The Use of Thyrogen® in the Treatment of Differentiated Thyroid Carcinoma: An Intraindividual Comparison of Clinical Effects and Implications of Daily Life

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Key words
- rhTSH
- thyroid cancer
- hypothyroidism
- diagnostic whole body

Abstract

Aim: Withdrawal of levothyroxine with resultant hypothyroidism is still used in preparation for I-131 diagnostic whole-body scan (DWBS) and thyroglobulin (TG)-measurement in patients afflicted with differentiated thyroid cancer (DTC). Recombinant human thyroid-stimulating hormone (rhTSH) enhances TSH stimulation obviating the clinical and economical consequences of hypothyroidism. Primary aim of this study was an intraindividual comparison of diagnostic follow-up measurements under these two sets of conditions by taking clinical and socio-economic parameters into account. Second aim was to determine a clear patient preference for the one method or the other.

Methods: This non-interventional observational study included patients (n=192 signed informed consent, n=128 protocol compliant patients without need for therapeutic intervention) with DTC first treated by thyroidectomy and radioiodine ablation. Control visits including I-131 DWBS were planned at 3–6 months post-thyroidectomy after a phase (KU 1) of thyroid hormone withdrawal (THW) and again after 6–12 months later in a euthyroid state under exogenous stimulation with rhTSH (KU 2). Study design was open, prospective and multicentric. Data collected consisted of patient information (SF-12® Health Survey), thyroid-specific results of clinical examinations and several aspects of daily life, e.g., employment, days of absence from work and other economic aspects.

Results: In contrast to KU 1, in KU 2 there is a highly significant improvement ($p<0.0001$) in all studied clinical symptoms and aspects of managing daily life. A significant increase of the SF-12® health survey score could also be identified. Mental score showed a higher increase than physical score. Included patients were less absent from work before KU 2, (absent 4.5%, median 4 days in euthyroid state [range 2–5 d]), vs. before KU 1 (absent 47.8%, median 10 days in hypothyroid state [range 1–30 d]). After KU 2 7.7% of the euthyroid patients was absent from work (median 5 days) while 37.5% was after KU 1 (median 6 days).

Conclusion: Included patients benefited subjectively and objectively from the use of rhTSH for diagnostic procedures in the treatment of DTC. A clear preference (127 of 128) of analyzed patients could be identified for exogenous stimulation with rhTSH.

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Introduction

The incidence of differentiated thyroid cancer (DTC) is increasing for several reasons, mainly due to the earlier detection of small papillary thyroid cancer (Woolam et al., 2000). After total or near total thyroidectomy followed by an ablative activity of I-131 patients are treated with thyroid hormone suppressive therapy (THST) (Reiners, 2008). For the detection of residual or recurrent thyroid cancer, I-131 diagnostic whole-body scans (DWBS) and thyroglobulin (TG) measurements are accepted modalities in the follow-up. In order to elevate the endogenous TSH levels and to increase the sensitivity of diagnostic procedures thyroid hormone therapy must be withdrawn. The resultant hypothyroidism has many concomitant phenomena, e.g., cognitive impairment (Münte et al., 2004), cerebral blood flow abnormalities (Constant et al., 2001, Nagamachi et al., 2004), emotional dysfunction and physical discomfort. THW is associated with cardiovascular effects in patients with DTC (Botella-Carretero et al., 2004). Beside the impact of hypothyroidism on the central nervous system, THW also deranges the lipid profile, renal system,

and effects hemostatic changes (Duntas and Biondi, 2007, den Hollander et al., 2005, Lien et al., 2000, Franchini, 2006, Botella-Carretero et al., 2006). THW may be hazardous for patients with underlying cardiovascular disease as was recently described by Goldberg, 2007. Quality of life and ability to work are significantly reduced (Luster et al., 2005). In the latter study a retrospective assessment of data was carried out. Recombinant human TSH (rhTSH) has been developed to provide TSH stimulation without THW. RhTSH has been approved as an adjunct for diagnostic procedures in patients with DTC (Luster et al., 2005). In the past few years more than 300000 patients were treated with rhTSH. Since 2005 rhTSH also has approval in Europe for ablation therapy and, since 2007, in the United States of America (FDA) (Haugen et al., 2008).

