Quality of life, clinical outcomes and safety of early prophylactic levothyroxine administration in patients with Graves' hyperthyroidism undergoing radioiodine therapy: a randomized controlled study

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Abstract

Objective: While radioiodine therapy is commonly used for treating Graves' disease, a prolonged and clinical hypothyroidism may result in disabling symptoms leading to deterioration of quality of life (QoL) of patients. Introducing levothyroxine (LT_4) treatment in the early post-therapeutic period may be an interesting approach to limit this phenomenon.
Methods: A multicenter, prospective, open-label randomized controlled trial enrolled 94 patients with Graves' hyperthyroidism randomly assigned to the experimental group ($n=46$) (group A: early prophylactic LT_4 treatment) or the control group ($n=48$) (group B: standard follow-up). The primary endpoint was the 6-month QoL. The secondary endpoints were other QoL scores such as Graves' ophthalmopathy (GO) outcomes, thyroid function tests and safety.
Results: The primary endpoint at 6 months was achieved: the mental composite score (MCS) of Short Form 36 (SF-36) was significantly higher in group A compared to group B ($P=0.009$). Four other dimension scores of the SF-36 and four dimension scores of the thyroid-specific patient-reported outcome (ThyPRO) significantly differed between the two groups, indicating better QoL in group A. After adjustment for variables, the early LT_4 administration strategy was found as an independent factor for only two scores of SF-36: the MCS and the general health (GH) score. There were no differences in GO, final thyroid status and changes in the anti-TSH receptor antibodies (TRAbs) levels between the two groups. No adverse cardiovascular event was reported.
Conclusion: Early LT_4 administration post-radioactive iodine (RAI) could represent a safe potential benefit for patients with regard to QoL. The optimal strategy taking into account administered RAI activities and LT_4 treatment dosage and timing remains to be determined.

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Introduction

Graves' disease (GD) is the commonest cause of hyperthyroidism (2% in women and 0.4% among men) (1, 2). Until present, there are two approaches for treating hyperthyroid patients, conservative or radical (destructive) measures. The first is based on the use of anti-thyroid drugs (ATDs) while the second is based on the use of either iodine-131 or total thyroidectomy. In Europe, the medical option is often preferred as a first-line approach with a risk of relapse between 51 and 68% after a complete initial course of therapy (at least 12 months) (3, 4). Radical options are mainly indicated for recurrences, resistance to (ATDs) or after drug-related adverse events (i.e. agranulocytosis and hepatitis), but patient's preference is also a relevant criterion to select the type of treatment.

Over many decades, radioiodine therapy has been used for treating Graves' disease with excellent cost-effectiveness ratios (5, 6) and no significant oncogenetic risks (7, 8, 9, 10). There is still no consensus regarding the most appropriate approach for treating Graves' hyperthyroidism with radioiodine (11, 12, 13, 14, 15, 16, 17). Administered radioactive iodine (RAI) activities can be either fixed (for ablation) or adjusted for different parameters such as thyroid mass, radioiodine effective period and thyroid uptake values (for either ablation or restoration of euthyroidism) (18, 19). Ablative approaches are increasingly being proposed for the treatment of Graves' disease in order to decrease the risk of persistent/recurrent hyperthyroidism. When an ablative strategy is chosen, a third of patients develop hypothyroidism within the first month, two-thirds by the second month and almost all patients after 3 months of 555 MBq activity of RAI. (20).

Therefore, it is crucial to prevent and to treat hypothyroidism after radioiodine therapy: firstly, hypothyroidism may induce deleterious symptoms such as fatigue, memory impairment, cognitive decline or depressed mood (21). These symptoms are the main cause of dissatisfaction regarding radioiodine therapy (22, 23, 24) and may lead to deterioration of quality of life (QoL) of patients (25); secondly, the hypothyroid state may also induce indirect economic costs through lost productivity and increased absenteeism (26); thirdly, radioiodine therapy increases the risk of developing *de novo* Graves' ophthalmopathy (GO) or worsening a pre-existing GO (27, 28, 29), which is also associated with alteration of QoL and social isolation (30). Therefore, Tallstedt *et al*. (31)proposed to administer levothyroxine (LT_4) in the early post-therapeutic period (50 μg daily started at 2 weeks post-RAI) in GD patients with minimally active GO in order to avoid profound hypothyroidism and potentially prevent *de novo* or worsening GO.

The aims of the present multicenter randomized controlled study were to evaluate the impact of early prophylactic (preventative) LT_4 administration following radioiodine therapy for Graves' hyperthyroidism in comparison to standard follow-up on QoL, anxiety and depression, cardiovascular parameters such as blood pressure (BP) and heart rate (HR), GO outcomes, thyroid function tests and anti-thyroid-stimulating hormone (TSH) receptor antibodies levels.

Subjects and methods

Design

A multicenter, prospective, randomized, controlled, open-label, two-parallel group study compared early prophylactic LT_4 administration (group A) following radioiodine therapy to standard follow-up (group B) in which patients were treated with LT_4 based on TSH and/or free T_4 (fT_4) concentrations. The study protocol was designed using the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement. Recruitment was performed in seven French nuclear medicine/endocrinology centers. The methodological support had been provided by the Clinical Research Unit, Assistance Publique-Hôpitaux de Marseille (AP-HM), France.

