjects were more prone to thyroid enlargement than others (Figure 4). The TV in one of the study subjects increased from 21 to 90 ml 30 hours after rhTSH, which promptly responded to a nonsteroidal antiinflammatory drug.

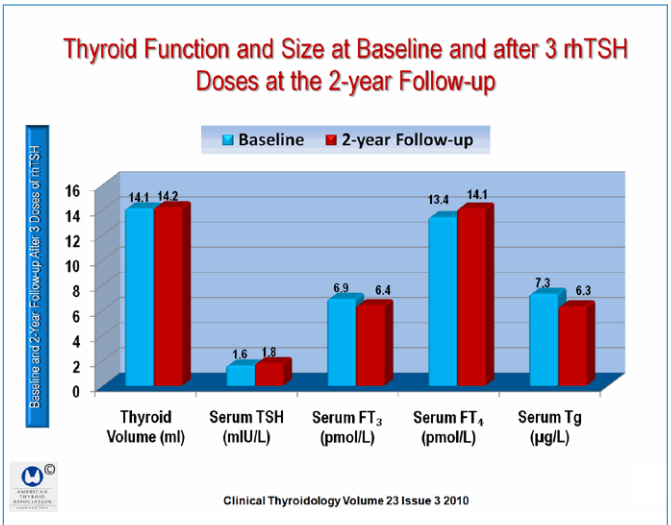

Figure 1. This figure shows differences in the baseline thyroid volume, and serum TSH, FT_3, FT_4, and serum thyroglobulin levels 2 years after three doses of rhTSH. *P = 0.093, †P = 0.77, ‡P = 0.9, ¶P = 0.21, and §P = 0.53, comparing thyroid volume change at baseline with thyroid volume at 2-year follow-up.

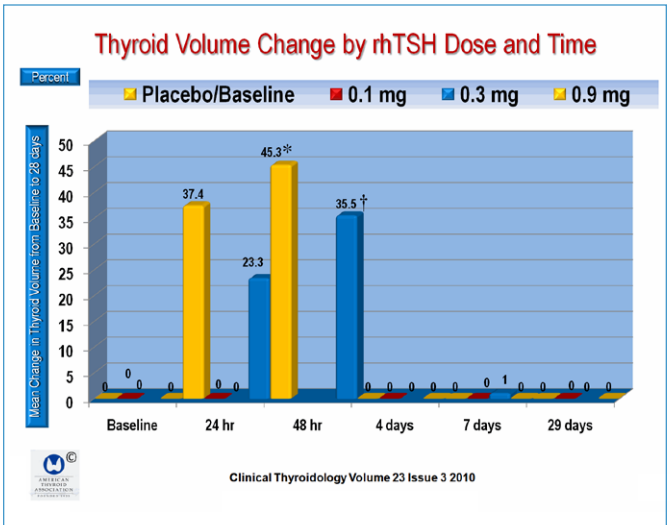

Figure 2. This figure shows the change in thyroid volume size after placebo and after 0.1, 0.3 and 0.9 mg of rhTSH and placebo. *P = 0.05, comparing changes after 0.3 mg rhTSH at 24 hours with those at 48 hours. †P = 0.02, comparing changes after 0.9 mg rhTSH at 24 and 48 hours.

Thyroid Function and Serum Thyroglobulin Response (Figure 5)

Serum TSH, FT_4, FT_3, and Tg did not change significantly from baseline after placebo injection (Figure 5). However, the 24-hour serum TSH showed a positive dose response in all four rounds (P<0.001) (Figure 5). After 24 hours, the serum TSH level showed a positive dose response that was found in all four rounds (P<0.001). The mean (±SD) TSH level was higher following 0.03 mg rhTSH (26.5±7.9 mIU/L) as compared with the response to 0.1 mg rhTSH (7.4±2.1 mIU/L) (P = 0.02); it was higher following 0.9 mg rhTSH (75.2±28.4 mIU/L), as compared with 0.3 mg rhTSH (P = 0.008).