In 2003 Dietlein published new procedure guidelines for I-131 DWBS in differentiated thyroid cancer (Dietlein et al., 2003). The two alternatives of an endogenous or an exogenous TSH stimulation are considered to be equal in sensitivity for the diagnostic use of radioiodine and for the measurement of TG. According to these guidelines, patients with DTC usually undergo a first DWBS 4–6 months after ablation. Within the first 2–5 years the DWBS should be repeated. In daily practice, the first DWBS was often performed under endogenous hypothyroidism in order to be able to treat thyroid remnant with a second ablative therapy. On the other hand, the second DWBS is usually performed under exogenous stimulation with rhTSH. This well evaluated procedure provided the basis for the present study. These guidelines were recently updated (Dietlein et al., 2007a, b) with more emphasis on rhTSH for diagnostic procedures.

Primary aim of this study was to evaluate clinical and economical differences between hormone withdrawal and exogenous stimulation using rhTSH. Further objectives were an intraindividual comparison of safety and tolerability of rhTSH as well as the detection of a personal preference for one of these two methods. Pharmaco-economic aspects are based on evaluated data, not on hypotheses or modelling. Additionally, a subgroup analysis has been performed with those patients who stopped levothyroxine for four weeks and with those patients who substituted liothyronin for the first two weeks.

Material and Methods

Study design

This non-interventional observational study on patients with DTC had an open, prospective and multicentric design. All patients underwent thyroidectomy followed by radioiodine treatment. Control visits including I-131 DWBS were planned after 3–6 months.

First control visit (KU 1) should be performed under conditions of hypothyroidism with a 2–5 week phase of withdrawal of thyroid hormone medication (THW). Control visit 2 (KU 2) was normally done 6–12 months after KU 1, under euthyroid conditions following TSH stimulation by administration of rhTSH (Thyrogen®).

This protocol reflected the clinical routine for these patients. According to the non-interventional character of the study, no study-specific procedures were specified and all treatment-relevant decisions were left up to the treating physician.

The decision to include a patient was made between initial therapy and KU 1. In case of inclusion, patient data as well as inclusion criteria and anamnestic data were recorded. Regarding the main focus of the study the following data ("efficacy data set") were collected prospectively at both visits:

- *Quality of life:* The quality of life was measured by the SF-12® health survey (Ware et al., 1996, Gandek et al., 1998), a validated patient questionnaire containing 12 items. The SF-12® was used in the standard 4-week recall period version reflecting the health status over the last four weeks. The 12 items cover physical and mental components. Therefore, for each patient three sum scores were evaluated: physical sum score, mental sum score and total sum score.
- *Clinical symptoms:* The presence of the following potential symptoms of hypothyroidism with a time focus of the previous four weeks was part of the patient interview performed by the treating physician: weight gain, fatigue/lethargy, concentration deficiency, sleep disorders, cold intolerance, constipation and hoarseness (modified from Billewicz et al., 1969). The results of the patient interview were specified by the treating physician as being "present", "questionable" or "not present".
- *Managing daily life:* Several aspects of daily life during the previous four weeks were also part of the patient interview covering employment, restrictions of occupation, days of absence from work, capability to care for family members, consultations, additional medication, car driving, accidents, means of travel to visit, attendance to visit, distance home-hospital and expected further days of absence from work.
- *Clinical findings:* Thyroid-specific results of clinical examination (modified from Billewicz, 1969) were: cold skin, dry skin, slowed movements, periorbital swelling, swelling of hands, decelerated ankle reflexes and pulse rate. All findings were rates as "present", "questionable" or "not present". Definitive present symptoms were compared.
- *Laboratory diagnostics:* Thyroid parameters of interest were: tetraiodothyronine, triiodothyronine, thyroid-stimulating hormone (TSH), thyroglobulin (TG), thyroglobulin recovery and thyroglobulin antibodies.
- *I-131 DWBS:* The result of the scintigraphy was rated as "negative", "positive", "questionable" or "not assessable".