Eligibility criteria

The inclusion criteria were as follows: age $\geq$18 years (without an upper limit), Graves' hyperthyroidism, absence or minimal GO (NOSPECS classification), absence of active GO (clinical activity score (CAS) $<$3), FT_4 and/or FT_3 below 1.5 times the upper reference limit before RAI, thyroid volume evaluated by US within 3 months preceding the trial $<$60 ml, withdrawal of ATD 5 days prior to radioiodine therapy regardless of the type or duration of treatment with ATDs and a negative pregnancy test. All patients gave their signed informed consents for participation. GO evaluation was assessed by a specialist ophthalmologist prior to inclusion.

The exclusion criteria were as follows: presence of thyroid nodules suspicious for malignancy, injection of iodinated radiographic contrast media within the 4 weeks prior to radioiodine therapy, concurrent or previous amiodarone treatment, previous history of major

concurrent chronic medical disorders, psychiatric disorders and chronic alcoholism.

Therapeutic strategies

For radioiodine therapy, all patients received 20 MBq of iodine-131/gram of thyroid tissue; the thyroid volume was evaluated by thyroid US.

The two therapeutic strategies were as follows:

i) Group A: in early prophylactic LT_4 treatment, patients allocated to this group received daily LT_4 (50 μg) starting 15 days post-radioiodine administration. Then, the dose of LT_4 was adapted to thyroid function tests at 1, 3 and 6 months.
ii) Group B: patients allocated to this group were followed up every 4 weeks and treated with LT_4 when needed.

LT_4 dose modification was standardized as follows:

i) TSH between 4.5 and 10 mU/l: LT_4 75 μg/day (25 μg/day added in patients already treated with the preventative 50 μg/day).
ii) TSH >10 mU/l: LT_4 between 1.6 and 1.8 μg/kg per day (while adding the dose difference in patients already treated with the preventative 50 μg/day).

Patients remained off ATDs with the possibility of re-treatment during follow-up, as judged by the clinicians.

Endpoints

Primary endpoint ▸ The primary endpoint was represented by the QoL score from the mental composite score (MCS) of the Short Form 36 (SF-36), assessed at 6 months post-RAI.

Secondary endpoints

i) The QoL was further assessed by additional scores: a) the MCS of SF-36 at 1 and 12 months post-RAI; b) the physical composite score of SF-36, the 8 dimension scores of the SF-36 and the thyroid-specific patient-reported outcome (ThyPRO) dimension scores at 1, 6 and 12 months post-RAI; and c) the changes in the different QoL scores between baseline, 1, 6 and 12 months post-RAI.
ii) The level of depression and fatigue was assessed at 1 and 6 months post-RAI using the self-administered Beck Depression Inventory (BDI) and the Modified Fatigue Impact Scale (MFIS) respectively. Anxiety was assessed with the Spielberger's State-Trait Anxiety Inventory (STAI).
iii) GO: at baseline, all patients were evaluated for GO by a specialist according to the European Group on Graves' Orbitopathy (EUGOGO) recommendations (examination of severity using NOPECS classification and assessment of activity using the CAS. Following RAI, patients were screened at each study visit for GO (clinical examination, EUGOGO questionnaire) and referred to an ophthalmologist if GO appearance or aggravation was suspected or observed.
iv) Thyroid status: cure/remission was defined as either euthyroidism (without ATD) or hypothyroidism. Following RAI, hypothyroidism was defined by the presence of FT_4 <10 pmol/l or TSH >4.5 mU/l. Treatment failure was defined as the need for retreatment with anti-thyroid medication, repeat RAI or thyroidectomy after initial therapy.
v) Anti-TSH receptor antibodies levels at 3 and 12 months were compared to baseline levels in two groups.

Safety ▸ Safety assessment was carried out at each clinical visit through the evaluation of symptoms and clinical signs of thyrotoxicosis, systolic and diastolic BPs and HR.

Study outline

Inclusion ▸ Inclusion of patients was performed by the nuclear physicians or endocrinologists. After inclusion, patients were randomized into one of the two groups after completing the consent forms.

Randomization ▸ Computer-generated randomized lists were drawn up before the beginning of the study by the clinical research unit of the AP-HM. The randomization was stratified by center, with a 1:1 allocation ratio.

Baseline assessment ▸ Physical signs and symptoms were evaluated by physicians. Patients filled out the first self-administered questionnaires including socio-demographic parameters, anxiety, depression, fatigue and QoL scales. A GO assessment was performed in addition to laboratory tests for baseline TSH, FT_4, FT_3 and anti-TSH receptor antibodies

Follow-up ▸ Follow-up visits took place at 1, 3, 6 and 12 months post-RAI. At each visit, the following data were

recorded: physical signs, symptoms and thyroid status. Depression, fatigue and QoL were assessed using patient-filled handouts containing all the relevant questionnaires at 1, 6 and 12 months. Thyroid function tests were performed locally. A GO assessment was carried out by a specialist ophthalmologist when specific symptoms according to the EUGOGO questionnaire were present. Anti-TSH receptor antibody levels were measured at 3 and 12 months post-RAI.