There was an increased response in FT_3 (Figure 7) and FT_4 (Figure 8), and Tg also showed a positive dose response that peaked at 24 to 48 hours for all three variables (Figure 6). There was a highly significant difference in the area under the curve (AUC) from day 0 to day 7 among the four rhTSH placebo doses, which gradually increased with higher doses of rhTSH. The AUC was greater with 0.3 mg as compared with 0.1 mg (P = 0.02) and with 0.9 mg as compared with 0.3 mg (P = 0.02) (Figure 6). After 0.1 mg rhTSH, the AUC for FT_3 and Tg was not statistically different from that for placebo (P = 0.06 and 0.24, respectively), but the AUC for FT_4 was significantly greater than that for placebo (P = 0.02). With each rhTSH dose, the Tg response showed considerable individual variation (Figure 6).

The individual who had the greatest thyroid enlargement after 0.9 mg rhTSH had the highest Tg concentration (1560 µg/L at 48 hours, vs. 13.20 µg/L, which was the highest level among the other eight subjects in the study round. After 0.03 mg

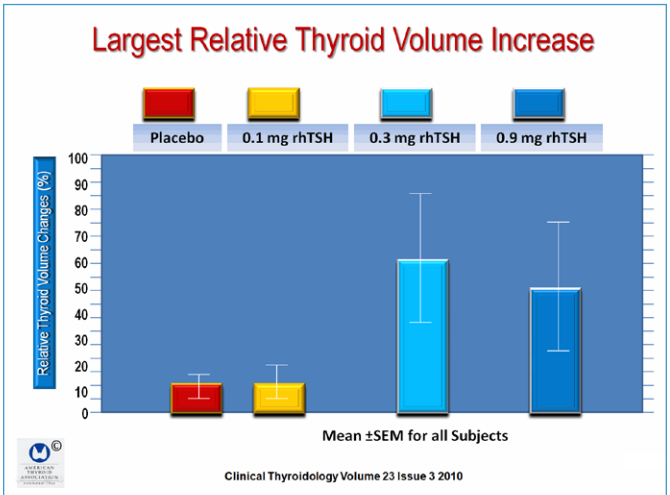

Figure 3. This figure shows the largest relative thyroid volume increases in all subjects, after receiving placebo and 0.1, 0.3, and 0.9 mg of rhTSH. This figure and Figure 4 are drawn from the data in Figure 2 of Fast et al.

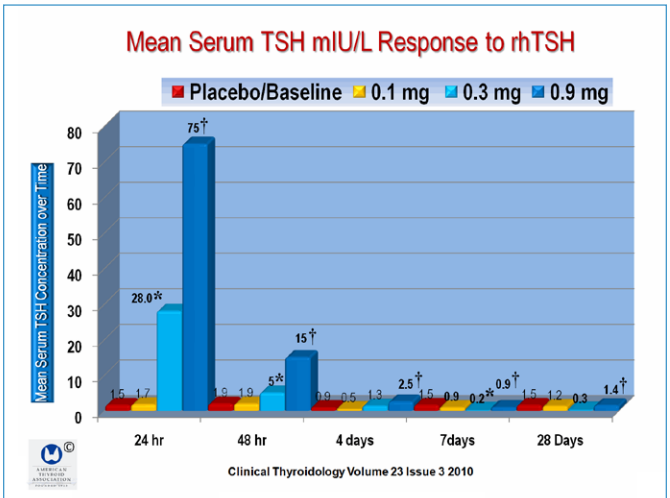

Figure 5. This figure shows the mean serum TSH (mIU/L) concentrations after placebo and 0.1, 0.3, and 0.9 mg of rhTSH. The mean serum TSH was higher following 0.3 mg as compared with 0.1 mg of rhTSH. *P<0.001 comparing all four rounds of placebo and 0.1, 0.3, and 0.9 mg rhTSH. *P<0.001 (the bold figures here and elsewhere are statistically significant changes).

