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CED-SOS Advice Report #5

Recombinant Humanized Thyroid Stimulating Hormone (rhTSH) Preparation Prior To Radioiodine Ablation in Patients Who Have Undergone Thyroidectomy for Papillary or Follicular Thyroid Cancer

J. Yoo, R. Cosby, and A. Driedger

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: May 14, 2007

This document was developed by the Program in Evidence-based Care in response to a request from the Committee to Evaluate Drugs (CED) for a review of the evidence on this topic. This document was developed by two clinical experts and one PEBC staff member. This document has been internally approved by PEBC management but has not been subject to a broader external review due to time constraints.

CED-SOS Advice Report #5 is comprised of 2 sections:

Section 1: A Clinical Practice Guideline
Section 2: A Systematic Review

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CED-SOS Advice Report #5: Section 1

Recombinant Humanized Thyroid Stimulating Hormone (rhTSH) Preparation Prior To Radioiodine Ablation in Patients Who Have Undergone Thyroidectomy for Papillary Or Follicular Thyroid Cancer: A Clinical Practice Guideline

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Question

What is the role of recombinant humanized thyroid stimulating hormone (rhTSH) preparation prior to radioiodine ablation (RA) in patients who have had thyroidectomy for papillary or follicular thyroid cancer? The outcomes of interest are serum TSH levels, results of post-therapy scans, iodine biokinetics in thyroid remnants, serum thyroglobulin, urinary iodine excretion, and quality of life (QOL).

Target Population

The target population is comprised of adult non-pregnant patients with papillary or follicular thyroid carcinoma who have undergone total, near-total, or sub-total thyroidectomy with gross complete resection of the disease and no known distant metastases.

Recommendations

There is a paucity of randomized controlled trial (RCT) evidence related to the clinical question, owing to the fact that thyroid cancer is a rare event. Based on the interpretation of evidence from randomized controlled trials, cohort studies, and retrospective studies, the following recommendations are made:

- Thyroid remnant ablation with radioiodine can be performed either following administration of rhTSH or following thyroid hormone withdrawal.
- In selected patients who cannot tolerate prolonged hypothyroidism or in patients who cannot achieve satisfactory elevation of endogenous TSH by means of thyroid hormone withdrawal, rhTSH may be the only option for radioablation.
- rhTSH has significantly improved measures of quality of life compared to thyroid hormone withdrawal.

Key Evidence

- One RCT, two cohort studies, and one retrospective study were located and reviewed.
- In three of the four studies, successful ablation rates (defined as a negative post-radioiodine ablation follow-up whole body scan [WBS]) were not significantly different in the rhTSH and the hypothyroid (HYPO) preparation states.
- The fourth study reports a significantly lower successful ablation rate in the rhTSH rate when success is defined as a negative WBS. However, if success is defined as a negative scan or undetectable serum thyroglobulin (Tg) level even with positive uptake in the thyroid bed, then the difference between these methods of RA is no longer significantly different.
- In all four studies, serum Tg at post-RA follow-up did not differ significantly between methods of RA preparation.
- Only one of the four studies assessing rhTSH preparation prior to RA reported QOL data. Consequently, QOL information was supplemented with results from three other studies assessing the use of rhTSH preparation for diagnostic monitoring purposes.
- All the studies assessing QOL demonstrated that QOL was decreased or significantly decreased when withdrawal of hormone therapy was the method of preparation used for either RA or diagnostic follow-up.

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CED-SOS Advice Report #5: Section 2

Recombinant Humanized Thyroid Stimulating Hormone (rhTSH) Preparation Prior To Radioiodine Ablation in Patients Who Have Undergone Thyroidectomy for Papillary Or Follicular Thyroid Cancer: A Systematic Review

J. Yoo, R. Cosby, and A. Driedger

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QUESTION

What is the role of recombinant humanized thyroid stimulating hormone (rhTSH) preparation prior to radioiodine ablation (RA) in patients who have had thyroidectomy for papillary or follicular thyroid cancer? The outcomes of interest are serum thyroid stimulating hormone (TSH) levels, results of post-therapy scans, iodine biokinetics in thyroid remnants, serum thyroglobulin, urinary iodine excretion, and quality of life (QOL).

INTRODUCTION

Endocrine cancers are rare events, and thyroid cancer is the most common of the endocrine cancers. The estimated number of new incident cases of thyroid cancer in Canada for 2006 was 2614 for women and 784 for men, whereas the estimated numbers of deaths owing to thyroid cancer in Canada for 2006 were 100 for women and 74 for men (1). In Ontario, thyroid cancer ranks 12th in incidence when men and women are combined, although this malignancy is much more common in women than men (2). Because thyroid cancer can recur decades after initial diagnosis and definitive treatment, those diagnosed with this disease require life-long surveillance and follow-up (3).