Visit data were complemented by data on hormone treatment, concomitant diseases and medication. During the second control visit (KU 2) the protocol of the thyrotropin test was specified including administration data, laboratory diagnostics and scintigraphy results. At the end of the observation, patients were asked to specify their preference for one of the diagnostic control procedures including their reasons as: "Thyrogen® test", "hormone withdrawal" or "undecided".

The documentation was supplemented by data on intended diagnostic and therapeutic procedures following the observational period. Data on adverse drug reactions and tolerability assessments were documented by both physicians and patients.

According to scale level, the evaluation of the data included descriptive parameters (mean, median, standard deviation, minimum, maximum) or frequencies and shift tables. Where indicated, intraindividual comparisons were performed by the Wilcoxon signed-rank test or the sign test of Dixon and Mood. Due to the non-interventional character of the study, the tests on significant differences between KU 1 and KU 2 remained exploratory.

Study was approved by local ethic committee.

Subgroup analysis

Based on the efficacy data set, three additional subgroup analyses were performed. The subgroups refer to the medication some weeks before the hypothyroidism phase of KU 1:

"T_3 patients": This subgroup included patients who were treated with T_4 (levothyroxine) followed by T_3 (liothyronine) and withdrawal for 2–3 weeks. The subgroup analysis compared KU 1 (hypothyroidism) with KU 2 (euthyroidism) for these patients (n=72).

"T_4 patients": This subgroup includes patients who were treated solely with T_4 and withdrawal for 4–5 weeks. The subgroup analysis compared KU 1 with KU 2 for 56 patients.

"T_3 patients" vs. "T_4 patients": This analysis compared the results of both subgroups.

Each of the subgroup analyses included the following parameters: quality of life, clinical symptoms (modified from Billewicz et al., 1969) and clinical findings (modified from Billewicz et al., 1969). Interindividual comparisons are performed by the chi^2 (χ^2) test.

Results

Patient data sets

192 patients in 25 German centres were included in this observational study. All patients signed informed consent. For this patient sample, the following data sets were compiled. In order to provide the same conditions for the comparison of the 2 control visit procedures, the "efficacy data set" excluded 64 patients from efficacy evaluation because of several reasons: observation discontinued due to non-compliance (n=27, 14.1%), scintigraphy positive at KU 1 (n=12, 6.3%), deviations from recommended procedure or documentation (e.g., retrospective or missing data, inconsistencies), substantially increased radioactivity at KU 2 (n=11, 5.7%). Positive scintigraphy and deviation were also found (n=8, 4.2%). Three patients (1.6%) missed the Thyrogen® prescription before KU 2. Three more patients were excluded (1.6%) for other reasons such as pregnancy, pregnancy intention, and relocation. Concerning the baseline parameters, the 64 excluded patients were not significantly different from those patients who were included in the efficacy data set.

The "safety data set" consisted of 142 patients and included the 128 patients of the efficacy data set plus 14 of the excluded patients who received at least one administration of rhTSH (Thyrogen®).

Baseline parameters

The efficacy data set included 128 patients (24.2% male, 75.8% female). The mean age of the patients was 51.6±14.8 years (mean±standard deviation).

The thyroid cancer was classified as papillary in 69.3%, as follicular in 22.0% and as follicular and papillary in 8.7% of the patients. The mean diameter of the thyroid cancer was 20.1±14.2 mm (mean±standard deviation). Nearly half of the patients were classified as stage T1. An affection of lymph nodes was detected in 19.7%. No distant metastases were found.

Concomitant diseases were described in 68.0% of the patients, most frequently cardiovascular diseases (33.6%) and metabolic diseases (24.2%). Concomitant medications were administered to 61.7% of the patients.

KU1 was performed at a median of 170 days after radioiodine ablation therapy. The median diagnostic activity was 370 MBq of I-131. In 14% of the patients the time period between ablation therapy and KU 1 was more than 270 days.