Assessment tools

Measurement of QoL ▸ QoL was assessed using the French versions of the SF-36 and the ThyPRO. SF-36 is a generic questionnaire (32) that has eight subscales (physical function (PF), social functioning (SF), role physical (RP), role emotional (RE), mental health (MH), vitality (V), bodily pain (BP) and general health (GH)), with scores ranging from 0 (low) to 100 (high QoL level). Two component summary measures of SF-36, namely, PCS and MCS respectively, can be calculated. Higher scores indicate higher QoL levels. The ThyPRO is an 84-item-specific questionnaire measuring QoL with 13 scales covering physical (four scales) and mental (two scales) symptoms, function and well-being (three scales) and participation/social function (four scales) (33). Each scale ranges between 0 and 100 with increasing scores indicating decreasing QoL (i.e. more symptoms or greater impact of disease).

Assessment of depression and anxiety ▸ The level of depression was assessed using the self-administered BDI. The BDI score range is 0–39, with higher scores indicating worsening depression (34).

The STAI is a self-reporting questionnaire consisting of 40 items leading to two scores, state and trait scores, ranging from 20 (absence of anxiety) to 80 (high anxiety) (35, 36).

The level of fatigue was assessed using the MFIS (37), describing three domains: (physical, psychological and psychosocial) with an index. Higher scores indicate higher fatigue levels.

Laboratory tests ▸ Thyroid function tests (TSH, free T_4 and free T_3) were performed with kits routinely used in each clinical center. Anti-TSH receptor antibodies were evaluated at baseline and during follow-up using one of the following two assays: Elecsys Anti-TSHR-Cobas (Roche Diagnostics) (functional sensitivity 0.9 IU/l) and TRAK human DYNOtest (BRAHMS Diagnostica GmbH, Berlin, Germany) (functional sensitivity 1.5 IU/l).

Ethical aspects, laws and regulations ▸ The study had been conducted in accordance with the Helsinki declaration and the French laws and regulations (Code de la Santé Publique, article L.1121-1/Loi de Santé Publique n 2004-806 du 9 août 2004 relative à la politique de santé publique et ses décrets d'application du 27 août 2006). Regulatory monitoring was performed by the sponsor. The approval of the French authorities, including the French Ethics Committee (Comité de Protection des Personnes Sud Méditerranée II) and the French Drug and Device Regulation Agency (Agence Nationale de Sécurité du Médicament) was obtained before beginning the study. The ClinicalTrials.gov identifier is NCT01295333.

Statistical analysis

Sample size ▸ The sample size was determined in order to obtain an 80% power to detect a ten-point difference (s.d. 15 pts) in QoL at 6 months as evaluated by the MCS of SF-36. With a significant P value of 0.05, these calculations showed that a total of 36 patients per group were needed; considering a potential 20% of patients being lost to follow-up at 6 months, a total of 90 patients were needed to be included. The final sample included 48 patients in the control group (group B) and 46 patients in the experimental group (group A); the QoL at 6 months was available for 43 and 39 patients respectively. No interim analysis was planned. Data were analyzed using SPSS version 17.0 Software.

Analysis ▸ The intention-to-treat population (including all subjects who were randomized and were at least evaluated at baseline) was used for the analysis. The normality of the variables was estimated using frequency histograms and the Shapiro test. The baseline parameters were presented per group (A and B) and compared using the χ^2-test or Fisher's exact test for categorical variables and Student's t-test for continuous variables.

LT_4 and ATD treatments, thyroid and ophthalmologic status were compared between the two groups.

The Mental Composite Scores of SF-36 assessed at 1, 6 (primary endpoint) and 12 months post-RAI were compared between the two groups using the Mann-Whitney test. The same comparison was performed for the other SF-36 and ThyPRO scores at each evaluation period (1, 6 and 12 months).

Changes in QoL scores between baseline and 6 months respectively were compared between the two groups, and the analysis of variation for repeated measurements was performed to compare changes over time (baseline, 1 and 6 months) between the two groups. The same analysis was performed for depression and fatigue scores (baseline, 1 and 6 months).

For each 6-month QoL score that differed between the two groups, multivariate analyses using multiple linear regressions were performed to determine variables potentially predictive of QoL levels. Variables relevant to the models were selected based on their clinical interest (gender and age) and/or a threshold P value <0.05 during univariate analysis. The final models expressed the standardized beta coefficients. The coefficient represents the change of the standard deviation in the dependent variable (QoL) resulting from a change of one standard deviation in the different independent variables. The independent variables with the higher standardized beta coefficients are the variables with a greater relative effect on QoL.

A subgroup analysis was performed comparing patients within group A (early prophylactic) that had no interruption of LT_4 during the first 3 months (A1), with the patients within group B (standard follow-up) that had no introduction of LT_4 during the first 3 months (B1).

All the tests were two-sided. Statistical significance was defined as $P<0.05$.

Results

Study population

Ninety-four patients were included in the present study. Four patients in group A were lost to follow-up before 6 months (one at 2 months, two at 3 months and one at 4 months) and three patients in group B (all at 3 months). The primary endpoint was available for 39 and 43 patients in groups A and B, respectively.

