Recombinant TSH (Thyrogen®) for ablation of thyroid remnant tissue post-thyroidectomy for thyroid cancer

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Summary

- 131I ablation of remnant thyroid tissue following a total or near-total thyroidectomy for thyroid cancer is carried out in the hypothyroid state to increase endogenous TSH release and thus promote uptake of radiodine into the remaining thyroid tissue. Usually thyroid replacement therapy has to be withheld from patients for 3 to 6 weeks before ablation in order to achieve an adequate TSH level. This can have a profound negative effect on the patient’s quality of life.

- Recombinant TSH (rhTSH, Thyrogen®) has been developed as a source of exogenous TSH and allows patients to remain on thyroid hormone replacement therapy whilst promoting radiiodine uptake and thyroglobulin production by thyroid cells. It is licensed for use in pre-therapeutic stimulation in low risk post-thyroidectomy patients maintained on hormone suppression therapy for the ablation of thyroid remnant tissue (in combination) with 131I.

- Data from a RCT (Pacini et al) showed comparable thyroid remnant ablation rates in patients prepared with rhTSH whilst on thyroxine (euthyroid group) and those in whom thyroid hormone had been withheld, but the euthyroid group was able to sustain a better quality of life and received less radiation exposure to the blood. In this study, 33 patients were randomised to the euthyroid group (received rhTSH) and 30 to the hypothyroid (control) group, who did not receive thyroid replacement therapy postoperatively. All patients with evaluable results in both groups were successfully ablated and based on criterion of no visible uptake alone, 24 of 32 euthyroid (75%) and 24 of 28 hypothyroid patients (86%) were successfully ablated (p = 0.3). Fractional uptake of radiiodine 48 hours after administration of 131I tended to be lower in the euthyroid group (p = NS) and the dose to the blood was also lower in this group (p < 0.0001). The euthyroid group improved in seven of eight physical and mental health domains between baseline and week 4 on the SF-36 scale whereas there was a decrease in quality of life in seven of eight SFF-36 domains in the hypothyroid group. Billewicz scores (degree of clinical hypothyroidism) were higher in the hypothyroid group compared with the euthyroid group at week 4 (p < 0.0001); the most common complaints in the hypothyroid group compared with the euthyroid group were cold intolerance (50% vs. 21%), weight increase (60% vs. 21%), constipation (43% vs. 3%), slow movements (50% vs. 12%), cold skin (47% vs. 12%) and periorbital puffiness (50% vs. 0%). However it is not known if there is a difference in long term outcomes between the two groups, particularly disease recurrence.

- A French prospective randomised open label study has also demonstrated that rhTSH preserves the quality of life of patients undergoing radioiodine remnant ablation (RRA).

- A retrospective analysis of patients followed up a median of 2.9 years after RRA found that rhTSH is associated with rates of persistent disease and clinically evident recurrence that are similar to those for traditional THW.

- Guidance from the Royal College of Physicians and the British Thyroid Association describe the following situations where rhTSH is the only possible or safe option for diagnostic purposes, ablation or therapy: hypopituitarism, functional metastases causing suppression of serum TSH, severe ischaemic heart disease, previous history of psychiatric disturbance precipitated by hypothyroidism, and advanced disease/frailty.

- According to the findings of a German cost effectiveness study which used data from the RCT (Pacini et al), the additional benefits of rhTSH (0.0495 QALY) are obtained with an incremental societal cost of 47 Euros, equating to an incremental cost per QALY of 958 Euros. This, the authors conclude, represents good value for money with the benefits to patient and society obtained at modest net cost. The additional costs of purchasing and administering rhTSH were largely offset by the ability to discharge the patient from the radio-protective unit earlier and more rapid return to work.