The time period between the last administration of thyroid hormone medication and KU 1 was 31 days (median) if T_4 was solely used for the thyroid hormone medication and 17 days (median) if T_3 was part of the thyroid hormone medication. A clinically relevant TSH-elevation was found in 110 (86%) patients. In 55 of 72 patients taking liothyronin for two weeks, the dosage was 60 µg/d, in one case it was 160 µg/d. For further 16 patients taking T_3 during withdrawal of T_4 the dosage was not documented or not retrievable. KU 2 was performed at a median of 285 days after KU 1 under THST.

Table 1 Change of SF-12® scores in comparison in hypothyroid state (KU 1) and under rhTSH (KU 2). A significant increase of the SF-12® health survey score under rhTSH is shown. The mental score showed a marginal higher increase than the physical score.

	Lower score (%)	No change (%)	Higher score (%)	Significance
physical	9.8	8.1	82.1	p<0.0001
mental	10.7	5.8	83.5	p<0.0001
sum score	7.4	2.5	90.1	p<0.0001

Table 2 Prevalence of diverse, definitive present, symptoms (%) at KU 1 and KU 2 is shown. All mentioned symptoms demonstrated a significant decrease (p<0.0001) at KU 2.

	KU 1 (n)	KU 1 (%) n=128	KU 2 (n)	KU 2 (%) n=128
sleeping disorder	64	50.4	8	6.3
lethargy	98	77.2	7	5.6
hoarseness	43	33.9	7	5.5
cold intolerance	59	46.8	6	4.7
weight gain	72	56.7	5	3.9
constipation	25	19.8	5	3.9
lack of concentration	61	48.0	5	3.9

Intraindividual analysis

Quality of life

The SF-12® health survey showed an intraindividual change of physical and mental symptoms in the different situations. During the hospitalisation at KU 1 the SF 12 sum score was 48.8±23.0% for physical, 49.4±23.1% for mental symptoms with a total sum score of 49.2±21.6%. For KU 2 under rhTSH stimulation there was a significant higher score (90.1%, complete data is shown in **Table 1**) of the physical (75.6±18.8%), mental symptoms (73.5±17.5%) and sum scores (74.5±16.4%) compared to KU 1.

Clinical symptoms

In KU 1 a wide spectrum of symptoms was specified by the treating physician as being "present" in the patient interview. Many symptoms which had been specified as definitely being "present" in the hypothyroid state were "not present" or "questionable" before KU 2.

In KU 2 there was a significant improvement (p<0.0001) in all reported symptoms (**Table 2**). Definitive present symptoms were compared in **Table 2**.

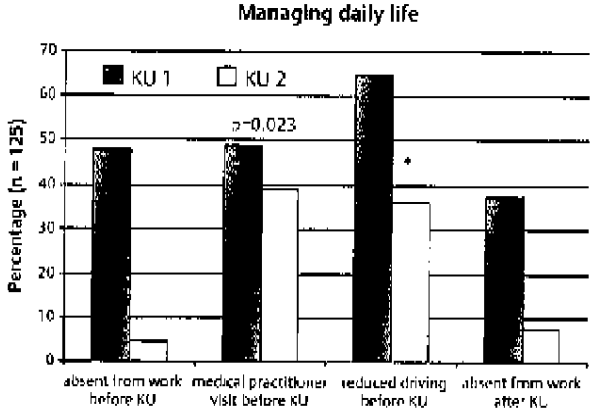

Fig. 1 Percentage of patients concerning absence from work before and after KU 1 (dark) and KU 2 (white), visits to a medical practitioner and reduced driving in direct comparison. The intraindividual comparison shows for the parameter "driving before KU" a significant ($p<0.01$) lower rate at KU 2, marked with a starlet (*).

Table 3 Extract of clinical findings at KU 1 and KU 2. All mentioned symptoms showed a significant decrease ($p<0.01$).