Patients' baseline characteristics at the time of RAI therapy are shown in Table 1. The mean age was 48.8 and 47.1 years in groups A and B, respectively. Socio-demographic parameters, anxiety scores (trait and state), fatigue levels and the QoL levels did not differ between the two groups at baseline except for the PCS, BP and GH scores of SF-36 and the sex-life score of ThyPRO with a significantly better QoL for group A. The mood disorders (BDI score) were significantly more frequent within group B than A.

The two groups displayed similar characteristics, with the exception of higher plasma FT_4 concentrations in group B ($P=0.017$). The average administered RAI activity was similar in the two groups, 410 ± 168 and 410 ± 165 MBq, respectively. Thyroid uptake values obtained in 64 patients (39 iodine-123 and 25 technetium-99m$^-$) and urinary iodine levels assessed in 35 cases were not statistically different between the two groups.

Follow-up in both groups

At 1-month post-RAI, 7/45 (16%) patients in group A were no longer on LT_4. Three of the seven patients developed hypothyroidism 1 month later. At 2 months, three additional patients were off LT_4. The decision to stop LT_4 administration in this group was left to clinicians' judgment, as this subgroup of patients experienced an increase in thyroid hormone levels. However, there were no adverse cardiovascular events reported in group A patients.

In group B, LT_4 administration was introduced in seven patients at 1-month post-RAI, while at 2 months, 11 additional patients were started on LT_4.

Very few patients in both groups required ATDs (Table 2).

QoL outcomes

At 6 months, the MCS of SF-36 (primary endpoint) was significantly higher (better QoL) in group A compared to B ($P=0.009$). Four other dimension scores of the SF-36 (RE, MH, SF and GH) and four dimension scores of the ThyPRO (emotional susceptibility, social impairment, sex life and cosmetics complaints) significantly differed between the two groups, indicating better QoL in group A. QoL changes between baseline and 6 months did not differ between the two groups except in certain domains only (data not shown). A statistically significant difference in the variation over time (baseline, 1 and 6 months) of QoL scores was observed between the groups for: i) SF-36: MCS (Figure 1) and five scores (RE, MH, SF, BP and GH) and ii) ThyPRO: the cosmetics complaints score; group B showed lower levels than A ($P<0.05$).

A subgroup analysis was performed after excluding patients that were retreated before 6 months or lost in follow-up. This subgroup analysis, comparing the 6-month QoL scores between the 32 individuals of group A (A1: early prophylactic without interruption of LT_4 during the first 3 months) and the 34 individuals of group B (B1: standard follow-up without introduction of LT_4 during the first 3 months), showed significantly higher QoL scores in most domains of SF-36 (RE, RP, MH, SF, GH and MCS) and ThyPRO

Table 1 Baseline characteristics.

	Group A ($n=46$)	**Group B** ($n=48$)	***P***
1. Sociodemographic parameters			
Age in years (mean ± S.D.)	48.8 ± 13.5	47.1 ± 12.9	0.544
Sex (female, *n*(%))	34 (74)	37 (77)	0.721
Education level (%)			0.268
Middle School	22 (49)	18 (38)	
High School	23 (51)	30 (63)	
Number of children, *n*(%)			0.105
0	13 (28)	7 (15)	
≥1	33 (72)	41 (85)	
Marital status, *n*(%)			0.739
Single	12 (26)	14 (29)	
Married	34 (74)	34 (71)	
Professional activity, *n*(%)			0.853
Yes	25 (54)	27 (56)	
No	21 (46)	21 (44)	
Tobacco status – smoker, *n*(%)	13 (28)	17 (35)	0.457
2. Anxiety, depression, and fatigue			
Spielberger trait[a] (20–80); mean ± S.D.	39.6 ± 11.1	41.1 ± 11.8	0.536
Spielberger state[a] (20–80); mean ± S.D.	42.1 ± 9.6	43.3 ± 9.4	0.530
Beck score[b] (0–39); median (IQR)	2.5 (1.0–7.0)	4.5 (2.3–10.0)	**0.037**
Beck classes (depression)			**0.014**
No	27 (59)	16 (33)	
Depression	19 (41)	32 (67)	
Fatigue[c]; median (IQR)			
Physical (0–36)	15 (6–21)	17 (8–26)	0.266
Cognitive (0–40)	9 (4–17)	15 (5.3–23)	0.136
Psychosocial (0–8)	2 (0.3–4)	4 (0.8–5.3)	0.125
Total (0–84)	27 (12–37)	32 (17–53)	0.129
3. Clinical characteristics			
GO (*n*)			
NOSPECS classification			0.237
0	44	48	
1	2	0	
Clinical activity score			0.495
0	46	48	
1–2	2	0	
Thyroid uptake (%); mean ± S.D.			
^{123}I (2 h)	23 ± 16	28 ± 26	0.388
^{99m}Tc (20 min)	7 ± 5	7 ± 7	0.887
Urinary Iodine concentration, μg/g Ur creatinine (mean ± S.D.)	180 ± 151	161 ± 122	0.691
ATD at the time of inclusion *n*(%)			0.673
Yes	24 (53)	23 (49)	
No	21 (47)	24 (51)	
Number of relapse (mean ± S.D.)	2.4 ± 1.0	2.0 ± 0.7	0.102
Time interval initial diagnosis/radioiodine (years) (mean ± S.D.)	6.46 ± 5.57	5.2 ± 4.4	0.240
Thyroid volume (ml); (mean ± S.D.)	20.4 ± 10.4	21.5 ± 10.3	0.595
TSH, mU/l; median (IQR)	0.19 (0.01–1.47)	0.07 (0.01–1.29)	0.404
Free T_4 (pmol/l) (mean ± S.D.)	15.6 ± 5.1	19.0 ± 8.3	**0.017**
Free T_3 pmol/l (mean ± S.D.)	5.9 ± 2.6	7.5 ± 4.6	0.068
Anti-TSH receptor antibodies; median (IQR)	4.18 (1.79–7.98)	3.70 (1.63–5.90)	0.314
Baseline concentration (U/l)	+296.0 (13–540)	+373.0 (0–830)	0.825
Changes at 3 months/baseline (%)	+39.5 (−17–106)	+48.0 (−29–539)	0.325
Changes at 12 months/baseline (%)	410 ± 168	410 ± 165	0.995
Administrated RAI activity (MBq) (mCi); (mean ± S.D.)	(11 ± 4.5)	(11 ± 4.5)	