Patients with differentiated thyroid carcinoma (papillary and follicular) are usually initially treated surgically with near-total or total thyroidectomy, followed by radioiodine (¹³¹I) ablation of any thyroid remnants (4). Currently, patients are prepared for RA by the withdrawal of thyroid replacement hormone, rendering them hypothyroid. The hypothyroid state increases endogenous TSH levels, which stimulates the uptake of ¹³¹I in any remaining thyroid cells (5). The resulting temporary hypothyroidism can cause substantial physiological and psychological comorbidities such as cold intolerance, periorbital puffiness, weight gain, constipation, and slow movements, negatively affecting QOL (6). Although the length of time varies, patients generally remain off thyroid replacement hormone for a minimum of four to six weeks and restart within a week after RA.

Genzyme Corporation (Cambridge, MA) developed recombinant humanized TSH (rhTSH) as a source of exogenous TSH. Using rhTSH for RA preparation allows patients to remain on thyroid replacement, thereby avoiding the associated comorbidities of hypothyroidism. The administration of rhTSH has proved to be a safe and effective method of stimulating ¹³¹I uptake in patients being monitored for persistent or recurrent thyroid cancer, while still maintaining a euthyroid state (7,8). Currently, however, standard practice limits the use of rhTSH to the diagnosis and surveillance of differentiated thyroid cancer.

Given the efficacy of rhTSH for diagnostic and surveillance purposes, a systematic review of the evidence for the use of rhTSH for the treatment of thyroid remnants, in those with differentiated thyroid cancer following near-total and total thyroidectomy, was warranted.

METHODS

This advice report was developed by the Program in Evidence-based Care (PEBC) following a request from the Committee to Evaluate Drugs (CED). Because there is currently no standing committee to develop topics related to thyroid cancer, the expertise of two clinical experts (JY and AD) in Ontario was sought. These two clinicians worked with the PEBC to review the available evidence and develop recommendations that the CED could consider when making a funding decision concerning this drug. This document has been internally approved by the PEBC but has not been circulated to a broader audience in Ontario for review and approval at this time because of time constraints.

This advice report, produced by the PEBC, is a convenient and up-to-date source of the best available evidence on the role of rhTSH preparation prior to RA in patients who have had thyroidectomy for papillary or follicular thyroid cancer and was developed through a systematic review of the available evidence. The body of evidence in this review is primarily comprised of randomized controlled trial data, cohort study data, and retrospective study data. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

The MEDLINE (January 1996 through January [week four] 2007) and EMBASE (1996 through week 05 2007) databases were searched for relevant evidence. The search terms used are shown in Table 1. Relevant articles were selected and reviewed by one reviewer, and the reference lists from those sources were searched for additional trials.

Table 1. Literature search strategy.

Search date	Database	Search Terms Used
February 2, 2007	MEDLINE	Thyroid cancer, thyroidectomy, radioactive iodine ablation, thyrotropin, randomized controlled trials
February 2, 2007	EMBASE	

Inclusion Criteria

Articles were selected for inclusion in the systematic review if they were fully published English language reports, involving human subjects, of randomized controlled trials (RCTs), cohort studies, and retrospective studies comparing radioiodine ablation (RA) preparation using rhTSH such that patients remain euthyroid throughout treatment and standard withholding of thyroid hormone therapy such that patients are rendered hypothyroid (HYPO) prior to and throughout treatment. Outcome measures of interest were serum TSH levels, results of post-therapy scans, iodine biokinetics in remnants, serum thyroglobulin, urinary iodine excretion, and QOL .

Exclusion Criteria

The following were not eligible for inclusion:

1. Letters, editorials, notes, and non-systematic reviews.
2. Trials with less than five patients in each of the treatment and control groups.
3. Trials of patients with known metastatic disease.
4. Trials in which there was no comparison group.

Synthesizing the Evidence

Due to the heterogeneity of the outcomes reported on and the varying designs of located studies, data were not pooled using meta-analytic techniques.

RESULTS

Literature Search Results

The MEDLINE search yielded 289 results, 20 of which were potentially relevant and ordered for full review. The EMBASE search yielded 102 results, seven of which were potentially relevant and not included in the MEDLINE search (Table 2).

Table 2. Literature search results.