	KU 1 (n)	KU 1 n=128	KU 2 (n)	KU 2 n=128
cold skin	40	31%	1	0.8%
dry skin	32	25%	3	2.3%
decelarated movement	41	32%	0	0%
periorbital swelling	55	43%	1	0.8%
swelling of the hands	33	26%	1	0.8%

Managing daily life

Data concerning occupational activity were available for 125 of the 128 patients. 55.2% of them were employed, 1.6% were trainees or students, 3.2% were jobless, 15.2% were housewives and 24.8% were pensioners.

Prior to KU 1 88.4% were limited in their daily life, 47.8% had been absent from their work. The median absence from work was 10 days (range 1–30 d) in the four weeks before KU 1. Additional medication was necessary in 20.8% while 48.8% consulted physicians/hospitals. 64.8% reduced the use of their motor vehicle or abstained completely. 39.2% of the observed patients were escorted to KU 1 due to their hypothyroid symptoms. 37.5% needed a sickness certificate for a median of 6 days after KU 1.

Before KU 2 38.9% consulted a medical practitioner, 4.1% were in-patients, a median of 1 day was recorded. 4.5% were absent from work before KU 2, the mean absence was 4 days (range 2–5 d). 9.1% of the employed patients or trainees were able to exercise their job with restrictions in the last four weeks before KU 2. 36.2% did not use a motor vehicle or avoided driving on their own. 7.7% of the euthyroid patients were planned to be absent from work after KU 2, the median was 5 days (see also ○ **Fig. 1**).

In this survey also the need for additional medication during both modalities of TSH stimulation was recorded. Under withdrawal of thyroid hormones, 20.8% of the patients needed additional pharmaceuticals and 36 different classified drugs were used. Before KU 2 11.2% of the patients needed additional medication and 17 different drug classes were in use.

Clinical findings

An extract of clinical findings at KU 1 and KU 2 is summarized in **Table 3**. The median heart rate is significant ($p<0.0001$), intraindividual compared, higher in KU 2 (72/min) than in KU 1 (68/min).

Laboratory findings at KU 2

Administration of rhTSH occured on days 1 and 2, with one exception (day 1 and day 3). Thyroid laboratory tests were performed on day 5 (70.8%) or day 6 (22.5%), respectively. In one case the blood sample was taken on day 4 and in 6 cases on day 3. In 5 patients fT_4 was clinically significantly elevated as was fT_3 in 2 patients.

I-131 DWBS

The result of the scintigraphy was rated as "negative", "positive" or "questionable". Both at KU 1 and at KU 2 the median administered activity was 370 MBq of I-131. DWBS were classified negative in 90.6% at KU 1 and in 98.4% of the cases at KU 2. 11 scans were questionable at KU 1 and 1 was positive. In this particular patient a thyroid remnant in the ductus thyreoglossus was found but classified as negative for tumour remnants. Normal follow-up was done. At KU 2 two DWBS were rated as "positive" and in one case an evaluation was lacking.

For 124 patients, follow-up visits after KU 2 were planned in routine intervals, in one case a DWBS under withdrawal of hormones was scheduled, two patients had to be re-treated with radioiodine activity and one patient has been sent to surgery.

Adverse reaction during rhTSH stimulation

The safety data set consisted of 142 patients. Altogether in 15 (10.6%) of the Thyrogen®-treated patients, 17 events, but no serious event, were recorded. Nausea was the most common symptom (n=7). One patient each complained about headache, palpitations, diarrhoea, fatigue, vertigo, hyperhydrosis, hot flash, flu-like feeling, feeling of being drunk and angina pectoris. All symptoms were completely reversible, in one case a slight nausea had to be treated with medication.

Preference analysis

All patients were asked about their preference for the stimulation of TSH. 127 of 128 patients reported rhTSH as their preferred method of choice. Only one patient was undecided, caused by physical integrity in hypothyroid state. Nevertheless all patients with adverse reactions decided rhTSH-Stimulation better, which might be a good equivalent to the symptoms caused by THW.

Moreover the very good drug tolerability and the significantly fewer symptoms were one more reason for patients' decision. Patients felt better, had more "power", could manage their job as usual and had no reduction in quality of life.