According to the eligibility criteria, ATDs were withdrawn 5 days prior to radioiodine therapy.
[a]Higher score, higher anxiety level.
[b]Higher score, more severe depression.
[c]Higher fatigue level.

Table 2 Evolution of LT_4 and ATD usage and percentages of change in FT_4 during the first 3 months post-RAI.

	Group A ($n=46$)	**Group B** ($n=48$)	***P***
Number of patients on-LT_4 at:			
1 month	46/46	0	$<10^{-3}$
2 months	38/45	7/48	$<10^{-3}$
3 months	36/45	18/48	$<10^{-3}$
Number of patients on ATD at:			
1 month	0	0	NS
2 months	1	2	NS
3 months	3	4	NS
% variation FT_4:			
1 month/baseline			$<10^{-3}$
Mean ± S.D.	30.2 ± 54.3	−2.9 ± 47.3	
Median (IQR)	16.5 (−1.7; 50.7)	−9.3 (−30.2; 17.5)	
2 months/baseline			0.114
Mean ± S.D.	15.1 ± 64.0	−3.9 ± 75.2	
Median (IQR)	−0.9 (−38.5; 57.5)	−16.0 (−55.4; 32.2)	
3 months/baseline			0.045
Mean ± S.D.	16.5 ± 89.3	−18.2 ± 43.4	
Median (IQR)	−5.2 (−30.2; 46.8)	−23.5 (−46.9; 13.8)	

NS, non-significant.

(anxiety, social impairment, daily life, sex life and cosmetics complaints). These findings are illustrated in Fig. 2.

Final thyroid status and ophthalmologic outcomes ▸

The thyroid status of patients is detailed in Table 3.

The majority of patients achieved euthyroidism (without ATDs) or hypothyroidism at 12 months post-RAI; 92.8% (83.3% hypothyroidism and 9.5% euthyroidism) and 93.3% (77.8% hypothyroidism and 15.5% euthyroidism) in group A and B respectively (Table 3). The levels of anti-TSH receptor antibodies were similar at baseline as were the changes during the 1-year follow-up after RAI treatment (Table 1).

Only two patients (one in each group) developed GO: (2.4 and 2.2% in group A and B respectively).

Safety

There were no adverse cardiovascular events reported throughout the study with no statistical difference between BP and HR readings between groups A and B. The median BP at 6 months was 126.5/75 and 130/80 mmHg for group A and B respectively.

In subgroup analysis, no single variable showed any statistically significant difference at any point of time.

Depression and fatigue

As depression was unbalanced at baseline between groups, the 1 and 6 months scores were not different. The fatigue levels and the variations over time (baseline, 1 and 6 months) did not differ between the two groups (data not shown).

Predictors of health quality outcomes

In order to determine the real effect of early LT_4 treatment on the 6-month QoL scores, multivariate models were performed with adjustment of the following variables: age, gender and unbalanced baseline parameters ($P<0.05$), i.e. the depression score and the plasma free T_4 levels. An independent model was performed for each 6-month QoL

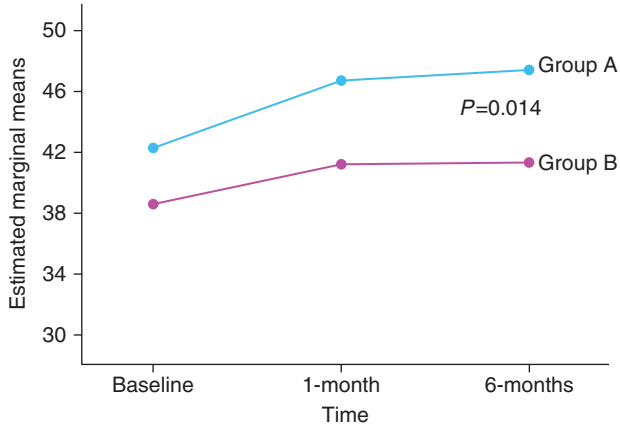

Figure 1
Variation overtime of the MCS of SF-36 in both groups, with statistical significance at 6 months.