Date	Database	Dates Searched	Hits	Ordered for Full Article Review
February 2, 2007	MEDLINE	1996 - January (week 4) 2007	289	20
February 2, 2007	EMBASE	1996 - Week 5 2007	102	7

Only four of the 27 articles ordered for full review were considered relevant. Of the four, a more recent paper by Barbaro et al (10) contained the entire dataset from an earlier paper (9), along with additional patients, and only the data from the larger and more recent study was extracted. Two additional relevant papers (11,12) that met the inclusion criteria but were not found in the literature search were forwarded by one of the authors (AD). Because these two papers reported different outcomes for the same RCT, the main study report from 2006 by Pacini et al (11) will be reported unless unique information is reported only in the second study (12). This fact will be noted when appropriate.

Of the four studies included in this systematic review, one study reported pharmaceutical industry support from Genzyme Corporation (11). In addition, two studies were supported by grant funding (13,14), and one study did not provide any information on the source of funding (10).

QOL was only reported in one study (11) used for this systematic review on the therapeutic use of rhTSH. Because QOL was deemed to be an important outcome for this review, studies evaluating rhTSH for diagnostic monitoring purposes that met the inclusion criteria for study design and reported on QOL were located and reviewed as well. Consequently, the section reporting QOL was supplemented with results from three other studies (8,15,16), all of which compared HYPO and rhTSH preparation for the diagnostic use of ¹³¹I.

Study Characteristics

Four studies (one RCT, two cohort, and one retrospective) involving 405 patients were located and reviewed (10,11,13,14) for this systematic review. Three of the four studies (10,11,14) were two-armed studies that compared rhTSH to HYPO for the preparation of patients for RA. The 2002 study by Pacini et al (13) included an extra arm in which the patients were rendered hypothyroid and were also given rhTSH, in addition to a HYPO and an rhTSH arm.

In all four studies (10,11,13,14), 0.9mg of rhTSH was administered intramuscularly on two consecutive days, followed by RA 24 hours after the second dose of rhTSH. A fixed dose of 30 mCi ¹³¹I was administered in two studies, (10,13) and a fixed dose of 100 mCi was administered in another study (11). In the final study (14) ¹³¹I doses were based on dosimetry and therefore varied from patient to patient. Patients in all four studies had previously undergone total or near-total thyroidectomy. Please refer to Table 3 for a summary of each study.

Table 3: Summary of study attributes.

Study	Treatments	Type of Study	n	Age	F	Type	Surgery
Pacini et al 2006 (11)	HYPO	RCT	30	20-68	24	papillary or follicular (no metastases)	total or near total thyroidectomy
	rhTSH		33		26		
Barbaro et al 2006 (10)	HYPO	Cohort	41	19-71	26	papillary or minimally invasive follicular	total thyroidectomy
	rhTSH		52		35		
Pacini et al 2002 (13)	HYPO	Cohort	50	17-75	36	papillary or follicular (no metastases)	total or near total thyroidectomy
	HYPO + rhTSH		42		30		
	rhTSH		70		53		
Robbins et al 2002 (14)	HYPO	Retrospective	42	42.2±17.5	17	papillary (83%) (Stages I-IV)	total or near total thyroidectomy
	rhTSH		45	49.9±13.3 ^a	27		

F=female; HYPO=hypothyroid; RCT=randomized controlled trial; rhTSH=recombinant humanized TSH

^ap < 0.05

Study Quality

The literature search only yielded one RCT (11) on the use of rhTSH therapeutically for preparation for RA. Although of good quality, this study enrolled only 63 participants, over a period of 21 months in nine study sites. However, a large prospective trial on this topic is unlikely given that the incidence of thyroid cancer is too low for a large trial to be feasible in a reasonable amount of time. Furthermore, the good prognosis and protracted nature of thyroid cancer means that it takes many years and even decades to reach certain endpoints (3). Therefore, from both a logistical and financial perspective, it is challenging to do large, long-term prospective trials. The cohort studies by Barbaro et al (10) and Pacini et al (13) and the retrospective review by Robbins et al (14) suffer from the limitation of these types of studies in general, namely, lack of randomization. Lack of randomization makes it unclear whether selection bias (either self-selection by patients or selection by physicians) affected the results of a given study.

Outcomes

Successful Ablation Rates and Serum Thyroglobulin Levels

All four studies reported on both of these outcomes. The complete reporting of these outcomes is included in Table 4.