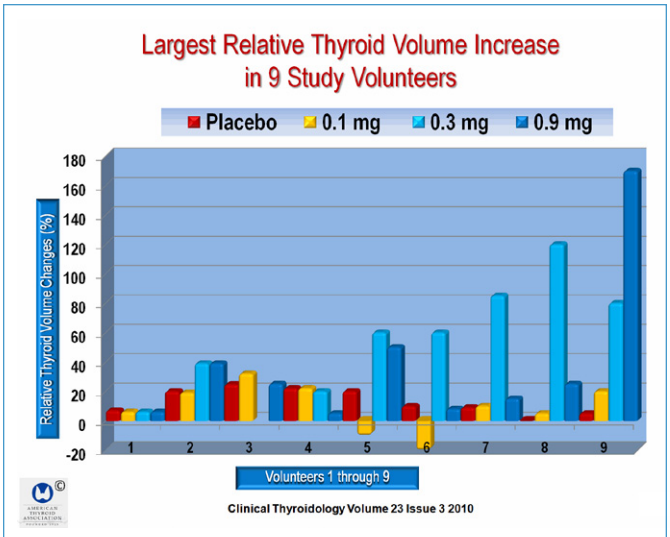

Figure 4. This figure shows the largest relative thyroid volume increase in the 9 study volunteers, which is significantly different from that among the 9 volunteers after injections with placebo and 0.1, 0.3, and 0.9 rhTSH.

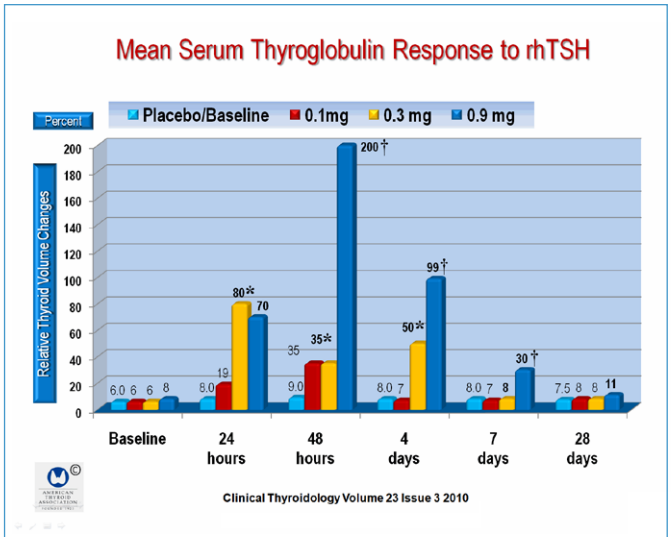

Figure 6. This figure shows the mean serum Tg response to rhTSH. The increase was greater following 0.3 mg rhTSH as compared with 0.1 mg (*P = 0.02) and even higher after 0.9 mg as compared with 0.3 mg (†P = 0.002).

rhTSH, the same individual again reached the highest Tg level (470 µg/L at 24 hours); the second highest level was 58 µg/L at 4 days in the same individual as in the 0.9-mg–rhTSH round

ADVERSE EFFECTS

In addition to the subject who had remarkable thyroid swelling, rhTSH caused various effects related to thyroid hyperfunction, including tachycardia, increased appetite, restlessness, perspiration, headache, nausea, and myalgia or visible thyroid enlargement, thyroid tenderness, or pain. At least one of these symptoms or signs appeared in seven individuals, as compared with five individuals after 0.3 mg rhTSH. Symptoms with or without signs were of short duration and self-limiting and occurred between 4 and 48 hours after rhTSH injection. Only one subject reported restlessness after 0.01 mg rhTSH between 24 and 48 hours after administration. At the end of the 2-year study period, thyroid function and size were unchanged as compared with those at study entry. Neither TSHRAb nor TPOAb developed in any of the subjects.

CONCLUSION

Doses of recombinant human TSH less than 0.1 mg are likely to cause fewer adverse events when given to patients with goiter. The symptoms are usually of short duration and self-limited.