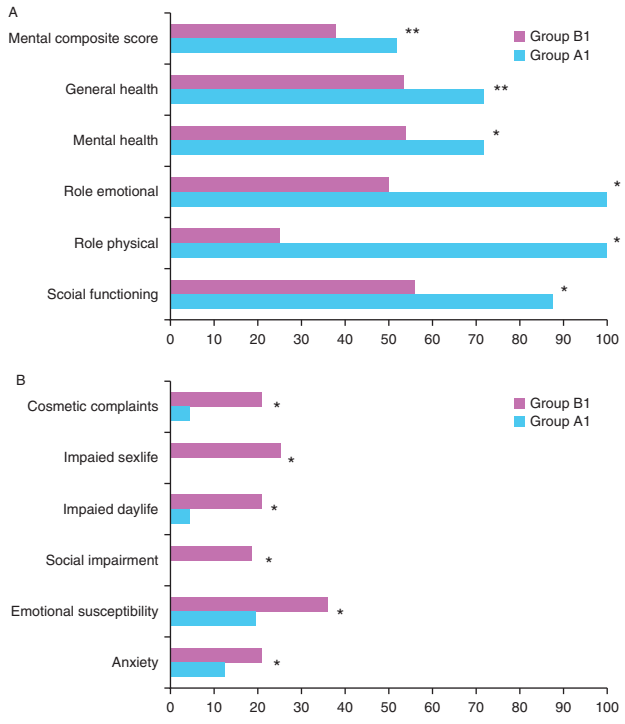

Figure 2

Comparison in QoL scores between early prophylactic without interruption of LT_4 (A1) *vs* standard follow-up without introduction of LT_4 (B1). A: SF-36; B: ThyPRO; *: $P<0.05$ **: $P<0.01$.

score that differed between the two groups: MCS, RE, MH, SF and GH for SF-36, and ES, SI, SL and CC for ThyPRO (Table 4). After adjustment, the early LT_4 treatment strategy was found as an independent factor for only two scores of SF-36, the MCS and the GH score. Depression was also associated with all the 6-month QoL scores. All the details are presented in Table 5.

Discussion

To the best of our knowledge, this is the first randomized controlled study that evaluates the impact of early LT_4 administration post-RAI on QoL in patients with Graves' disease. Furthermore, homogeneity was achieved by standardizing the administered radioiodine activities based on thyroid mass, along with standardized LT_4 administration regimens throughout the entire study period.

The principal conclusions that can be drawn from this study include: i) a slightly better QoL associated with early LT_4 administration post-RAI therapy, which is not associated with adverse cardiovascular events or significant increases in BP or HR; ii) a high success rate of thyroid volume-adjusted RAI in both groups; and iii) a lower rate of radioiodine-induced ophthalmopathy (RAI-induced GO) in the study population compared to previous studies despite the short-term follow-up.

At 6 months post-RAI, the QoL of patients with early systematic LT_4 administration appeared significantly better than that of patients allocated to the standard protocol. Although this benefit in QoL scores appeared modest, this improvement was observed in several domains of the generic and the specific QoL questionnaires. While the objective control of the disease did not really differ between the two strategies, it is now well-recognized that the parameters of disease control and the physicians' perceptions do not reflect all the aspects that patients consider important in their lives (38). Patient-reported outcomes (PROs) can provide supplementary clinical relevance in the evaluation of disease progression, treatment and the management of care provided to patients with chronic disease. Large international agencies encourage and recommend the assessment of QoL and psychological well-being (39, 40) and the CONSORT statement provides recent evidence-based recommendations to improve the completeness of reporting of PROs (41).

In terms of subgroup analysis, the difference in QoL scores was well-observed between group A patients who remained on LT_4 (subgroup A1) vs group B patients who had not yet had LT_4 introduced during the first 3 months (subgroup B1).

As observed from Table 4, there were no significant differences in QoL scores between group A and B at 1 and 12 months respectively. This could be explained by the fact that differences in thyroid status were less evident at those periods.

Unfortunately, depression levels at baseline were not similar between the two groups. However, after

Table 3 Clinical outcomes after RAI.

	Group A ($n=46$)	**Group B** ($n=48$)	***P* value**
Hypothyroidism[a]	35/42 (83.3%)	35/45 (77.8%)	
Euthyroidism[a]	4/42 (9.5%)	7/45 (15.5%)	0.723[b]
Treatment failure	3/42 (7.1%)[c]	3/45 (6.7%)[d]	
De novo GO	1/42 (2.4%)	1/45 (2.2%)	1.000
Lost to follow-up <12 months	4	3	0.711

[a]Thyroid status at 12 months post-RAI.
[b]Freeman–Halton test.
[c]All three patients re-treated with RAI at 6, 8 and 12 months respectively.
[d]One was operated at 4 months while the remaining two received ATD.

Table 4 Comparison of QoL scores (generic and specific questionnaires) between groups.