The RCT, reported by Pacini et al (11), compared RA preparation in 63 patients, which was accomplished either by rendering them hypothyroid by thyroid hormone withdrawal or by administering rhTSH while allowing patients to remain euthyroid. In this study, a 100 mCi dose of ¹³¹I was administered. At eight months follow-up, 86% of those in the HYPO group and 75%

of those in the rhTSH group had a negative WBS and, as a result, were considered successfully ablated ($p=0.3$). The rate of successful ablation increased to 100% in both groups when success was defined as less than 0.1% ^{131}I uptake in the thyroid bed. Furthermore, 86% and 83% of the HYPO and rhTSH groups, respectively, had serum Tg levels less than 1 ng/mL.

The cohort study reported by Barbaro et al (10) compared RA preparation in 93 patients divided into HYPO and rhTSH groups. Those in the HYPO group were not provided hormone replacement therapy from the time of thyroidectomy until after RA, a period of time that ranged from 42 to 91 days. Of note, those in the rhTSH group had their thyroid hormone withdrawn for four days. L-T4 was discontinued the day before the first dose of rhTSH and resumed the day after the administration of a 30 mCi therapeutic dose of ^{131}I . The rates of successful ablation were similar between the two groups of patients (p not reported). At one-year follow-up, 75.6% of those in the HYPO group and 76.9% in the rhTSH group had a negative WBS, indicating a successful ablation. Serum Tg levels were less than 1 ng/ml in 78.0% of the HYPO group and 86.5% in the rhTSH group.

Another cohort study, reported by Pacini et al (13), compared RA preparation in 162 patients. However, in addition to the HYPO and rhTSH groups, there was a third group that was prepared by both thyroid hormone withdrawal and the administration of rhTSH (HYPO + rhTSH). A 30 mCi dose of ^{131}I was given to all patients. In this study, the rates of successful ablation were significantly lower in the rhTSH group when success was defined as a negative WBS. At six to 10 months follow-up, 84% and 78.5% of those in the HYPO and HYPO + rhTSH groups, respectively, had a negative WBS, whereas only 54% ($p<0.0001$ and $p<0.01$) of those in the rhTSH group did. However, guidelines published by the American Thyroid Association (17) indicate that serum Tg is the best indicator for successful ablation. Using this criterion, the successful ablation rates were 88%, 95%, and 74.1% in the HYPO, HYPO + rhTSH, and rhTSH groups, respectively, and not significantly different.

Finally, Robbins et al (14), reported retrospectively on a comparison of HYPO and rhTSH in 87 patients. Overall, 82.8% of the patients had papillary carcinoma, with the rest of unknown diagnosis, and 63.2% had Stage I or II disease. This study was unique among those reviewed in that it calculated dosage of ^{131}I individually, based on dosimetry, rather than administering a standard fixed dose. The mean dose for both groups was greater than 100 mCi. Follow-up at approximately one-year post-ablation demonstrated that 80.9% of HYPO and 84.4% of rhTSH patients had a complete response, defined as complete ablation of all radioiodine uptake in the thyroid bed. In addition, the serum Tg levels at this follow-up were 0.65 and 0.5 ng/ml in the HYPO and rhTSH groups, respectively. Overall, there was no significant difference between the groups on measures of successful ablation.

Table 4: Rates of successful ablation and serum thyroglobulin levels by study.

Study	Comparison	¹³¹ I Dose	Successful Ablation		Serum Tg < 1ng/ml at 6-12 Month FU
			Negative WBS	Other Definitions	
Pacini et al 2006 (11)	HYPO	100 mCi	86.0%	100% ^a	86.0%
	rhTSH		75.0%	100% ^a	83.0%
Barbaro et al 2006 (10)	HYPO	30 mCi	75.6%	NA	78.0%
	rhTSH		76.9%		86.5%
Pacini et al 2002 (13)	HYPO	30 mCi	84.0% (p<0.0001) ^b	88% ^c	83.3% ^d
	HYPO+rhTSH		78.5% (p<0.01) ^b	95% ^c	84.8% ^d
	rhTSH		54.0%	74.1% ^c	86.8% ^d
Robbins et al 2002 (14)	HYPO	Based on dosimetry ^e	80.9%	NA	0.65 ng/ml ^f
	rhTSH		84.4%		0.50 ng/ml ^f

FU–follow-up; HYPO–hypothyroid; NA–not applicable; rhTSH–recombinant humanized TSH; Tg–thyroglobulin; WBS–whole body scan

^asuccessful ablation is defined as no visible uptake of <0.1% uptake in post-therapy WBS.

^bcompared to rhTSH alone.

^csuccessful ablation is defined as a negative post-therapy WBS or undetectable serum Tg even with positive uptake in the thyroid bed.

^dbased on those patients who had a successful ablation.