Subgroup analysis T_3/T_4

An additional analysis of two subgroups of patients treated either solely with T4 for suppression therapy followed by THW and patients experiencing a T4/T3 switch with T3 medication up to 10 days before DWBS were performed (see also **Table 4**). 72 Patients were treated with T3 before KU 1. There is no difference between these group and the patients treated only with T4 according to age, sex or histologic diagnosis. An interindividual analysis using the χ^2 test showed no significant difference between these two groups to all investigated objectives. No sig-

Table 4 Extract of clinical findings in hypothyreot state at KU in direct comparison between the subgroup treated with T3 and solcy with T4. There is no significant difference between these both subgroups.

	T3+T4 n=128	T4 n=56	T3 N=72	p-value
sleeping disorder	50.4	41.9	53.9	0.17
hoarseness	33.9	30.7	36.9	0.75
cold intolerance	46.8	45.2	48.4	0.92
weight gain	56.7	48.4	64.2	0.06
constipation	19.8	21.0	18.8	0.92
lack of concentration	48.0	42.0	53.8	0.37

nificant difference is to be seen in the presented clinical symptoms or the clinical findings. Even economical parameters, including absence from work, additional visits of physicans or the lowering of driving showed rare variation. For some clinical symptoms (see also **Table 4**), for example lack of concentration and weight rise, the T3 treatment shows a higher percentage of affected patients.

A highly significant ($p<0.01$) change according to the SF-12 quality of life, hypothyroid symptoms, additional physician visits, number of days absent from work, additional medication and thyroid-specific symptoms was observed between both withdrawal schedules and the rhTSH group.

Discussion

This survey of a relatively large group of patients who had been thyroidectomized and received radioiodine ablation for DTC revealed that the hypothyroidism resulting from THW as a preparation method for DWBS is often not only uncomfortable for the individual, but costly for society. Almost three-quarters of the patients presented with clinical symptoms, and showed multi-symptomatic hypothyroidism during withdrawal. More than two-thirds of the survey patients in hypothyroidism reported a restricted or precluded performance of activities of daily living, whereas less than a tenth of them experienced this under rhTSH.

In about half of the patients, hypothyroid complaints led to a median of 10 missing work days before KU 1. An economical valuation and estimation of the cost effectivness of these data is planned to be done separately. Two-thirds of patients drove motor vehicles while hypothyroid, despite medical advice to the contrary. This could be associated with harmful consequences as was recently described by Rosenthal, 2007.

Nearly all the patients (127 of 128) preferred rhTSH administration over thyroid hormone withdrawal, only one patient was undecided. In a previous study, one-fifth of the patients indicated a preference for thyroid hormone withdrawal. This finding was considered by the authors to be attributable to a lack of experience with rhTSH (Luster et al., 2005). Limitations of this study were the retrospective assessment of data and the assumptions made in the pharmaco-economic estimations.

A 25-patient study from the Netherlands found a 100% incidence of physical or mental hypothyroid symptoms during thyroid hormone withdrawal; 48% of patients rated these symptoms as serious or very serious (Nijhuis et al., 1999). 45% patients of this study reported that, during thyroid hormone withdrawal, they worked unproductively. It is reported in this study that roughly 59% of work hours are missed during the withdrawal period, this represents a loss of 2,5 million Euro per year to that country. The Dutch investigators found lower rates of hypothyroid-related primary-care physician visits than we did (16% vs. 49%). Additional medication use was registered at a similar rate under withdrawal of hormones (24% vs. 21%). Their patients were younger (mean age 41 years vs. 52 years). They did not report on specialist physician, hospital visits or hospitalization.

Our findings, with regard to clinical symptoms, generally agree with those of other studies in patients who underwent THW at some point after primary surgery for DTC. An American study (n=34) using a validated thyroid cancer-specific survey found a statistically significant worsening of fatigue and sleeping disorders, as well as of employment motivation, time away from work and quality of work compared to the time taking thyroid hormones (Dow et al., 1997).