- Cost of 900 mcg vial Thyrogen is £232.50; cost of treatment (2 doses) for ablation is £465.
Recombinant TSH (rhTSH, Thyrogen®) has been developed as a source of exogenous TSH and allows patients to remain on thyroid hormone replacement therapy whilst promoting radiiodine uptake and thyroglobulin production by thyroid cells. It is licensed for use in post-thyroidectomy patients maintained on hormone suppression therapy for:

1. Pre-therapeutic stimulation in low risk patients for the ablation of thyroid remnant tissue (in combination) with 3.7 GBq 131I.
2. Detection of thyroid remnants and well-differentiated thyroid cancer, along with serum thyroglobulin testing.

The recommended dose regimen is two doses of 0.9 mg administered at a 24-hour interval by intramuscular injection, with the second dose given 24 hours before radioiodine imaging or ablation.

Guidance from the Royal College of Physicians and the British Thyroid Association describe certain situations where rhTSH is the only possible or safe option for diagnostic purposes, ablation or therapy:

- Hypopituitarism
- Functional metastases causing suppression of serum TSH
- Severe ischaemic heart disease
- Previous history of psychiatric disturbance precipitated by hypothyroidism
- Advanced disease/frailty.

The guidance also advises caution when rhTSH is used where there is a known or suspected tumour close to the central nervous system due to the risk of inducing swelling; steroid cover is recommended in such cases. Furthermore, rhTSH is known to cause a transient but significant rise in serum thyroid hormone concentrations if functioning thyroid tissue is present. Therefore, caution should be exercised in patients with large thyroid remnants.

Epidemiology

Thyroid cancer is the most common malignant endocrine tumour, but represents only about 1% of all malignancies; its incidence appears to be increasing slowly. Between 1971 and 1995, the annual UK incidence was reported at 2.3 per 100,000 women and 0.9 per 100,000 men, with approximately 900 new cases and 250 deaths recorded in England and Wales due to thyroid cancer every year. In 2001, data from Cancer Research UK showed 1200 new cases in England and Wales, with a reported annual incidence for the UK of 3.5 per 100,000 women and 1.3 per 100,000 men.

Evidence

Reports of ablation therapy under rhTSH stimulation have been published in the literature as clinical trials, case series and individual case reports. Two prospective studies have compared ablation success rates for patients given rhTSH and those who had thyroid hormone therapy withheld or discontinued.

Pacini et al conducted a randomised, controlled study to ascertain if preparation of patients with rhTSH whilst on thyroxine results in a comparable rate (within 20%) of successful ablation compared to withholding thyroid hormone, using a fixed dose of 131I (3.7 GBq). Successful ablation was defined as no visible uptake or if visible, less than 0.1% on a whole body radioiodine scan 8 months after radiiodine therapy. Within 14 days of thyroidectomy, patients were randomised to the euthyroid group (n=33) receiving rhTSH (0.9mg by IM injection on 2 consecutive days followed by 131I a day later) or to the hypothyroid group (n=30) who did not receive thyroid replacement therapy postoperatively. All patients with evaluable results in both groups were successfully ablated; based on criterion of no visible uptake alone, 24 of 32 euthyroid (75%) and 24 of 28 hypothyroid patients (86%) were successfully ablated (p = 0.3). Fractional uptake of radiiodine 48 hours after administration of 131I tended to be lower in the euthyroid group, though the difference was not statistically significant; the dose to the blood was also lower in this group (p < 0.0001). The euthyroid group improved in seven of eight physical and mental health domains between baseline and week 4 on the SF-36 scale whereas there was a decrease in QoL in seven of eight SFF-36 domains in the hypothyroid group. This study reported comparable thyroid remnant ablation rates in the two groups but the euthyroid group was able to sustain a better quality of life and received less radiation exposure to the blood. However it is not known if there is a differ-
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ence in long term outcomes between the two groups, particularly disease recurrence.1