^emean (SD) dose is 128.9(74) mCi and 110.4(65) mCi for HYPO and rhTSH groups respectively

^fmedian Tg level.

Adverse Events

There were some adverse events associated with both methods of RA preparation. Pacini et al (11) reported mild and transient nausea and fatigue in some patients in both groups. Additionally, some patients in the rhTSH group experienced a loss in taste, and some patients in the HYPO group experienced skeletal pain. Barbaro et al (10) report that there were no significant side effects after the administration of rhTSH. Neither of the remaining two studies (13,14) reported any information concerning adverse effects.

Serum Thyroid Stimulating Hormone (TSH) Levels

As expected, baseline serum TSH levels in the HYPO-group patients were significantly higher than those in the rhTSH groups. The administration of rhTSH led to significant increases in serum TSH levels from baseline levels in all the studies that reported on this variable. Serum TSH levels are considered sufficient for radioiodine therapy when they reach 25-30 mU/L (5,14). Please refer to Table 5 for serum TSH levels.

Table 5. Serum TSH levels.

Study	Comparison	Serum TSH Mean (SD)	
		Basal	After rhTSH
Pacini et al 2006 (11)	HYPO	83.0(51) mU/L	NA
	rhTSH	1.1(1.3) mU/L	NR
Barbaro et al 2006 (10)	HYPO	50(3) mU/L	NA
	rhTSH	0.04-0.35 ^a mU/L	126(10) mU/L
Pacini et al 2002 (13)	HYPO	63.2(19.6) mU/L ^b	NA
	HYPO+rhTSH	71.0(35.9) mU/L ^b	281(97.0) mU/L ^b (p<0.0001)
	rhTSH	1.30(2.5) mU/L ^b (p<0.0001)	126(44.8) mU/L ^b (p<0.0001)
Robbins et al 2002 (14)	HYPO	97.5(50) mU/L	NA
	rhTSH	6.0(9.5) mU/L	105.1(45.4) mU/L

HYPO–hypothyroid; NA–not applicable; rhTSH–recombinant humanized TSH; SD–standard deviation; TSH–thyroid stimulating hormone

^aonly range reported.

^bPacini et al 2002 report serum TSH levels in µU/mL. This is equivalent to mU/L.

Iodine Biokinetics

Baseline 24 hour ¹³¹I uptake, following the administration of a tracer dose of ¹³¹I, was only reported in two papers. In the Pacini et al (13) report, baseline 24-hour ¹³¹I uptake in the HYPO and HYPO+rhTSH groups was 5.8(5.7)% and 5.4(5.7)%, respectively, and not significantly different. No baseline value was reported for the rhTSH group. Following the administration of rhTSH, mean 24-hour ¹³¹I uptake was 9.4(9.5)% in the HYPO+rhTSH group, which was significantly higher than the baseline level (p<0.0001) and 2.5(4.3)% in the rhTSH group. The rhTSH value was significantly lower than the HYPO+rhTSH level (p<0.0001). Robbins et al (14) reported median baseline 24-hour ¹³¹I uptake values that were significantly different between the HYPO and rhTSH groups (1.65% and 0.9%, respectively; p=0.05) but did not report values following the administration of rhTSH. Barbaro et al.(10) only evaluated 24-hour ¹³¹I uptake on a subset of patients after the administration of rhTSH but found that the HYPO and rhTSH groups did not differ significantly (3.30% versus 2.29%, respectively). Only two studies reported post-ablation ¹³¹I uptake (11,14), and the difference between the HYPO and rhTSH groups in each study was not significantly different. Please refer to Table 6 for 24 hour ¹³¹I uptake.

Other measures of iodine biokinetics such as mean effective half-life and mean residence time are only reported in the recent paper by Pacini et al (11). These authors reported mean effective half-life to be 48.0(52.6) hours in the HYPO group and 67.6(48.9) hours in the rhTSH group, a significant difference (p=0.011). Mean residence time in the HYPO and rhTSH groups were 1.4(1.5) and 0.9(1.3) hours, respectively, and were not significantly different. Finally, mean dose to the blood was significantly higher in the HYPO group compared to the rhTSH group (0.167 versus 0.109, p<0.0001). Overall, the patients in the rhTSH group had a higher does of radiation to the remnants and a 30% reduction of whole body radiation dose compared to the patients in the HYPO group (12).

Table 6. Iodine biokinetics in remnants: 24-hour ¹³¹I uptake.