	Baseline			Month 1			Month 6			Month 12		
	Group A	Group B	*P*	Group A	Group B	*P*	Group A	Group B	*P*	Group A	Group B	*P*
SF-36[a]												
Mental component summary	41 (31–49)	39 (31–47)	0.418	47 (40–52)	41 (33–51)	0.058	52 (41–56)	40 (32–51)	0.009	48 (35–55)	47 (37–51)	0.368
Physical component summary	49 (42–56)	45 (36–51)	**0.022**	50 (43–55)	46 (37–53)	0.081	50 (41–55)	50 (40–53)	0.323	51 (38–55)	51 (43–54)	0.820
Physical Function	85 (55–97)	75 (46–90)	0.145	90 (70–100)	75 (45–95)	0.096	85 (70–100)	85 (65–95)	0.636	90 (66–100)	85 (70–100)	0.982
Social Functioning	63 (50–88)	50 (38–88)	0.215	75 (50–91)	63 (50–88)	0.081	88 (50–100)	63 (50–88)	0.034	88 (50–100)	81 (53–100)	0.833
Role Physical	75 (25–100)	50 (0–100	0.166	75 (25–100)	25 (0–100)	0.115	100 (25–100)	50 (0–100)	0.086	100 (0–100)	100 (50–100)	0.516
Role-emotional	67 (34–100)	67 (0–100)	0.251	67 (0–100)	67 (0–100)	0.223	100 (67–100)	67 (0–100)	0.017	100 (33–100)	100 (33–100)	0.615
Mental health	60 (43–69)	52 (40–71)	0.231	68 (56–77)	64 (40–76)	0.082	72 (52–84)	60 (41–76)	0.044	68 (51–81)	64 (49–72)	0.219
Vitality	45 (25–66)	50 (30–60)	0.585	55 (39–71)	45 (30–65)	0.069	60 (30–75)	50 (30–60)	0.214	53 (35–75)	55 (35–65)	0.390
Bodily pain	84 (52–90)	57 (41–84)	**0.006**	82 (52–90)	62 (41–90)	0.034	84 (51–90)	63 (41–84)	0.185	84 (42–90)	73 (54–89)	0.895
General health	65 (47–77)	56 (42–72)	**0.026**	67 (61–78)	57 (37–72)	0.005	72 (55–87)	56 (41–71)	0.004	70 (55–87)	62 (47–77)	0.073
ThyPRO[a]												
Goitre symptoms	8 (2–14)	11 (5–24)	0.084	9 (2–18)	16 (4–27)	0.120	5 (0–7)	8 (0–24)	0.181	6 (0–9)	6 (0–24)	0.794
Hyperthyroid symptoms	28 (15–38)	39 (19–53)	0.070	19 (13–38)	25 (13–47)	0.372	13 (5–25)	19 (9–28)	0.325	13 (6–31)	20 (6–41)	0.183
Hypothyroid symptoms	19 (6–38)	25 (13–36)	0.247	19 (6–38)	19 (6–31)	0.765	16 (0–38)	19 (6–38)	0.603	9 (0–44)	19 (6–31)	0.561
Eye symptoms	9 (3–20)	14 (6–31)	0.082	9 (2–21)	11 (3–25)	0.343	5 (0–18)	13 (4–25)	0.071	6 (0–16)	9 (3–22)	0.118
Tiredness	59 (32–75)	57 (43–79)	0.298	43 (28–61)	57 (29–79)	0.261	30 (14–68)	50 (29–71)	0.084	36 (14–60)	46 (25–57)	0.412
Cognitive problems	17 (4–35)	21 (4–48)	0.569	17 (3–30)	21 (0–46)	0.445	8 (0–33)	17 (0–46)	0.524	10 (3–42)	8 (0–25)	0.376
Anxiety	29 (17–50)	38 (17–61)	0.287	17 (8–29)	21 (8–46)	0.243	13 (0–17)	17 (8–42)	0.055	17 (0–25)	17 (8–33)	0.201
Depressivity	21 (13–47)	21 (14–38)	0.912	14 (11–32)	17 (11–32)	0.312	14 (7–29)	21 (7–43)	0.173	16 (7–29)	18 (12–34)	0.216
Emotional susceptibility	38 (22–58)	42 (23–58)	0.489	25 (13–33)	28 (14–61)	0.108	19 (6–36)	33 (14–47)	0.031	18 (6–42)	22 (12–36)	0.267
Social impairment	16 (5–33)	19 (6–44)	0.378	6 (0–19)	13 (6–31)	0.048	0 (0–19)	13 (0–31)	0.004	0 (0–13)	6 (0–19)	0.196
Impaired daylife	13 (4–29)	25 (6–53)	0.060	10 (0–31)	21 (0–42)	0.283	4 (0–35)	13 (4–29)	0.084	2 (0–25)	5 (0–20)	0.833
Sexlife	6 (0–50)	25 (0–75)	**0.043**	6 (0–56)	25 (0–59)	0.391	0 (0–47)	25 (0–63)	0.034	0 (0–25)	25 (0–50)	0.224
Cosmetic complaints	10 (0–26)	17 (1–52)	0.135	4 (0–17)	13 (0–46)	0.076	4 (0–29)	21 (0–54)	0.050	4 (0–42)	15 (0–57)	0.132

M1, M6 and M12, 1-, 6- and 12-month post-RAI; Med (IQR), median (interquartile range); Bold values, *P* value <0.05.
[a]Higher scores indicate higher QoL levels;
[b]Higher scores indicate greater impact of symptoms on QoL.

Table 5 Impact of early LT_4 administration on QoL dimensions at 6 months after adjustment (multivariate analysis, standardized beta coefficients).