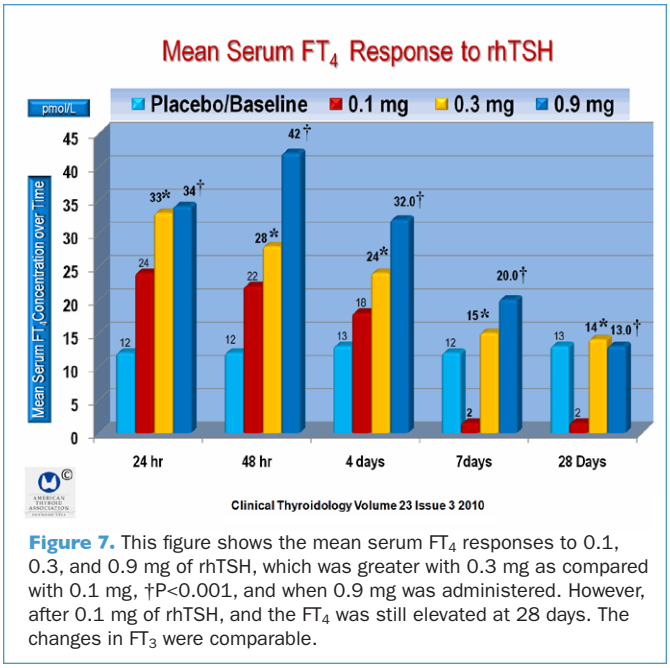

Figure 7. This figure shows the mean serum FT_4 responses to 0.1, 0.3, and 0.9 mg of rhTSH, which was greater with 0.3 mg as compared with 0.1 mg, †P<0.001, and when 0.9 mg was administered. However, after 0.1 mg of rhTSH, and the FT_4 was still elevated at 28 days. The changes in FT_3 were comparable.

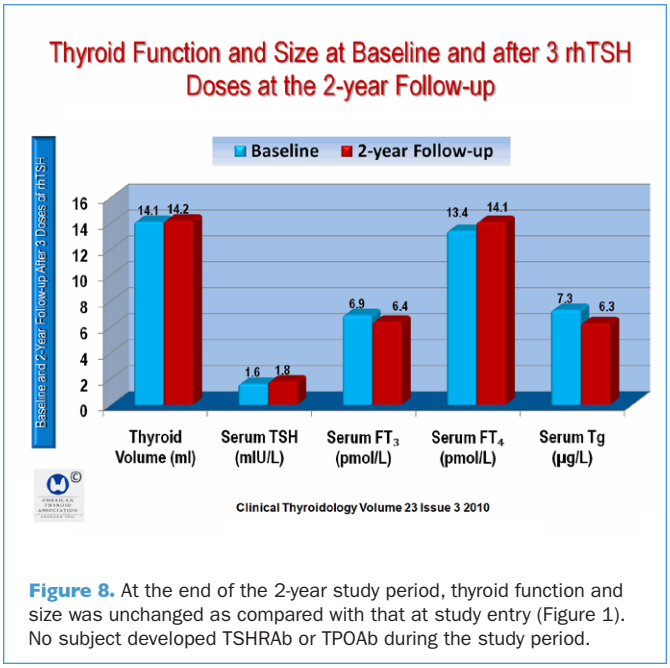

Figure 8. At the end of the 2-year study period, thyroid function and size was unchanged as compared with that at study entry (Figure 1). No subject developed TSHRAb or TPOAb during the study period.

COMMENTARY

This study demonstrates that acute thyroid swelling was induced by rhTSH, which was partly dose- dependent. The authors concluded that the swelling was most likely triggered above a certain threshold that varies among individuals. Thyroid enlargement of 35 to 45% was noted when either 0.3 or 0.9 mg of rhTSH was administered, which was not observed after 0.1 mg of rhTSH. Serum rhTSH-stimulated Tg concentrations were also dose-dependent and varied considerably among study subjects. The peak serum Tg level correlated with the extent of thyroid enlargement, and the same individuals had an increase in both Tg and thyroid volume, suggesting individual differences in sensitivity to rhTSH. The authors offer the caveat that the extent to which these findings can be extrapolated to patients with multinodular goiter (MNG) is not clear.