Study	Comparison	24-Hour ¹³¹ I Uptake Mean (SD) %		
		Pre-rhTSH	Post-rhTSH	Post-ablation
Pacini et al 2006 (11)	HYPO	NR	NA	0.9(1.1) ^a
	rhTSH	NR	NR	0.5(0.7) ^a
Barbaro et al 2006 (10)	HYPO	NR	3.30(0.7) ^b	NR
	rhTSH	NR	2.29(0.45) ^b	NR
Pacini et al 2002 (13)	HYPO	5.8(5.7)	NA	NR
	HYPO+rhTSH	5.4(5.7)	9.4(9.5) (p<0.0001) ^c	NR
	rhTSH	NR	2.5(4.3) (p<0.0001) ^d	NR
Robbins et al 2002 (14)	HYPO	1.65 ^e	NA	0.25 ^e
	rhTSH	0.9 ^e (p=0.05)	NR	0.17 ^e

HYPO-hypothyroid; NA-not applicable; NR-not reported; rhTSH-recombinant humanized TSH; SD-standard deviation

^a48-hour ¹³¹I Uptake.

^b only evaluated on a subset of patients.

^c comparison within HYPO+rhTSH group pre- and post-rhTSH.

^d comparison between HYPO+rhTSH and rhTSH at post-rhTSH.

^e median value.

Quality of Life

QOL was only reported in one of the papers (11) used for this systematic review for assessing rhTSH preparation prior to RA. Because this outcome was deemed to be important for this review, studies evaluating rhTSH for diagnostic monitoring purposes that met the inclusion criteria for study design and reported on QOL were located and reviewed in this section as well. Consequently, QOL information was supplemented with results from three other studies (8,15,16), all of which compared HYPO and rhTSH preparation for the diagnostic use of ¹³¹I. Two of these studies were repeated measure studies (15,16), and the third was a cohort study (8). All the studies demonstrated that QOL was worse in the HYPO group compared with either baseline values and/or the rhTSH group. Pacini et al (11) assessed QOL using the Billewicz Scale and the Short Form (SF)-36. In this study, participants in the HYPO group scored higher (i.e., worse) on six of the 14 signs and symptoms of hypothyroidism on the Billewicz Scale as compared to the rhTSH group (p<0.0001). In addition, the change from baseline to week four was significantly different in the euthyroid group from the change observed in the hypothyroid group for five of the eight health-related quality of life (HRQOL) domains of the SF-36 (Table 7). Schroeder et al (16) expressly set out to assess and compare QOL in those undergoing preparation for diagnostic evaluation using TSH withdrawal and rhTSH. These authors determined that QOL in the HYPO group was significantly worse on all 14 signs and symptoms of hypothyroidism on the Billewicz scale (p<0.001) as compared to the rhTSH group. Likewise, they found that those in the HYPO group had significantly lower QOL on all eight HRQOL domains on the SF-36 (p<0.0001) and on the physical (PCS) and mental (MCS) composite scores of the SF-36 (p<0.0001 for each) in comparison to the rhTSH group.

Ladenson et al (8) also found that QOL was significantly worse in the HYPO group, as compared to the rhTSH group, on all signs and symptoms of hypothyroidism on the Billewicz scale ($p < 0.001$). This group of researchers also assessed QOL using the Profile of Mood States scale (POMS) and reported that the HYPO group had significantly worse QOL on all six states measured on the POMS in comparison to the euthyroid group ($p < 0.001$). Finally, in 2002, Ladenson (15) compared QOL in HYPO and rhTSH groups and found that the HYPO group had significantly worse QOL on five of the six states assessed on the POMS as well as on the PCS of the SF-36, although probability values were not reported in this article.

Table 7. Quality of life.