		SF-36					ThyPRO			
		MCS	RE	MH	SF	GH	ES	SI	SL	CC
Age	ß	−0.172	−0.295	−0.150	−0.129	−0.013	0.082	0.096	0.078	−0.108
	P	0.08	**0.003**	0.122	0.194	0.901	0.411	0.333	0.909	0.251
Gender[#]	ß	−0.082	0.012	−0.174	−0.126	−0.117	0.065	0.107	−0.038	0.149
	P	0.413	0.905	0.082	0.216	0.262	0.531	0.296	0.736	0.128
Baseline FT_4	ß	0.043	−0.004	0.017	0.034	0.105	−0.020	0.023	−0.025	0.054
	P	0.661	0.965	0.858	0.735	0.306	0.839	0.816	0.825	0.574
BDI	ß	−0.421	−0.420	−0.415	−0.410	−0.324	0.473	0.471	0.392	0.507
	P	**$<10^{-3}$**	**$<10^{-3}$**	**$<10^{-3}$**	**$<10^{-3}$**	**0.003**	**$<10^{-3}$**	**$<10^{-3}$**	**0.001**	**$<10^{-3}$**
Group°	ß	−0.207	−0.172	−0.158	−0.162	−0.286	0.093	0.042	0.114	0.118
	P	**0.042**	0.086	0.114	0.113	**0.007**	0.365	0.685	0.325	0.227

ß, standardized beta coefficient (ß represents the change of the S.D. in QoL score resulting from a change of one S.D. in the independent variable). [#]0 man, 1 woman; °0 group A, 1 group B; Bold values: $P<0.05$.

adjustment, only two dimensions of the generic QoL questionnaire were impacted by the early LT_4 administration strategy. Meanwhile, all the dimensions were influenced by the depressed mood that appeared as a strong predictor of lower QoL (42). Surprisingly, in our study, the generic questionnaires outperformed the thyroid-specific questionnaire in detecting differences over time. In comparison with the open-label design of the study, a double-blind study with the use of a placebo in the control group would have provided a higher level of evidence (43). However, our main focus was to assess the interest of the therapeutic strategy in its globality including the inconvenience of medication intake, compared to the control strategy. We cannot, however, exclude that the open-label design of our study could have probably overestimated the QoL differences between the two groups. Moreover, since our patients had a mean diagnosis of Graves' disease of 5–6 years duration, we do not know if our results would be observed in patients treated shortly with ATD before radioactive treatment.

Radioactive treatment should be performed according to the ALARA ('as low as reasonably achievable') principle. This means that for a predefined therapeutic goal, the lower the administered activity, the better it is from the radiation safety point of view. We used a mass-adjusted calculation of radioiodine activity based on 20 MBq/g (0.5 mCi/g) of thyroid tissue. Our results are comparable with other studies that have used more complex calculations to determine radioiodine activities. In the majority of our patients, hypothyroidism was observed, a finding that is in coherence with the administered radio ablative activities. As expected, the percentage of variation in FT_4 pre-RAI and post-RAI was significantly less in group A. However, ten patients in group A had stopped LT_4 by 3 months due to persistent hyperthyroidism or hyperthyroxinemia, which was even aggravated in a few patients. One could argue the use of T_3 for thyroid supplementation in order to better monitor the decline of thyroid function after radioiodine. However, this treatment is less convenient than LT_4, since it has to be taken twice or three times daily.

Despite the fact that none of our patients experienced adverse cardiovascular events including those with persistent hyperthyroidism, we have to consider the relatively young age of the population included in our trial: mean age of 48.8 and 47.1 years in groups A and B respectively, who had only moderate thyrotoxicosis prior to inclusion. It is worth noting that this could have had more serious outcomes in fragile or at risk populations with more severe hyperthyroidism prior to RAI. Additionally, one must be careful before extrapolating these findings to elderly patients that often have higher cardiovascular morbidity and who may require transient treatment with ATDs after RAI.

As shown from our results, the rate of RAI-induced GO was about 2% (2/94) which is lower compared to previous studies. In fact, different rates of RAI-induced GO have been reported in the literature largely due to heterogeneity of patient populations. The main recognized predictors of RAI-induced GO are: smoking, highly elevated pre-treatment titers of anti-TSH receptor antibodies, significant hyperthyroidism and severe and prolonged post-RAI hypothyroidism with either suboptimal or delayed LT_4 supplementation. In addition, an exaggerated post-RAI increase of anti-TSH receptor antibodies could also be considered as a risk factor for RAI-induced GO[49]. Different approaches have been explored to minimize the risk of

RAI-induced GO, for example a better selection of candidates for RAI, improved management of iatrogenic hypothyroidism and the prophylactic use of glucocorticoids. Interestingly, the lower rate of RAI-induced GO in our study could be related to the inclusion criteria of the protocol such as exclusion of preexisting active GO, relatively small thyroid glands, well-controlled hyperthyroidism prior to treatment, regular follow-up post-RAI, long duration of Graves' disease with low levels of anti-TSH receptor antibodies, in addition to a low percentage of active smokers among our patients.

Conclusion

Early administration of LT_4 post-RAI seems to represent a safe potential benefit for patients with regard to QoL. This could be even more beneficial when higher activities of radioiodine are used, since the risk of severe and early hypothyroidism is greater. The optimal strategy taking into account administered RAI activities and LT_4 administered dosages and timing remains to be determined by more randomized controlled clinical studies.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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