QoL has been further studied in a French prospective randomised controlled, open-label single centre study (n = 74) comparing thyroid cancer patients prepared with either thyroid hormone withdrawal (THW) or rhTSH prior to radioiodine remnant ablation (RRA).7 Thyroxine was initiated in both groups after thyroidectomy, and 1 week later, patients were randomised into two groups: the hypothyroid group, in which patients discontinued thyroxine for 5 weeks and restarted it the day after RRA, or the rhTSH group, in which patients continued thyroxine and received rhTSH one to two weeks later. RRA was carried out in the hypothyroid group 6 weeks postsurgery and in the rhTSH-group 2-3 weeks postsurgery (24h after the second injection of rhTSH). The FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue), which was administered from the early postoperative period to 9 months, assesses QoL in cancer patients. It includes the generic CORE questionnaire Functional Assessment of Cancer Therapy-General (FACT-G) which contains general questions divided into four primary QoL domains: Physical Well-Being, Social/family Well-Being, Emotional Well-Being, and Functional Well-Being, and an additional Fatigue Subscale (FS) directly related to the impact of fatigue on daily activities. Three scores could be derived, with higher scores associated with higher QoL levels: FACT-G total score, FACIT-F total score and FACIT-F Trial Outcome Index (TOI). There was a statistically significant decrease in QoL from baseline to the ablation period in the hypothyroid group, with statistically significant differences in FACIT-F TOI (p< 0.01), FACT-G total score (p= 0.005) and FACIT-F total score (p=0.003). By contrast, QoL was preserved in the rhTSH group. FACIT-TOI changes were only affected by the modality of TSH stimulation performed for RRA. However, from 3 to 9 months, changes in QoL scales and subscales between the two groups were no longer statistically different. In addition, there was no difference in ablation success between the rhTSH and hypothyroidism groups (91.7% and 97.1% respectively). A higher rate of persistent thyroid remnants was observed in the rhTSH arm, although in most cases uptake was < 0.1% and considered of no clinical significance.7

Disease recurrence was examined in a retrospective analysis of consecutive patients with differentiated thyroid cancer (93% papillary, 71% female, mean age 47 6 years) prepared with either THW (n = 74) or rhTSH (n = 320) prior to RRA. Patients were assessed a median of 2.5 years after RRA and similar rates of clinically evident disease recurrence (4% rhTSH vs. 7% THW, p = NS) and residual thyroid bed uptake without other evidence of persistent disease (4% rhTSH vs. 7% THW, p= NS) were reported. When the definition of no clinical evidence of disease included a suppressed thyroglobulin level of < 1 ng/mL and a stimulated thyroglobulin level of <2 ng/mL, rhTSH-assisted RRA was associated with statistically significantly higher rates of no clinical evidence of disease (74% rhTSH vs. 55% THW, p = 0.02) and statistically significantly lower rates of persistent disease (19% rhTSH vs. 32% THW, p = 0.02).8

Adverse events

In the RCT (Pacini et al), eight patients in each group reported mild and transient symptoms, these included nausea, fatigue, taste loss and skeletal pain. Billewicz scores (degree of clinical hypothyroidism) were higher in the hypothyroid group compared with the euthyroid group at week 4 (p < 0.0001); the most common complaints in the hypothyroid group compared with the euthyroid group were cold intolerance (50% vs. 21%), weight increase (60% vs. 21%), constipation (43% vs. 3%), slow movements (50% vs. 12%), cold skin (47% vs. 12%) and periorbital puffiness (50% vs. 0%).1

Economic/cost implications

Cost of 900 mcg vial is £232.50, cost of treatment (= 2 doses) for ablation is £465 (BNF Sept 2008 no 56).

According to the findings of a German cost effectiveness study using data from the RCT, the additional benefits of rhTSH (0.0495 QALY) are obtained with an incremental societal cost of 47 Euros, equating to an incremental cost per QALY of 958 Euros. This, the authors conclude, represents good value for money with the benefits to patient and society obtained at modest net cost. The additional costs of purchasing and administering rhTSH were largely offset by the ability to discharge the patient from the radio-protective unit earlier and more rapid return to work.2

Issues for consideration

Can the additional cost of using rhTSH over THW prior to ablation of thyroid remnant tissue post-thyroidectomy for thyroid cancer be justified based on the current evidence on preservation of quality of life and European cost effectiveness data?
References


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The document reflects the views of LCNDG and may not reflect those of the reviewers

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