Study	Administration of QOL Scales	Billewicz	POMS	SF-36
Pacini et al 2006 (11)	<ul style="list-style-type: none"> baseline immediately before ablation 1 month after ablation 	<p>14 SIGNS & SYMPTOMS at week 4 significant difference in scores between HYPO and rhTSH ($p < 0.0001$) with HYPO scores higher before ablation and 1 month after ablation compared to baseline for:</p> <ul style="list-style-type: none"> cold intolerance (50vs21%) weight gain (60vs21%) constipation (43vs3%) slow movements (50vs12%) cold skin (47vs12%) periorbital puffiness (50vs0%) 	NR	<p>8 HRQOL DOMAINS at week 4 scores lower in HYPO in 7 domains compared to baseline for:</p> <ul style="list-style-type: none"> physical functioning role-physical general health vitality social functioning role-emotional mental health <p>In 5 of 8 domains, the change from baseline to week 4 was significantly different in HYPO group than the change in the rhTSH group for:</p> <ul style="list-style-type: none"> physical functioning ($p < 0.016$) role-physical ($p < 0.018$) vitality ($p < 0.0001$) social functioning ($p < 0.0001$) mental health ($p < 0.002$)
Schroeder et al 2006 (16) ^a	<ul style="list-style-type: none"> baseline day of WBS (i.e. 48 hours after ¹³¹I) 	<p>14 SIGNS & SYMPTOMS all scores higher in HYPO compared to rhTSH ($p < 0.001$)</p>	NR	<p>8 HRQOL DOMAINS all scores lower in HYPO compared to rhTSH ($p < 0.0001$ each)</p> <p>PCS score lower in HYPO ($p < 0.0001$)</p> <p>MCS score lower in HYPO ($p < 0.0001$)</p>
Ladenson, 2002 (15) ^a	<ul style="list-style-type: none"> baseline day of WBS (i.e. 48 hours after ¹³¹I) 	NR ^b	<p>HYPO group, significantly worse compared to rhTSH for:</p> <ul style="list-style-type: none"> fatigue depression anger tension confusion <p>($p = \text{NR}$)</p>	<p>PCS score significantly lower in HYPO compared to rhTSH ($p = \text{NR}$)</p> <p>MCS no difference between HYPO and rhTSH</p>
Ladenson et al 1997 (8) ^a	<ul style="list-style-type: none"> baseline day ¹³¹I given 	<p>14 SIGNS & SYMPTOMS all scores higher in HYPO compared to rhTSH ($p < 0.001$)</p>	<p>HYPO group, significantly worse compared to rhTSH for:</p> <ul style="list-style-type: none"> fatigue depression anger tension confusion vigour <p>($p < 0.001$)</p>	NR

HRQOL—health related quality of life; HYPO—hypothyroid; MCS—mental composite score; NR—not reported; PCS—physical composite score; POMS—Profile of Mood States; rhTSH—recombinant humanized TSH; vs—versus

^apapers on diagnostic follow up/monitoring.

^bauthors report Billewicz scale used, but no data is reported.

DISCUSSION

A systematic review of the available evidence on the use of rhTSH compared to thyroid replacement hormone withdrawal for radioiodine ablation preparation yielded four relevant studies consisting of one RCT, two cohort studies, and one retrospective study. Examination of the outcomes of these studies revealed that the use of rhTSH for RA preparation is not different from thyroid hormone withdrawal with respect to achieving successful ablation. Three of the four studies reviewed demonstrated similar rates of negative WBS by both methods of preparation (10,11,14). The last study demonstrated similar rates of successful ablation when the definition was broadened to include a negative WBS or undetectable serum Tg even with positive uptake in the thyroid bed (13). Following surgery and RA, serum Tg measured following TSH stimulation using either method of preparation is considered to be a sensitive indicator of residual thyroid tissue. Using this criterion, hypothyroid and euthyroid patients in all four studies had similar rates of successful ablation, indicated by the low rates of serum Tg levels (<1ng/ml) at six to 12 month post-ablation follow-up.

Serum TSH levels are considered sufficient for radioiodine therapy when they reach 25-30 mU/L (5,14). In all the studies reviewed, serum TSH in the hypothyroid patients was more than sufficient for the adequate uptake of ¹³¹I uptake and ranged from 50±3 mU/L to 97.5±50 mU/L. Three studies reported serum TSH levels following the administration of rhTSH that were also sufficient for the ¹³¹I uptake needed for RA therapy and ranged from 105.1±45.4 mU/L to 281±97.0 mU/L.

Successful ablation is defined by some researchers by the post-ablation 24-hour ¹³¹I uptake in the thyroid bed, with the cut-off for success being less than 1% of the administered dose (18). Of the two studies that reported this particular outcome (11,14), both demonstrated 24-hour ¹³¹I uptake to be less than 1%, with no significant difference between those prepared by thyroid withdrawal and those prepared by rhTSH.

In the earlier Pacini et al (13) study and in the Barbaro et al (9) study, a fixed dose of 30mCi of ¹³¹I was administered to all patients, whereas in the more recent Pacini et al (11) study, a larger fixed dose of 100 mCi was administered. In the Robbins et al (14) study, the dose of ¹³¹I administered was calculated for each individual patient, based on dosimetry. The mean dose in both groups was well above 100 mCi. The higher dose of ¹³¹I might result in higher successful ablation rates. The 30 mCi dose has never had a biological justification but came into use prior to 1997 in an attempt to avoid costly hospitalization in the United States (US) after the US Nuclear Regulatory Commission declared that doses greater than 32 mCi required the institutional isolation of patients. This rule was modified in 1997 to allow patients to receive higher doses of ¹³¹I without hospitalization as long as they did not expose the general public to a dose greater than or equal to 500mrem (19).