In another recent publication, Schroeder et al., 2006 re-analyzed data from the pivotal phase 3 study of rhTSH in the diagnostic follow-up of DTC, comparing SF-36 QOL scores in 228 thyroidectomized DTC patients when on and off thyroid hormone with the scores of the US general population or the scores of patients with several morbidities. These authors found that, on thyroid hormone therapy, the DTC patients had SF-36 QOL scores at or above the US general population norms in six of eight domains addressed (e.g., physical functioning, bodily pain, vitality and role emotional). After thyroid hormone withdrawal, however, the DTC patients had SF-36 QOL scores significantly lower than these norms in all eight domains. Interestingly, after thyroid hormone withdrawal, the DTC patients had significantly lower SF-36 QOL scores than did even patients with heart failure or migraine in six of eight domains, or patients with chronic clinical depression in three of eight domains.

Duntas and Biondi (2007) showed in a recent review that acute hypothyroidism induced by THW seriously affects multiple organs and systems and, especially in severe cases, can impair quality of life. The use of rhTSH obviates the clinical and economical consequences of hypothyroidism which counterbalance the cost of the product, and promotes compliance while preserving the patient's normal daily functioning and productivity. No significant differences were found in the comparison of complete THW and bridging with T_3. Leboeuf showed that preparation for DWBS with T_3 did not prevent profound hypothyroidism and delayed the TSH elevation required for DWBS (Leboeuf et al., 2007). The clear preference of the included patients for exogenous stimulation was shown also in the substantial promotion of compliance in the treatment of DTC (Cohen et al., 2004).

Haugen et al. showed that rhTSH-aided DWBS is equivalent in the diagnostic follow-up and ablation settings. The use of rhTSH allows more predictable timing and more rapid TSH elevation than does withdrawal of hormones (Luster, 2006). In particular, rhTSH administration may allow the ablation to be performed sooner after surgery, permitting patients to complete initial therapy of DTC and move on with their lives some weeks earlier (Borget et al., 2007, Borget et al., 2008, Mernagh et al., 2006).

Although our observational study was prospective and multicentric, there are some limitations that have to be mentioned. Drawback of this study is that all patients were first evaluated on thyroid hormone withdrawal. It was the first post therapy evaluation, so it could result in more anxiety and mental discomfort when compared to second diagnostic evaluation performed under rhTSH stimulation. KU 1 was in median done 170 days after remnant ablation; an impact of the surgery on the results of KU 1 is thus unlikely but cannot be excluded with certainty. In

14% of the patients the time period between ablation therapy and KU 1 was more than 270 days, this might have an influence on SF 12 or the clinical findings.

A large number of included patients had to be excluded from the data analysis. In most cases observation was discontinued due to non-compliance and lacking data. Evidence for a recurrence or a remnant led to exclusion as well as, e.g., pregnancy. Concerning baseline parameters, the 64 excluded patients were not significantly different from those patients who were included in the efficacy data set.

Regarding the economic estimation, for example absence from work, patients during hormone withdrawal could be more willing to ask for sick leave because it is common practice and is reimbursed by health insurance. The second possible bias in this particular finding is the possible threat of diagnosis. Moreover the later control visit is in a higher stat of motivation to go to work due to fear to loose the job.

For patients taking T_3 during withdrawal of T_4 the dosage scheme of T3 was not clearly documented or was not retrievable.

Conclusion

The data on SF-12® health survey, clinical symptoms and management of daily life indicated a statistically highly significant improvement of life quality by use of rhTSH for all included patients, even if this effect is perhaps partially exaggerated. Side effects of rhTSH occurred in 15 out of 142 patients and were classified as low-grade reaction. There was a clear preference of 127 out of 128 patients for exogenous stimulation with rhTSH in intraindividual comparison to withdrawal of hormones. Only one patient was undecided, caused by physical integrity in hypothyroid state. From the clinical point of view the exogenous stimulation is preferable, also in terms of the low rate of side effects. In our study there is no significant difference between patients quality of life solely treated with T4 for suppression therapy followed by TIIW and patients experiencing a T4/T3 switch with T3 medication up to 10 days before diagnostic whole-body scan.

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