Over the past decade, the therapeutic use of rhTSH-stimulated radioiodine (^{131}I) has been carefully explored in patients with benign nontoxic MNG. In 2000 to 2004, several studies (1-4) investigating the doses of rhTSH for this indication used approximately 0.01 to 0.9 mg of rhTSH. Still, a single low dose of rhTSH was found to significantly enhance thyroid ^{131}I uptake in patients with MNG. Nevertheless, rhTSH doses of 0.01 mg increased the serum TSH about threefold, and serum T_3 and T_4 concentrations likewise increased significantly. A 2004 study (5) of the long-term effects of ^{131}I given at a median activity of approximately 5 to 15mCi found after a 36-month follow-up that goiter volume was reduced significantly, and after 3 years, goiter was no longer present in 76% of the patients. Nonetheless, some patients had symptoms of hyperthyroidism with or without cervical compression after rhTSH therapy, as opposed to only one patient during placebo treatment (5).

The authors of the present study have made a number of important contributions concerning the use of rhTSH-stimulated ^{131}I for the nonsurgical treatment of benign nontoxic MNG. In 2004, Nielson and associates (6) first studied the effect of rhTSH on thyroid function and ultrasonographically determined thyroid volume in healthy male volunteers. The use of 0.9 mg of rhTSH was found to profoundly stimulate thyroid size and function 1 to 14 days after the rhTSH injection. Serum TSH increased from 2.03 mIU/L (range, 0.99 to 3.07) to more than 200 mIU/L (range, 78.9 to >200), which rapidly declined

4 hours later. Mean serum FT_4 and FT_3 peaked at 48 hours, with levels approximately 30% above baseline (P<0.001). The conclusion was that 0.9 mg of rhTSH may result in a profound stimulation, not only of thyroid function but also of thyroid size and that further dose-response studies are needed to clarify the potential hazards of this therapeutic regimen.

In 2006, the authors of the article under discussion (7) found that injection of 0.3 mg of rhTSH produced goiter enlargement in up to 24% of patients with MNG, raising the concern that this might lead to significant cervical compression when using rhTSH to augment ^{131}I uptake in patients with MNG. The authors concluded that the use of lower rhTSH doses needs to be explored and that further dose-response studies are needed to clarify the potential hazards of this therapy before its routine use for MNG.

In 2009, Fast and associates (8) pointed out that conventional ^{131}I therapy has been used for two decades as an effective and safe alternative to surgery in the treatment of symptomatic nontoxic MNG. They further call attention to the fact that since much higher ^{131}I activities are used when treating nontoxic rather than toxic MNG, there has been reluctance to use this treatment method in many countries, and the ^{131}I uptake in a nontoxic MNG is low, making ^{131}I therapy less feasible. The authors opined that another important matter is the negative correlation between the initial goiter size and goiter volume reduction. With its ability to more than double the thyroidal ^{131}I uptake, rhTSH increases the absorbed radiation dose and thus enhances the reduction of goiter volume by 35 to 56% at the expense of up to a fivefold higher rate of permanent hypothyroidism. The authors suggest that another option is to reduce the amount of ^{131}I with rhTSH preparation, which induces a significant increase in ^{131}I uptake. Extrathyroidal irradiation thus can be reduced without compromising the efficacy of rhTSH-stimulated ^{131}I therapy. They concluded that while still under study, rhTSH-augmented ^{131}I therapy for nontoxic MNG may considerably alter the nonsurgical treatment of benign nontoxic MNG.

The current study by Fast and associates is the next phase in the development of this therapy for patients with benign nontoxic MNG. This is the first study in which the same individuals were given rhTSH repeatedly. Also, in no subjects did the thyroid gland have signs of damage affecting thyroid size, morphology, or function. They acknowledge that theoretically, an acute thyroiditis-like alteration due to rhTSH stimulation might elicit the development of thyroid autoantibodies. Yet, except for a single subject in whom a low titer of TgAb developed on day 28 after 0.3 mg of rhTSH, this otherwise did not happen in this study. The authors suggest that large-scale confirmation trials are needed to fully support this study. Lastly, the authors suggest that the optimal dose of rhTSH in the context of ^{131}I therapy for nontoxic MNG remains to be established.

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