Other biokinetic measures were reported only in the Pacini et al RCT (11). The authors measured the mean residence time of ¹³¹I and found no difference in the hypothyroid and the euthyroid patients. However, they did find that the mean effective half-life was significantly higher in the euthyroid patients, whereas the mean dose to the blood was significantly lower in this group. This finding suggests that preparation using rhTSH results in a lower dose of radiation to the blood. This difference is attributable to the impairment of renal function during hypothyroidism (12). Consequently, a lower dose of radiation to the blood may result in a lower risk of radiation-induced cancers (20), although this would need to be confirmed in future trials designed to assess this endpoint.

In the papers used to assess QOL, a total of three different QOL scales were used: the Billewicz Scale, the POMS, and the SF-36. No matter which measurement scale was used, the QOL was significantly better in those patients prepared with rhTSH than in those who were prepared by thyroid hormone withdrawal. Of the three studies that used the Billewicz scale (8,11,16), two (8,16) reported that QOL was significantly worse in the hypothyroid patients for all 14 signs and symptoms of hypothyroidism compared to the euthyroid patients (p<0.001 in each

study), and the other study (11) found that QOL was worse in the hypothyroid patients on six of the 14 symptoms of hypothyroidism compared to baseline. The POMS was used in two studies (8,15) and demonstrated that QOL was significantly worse for the hypothyroid group in five of the six (p not reported) (15) and six of the six ($p < 0.001$) (8) mood states assessed in this scale, respectively. Finally, three studies evaluated QOL using the SF-36 (11,15,16). Pacini et al (11) report that QOL was lower in the HYPO group for seven of the eight HRQOL domains measured, compared to baseline. Furthermore, the change in QOL from baseline to week four was significantly higher in the rhTSH group for five of the eight HRQOL domains as compared to the change in QOL over the same time frame in the HYPO group. Schroeder et al (16) found that, compared to the euthyroid group, the hypothyroid group had a lower QOL for all eight HRQOL domains ($p < 0.0001$ each) as well as the PCS ($p < 0.0001$) and MCS ($p < 0.0001$) in the SF-36. Lastly, in 2002, Ladenson reported that the hypothyroid patients had significantly worse QOL for the PCS but not the MCS of the SF-36 {Ladenson, 2002 154 /id}. It is clear that preparation by rhTSH results in much lower comorbidity and consequently a much better QOL than does preparation by thyroid hormone withdrawal.

Although there is no published data on the economic impact to patients, it is commonly acknowledged that patients will miss very little work using rhTSH as compared to hormone withdrawal. In some situations, up to three months of work will be missed because of the debilitating effect hypothyroidism can have on some patients.

In 2006, the American Thyroid Association Guidelines Taskforce published its guideline for the management of patients with differentiated thyroid cancer. The taskforce gave a level B recommendation for the use of either thyroid hormone withdrawal or rhTSH for radioiodine remnant ablation (17). Moreover, the European Commission has approved the use of rhTSH for radioiodine remnant ablation in low-risk post-thyroidectomy patients (21).

Finally, there are some people who cannot achieve satisfactory levels of endogenous TSH with thyroid hormone withdrawal and others for whom hypothyroidism is contraindicated because of other medical disorders. Studies done with these populations demonstrate that the use of rhTSH is a viable option in many cases (22,23).

There is not a vast quantity of evidence for the therapeutic use of rhTSH, and there are potential biases inherent in non-randomized data. However, there is definitely consistency in all the studies reviewed in terms of the direction of the effect regarding the use of rhTSH as a method of preparation for radioiodine ablation of thyroid remnants.

CONCLUSIONS

Based on the evidence available, the use of rhTSH for RA preparation, following total or near-total thyroidectomy in those with papillary or follicular thyroid cancer, appears to be equivalent to the traditional method of preparation by thyroid hormone withdrawal. Recombinant humanized TSH allows patients to remain euthyroid, thereby avoiding the comorbidities of hypothyroidism and resulting in a better quality of life.

CONFLICT OF INTEREST

Two authors (JY and RC) of this report declared that there were no potential conflicts of interest related to the topic of this CED-SOS advice report. One author (AD) declared research support from Genzyme Corporation for the development and maintenance of a thyroid cancer database. This author has also received honoraria from Genzyme exceeding \$5000 annually, all of which has been signed over to the research fund of the Department of Nuclear Medicine at London Health Sciences Centre.

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CED-SOS ADVICE REPORT #5

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