Prevention of overt hypothyroidism following radioactive iodine therapy for Graves' disease; a novel protocol with implications for future studies

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Prevention of overt hypothyroidism following radioactive iodine therapy for Graves' disease; a novel protocol with implications for future studies

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I. Specific Aims

We aim to test the hypothesis that early treatment with levothyroxine after radioactive therapy for Graves' disease will prevent overt hypothyroidism (primary outcome).

II. Background and Significance

The most common method of treating Graves' disease (GD) in the US relies on rendering the patient hypothyroid with the use of radioactive iodine (RAI) ablation of the thyroid gland followed by lifelong replacement with thyroid hormone (levothyroxine). Our current practice is to reevaluate GD patients 2-4 months after their therapy with RAI. At that time their hyperthyroidism is expected to have been resolved, however the majority are clearly hypothyroid at that point. While many are asymptomatic or minimally symptomatic, some are frankly hypothyroid with related troublesome symptoms (cold intolerance, sleepiness, fatigue, weight gain, hoarse voice etc.).

We and others have identified hypothyroidism following treatment of GD as a risk factor for the development of future Graves' ophthalmopathy (GO), a potentially vision-threatening complication of GD[1-3]. These studies show that development of hypothyroidism increases the risk of developing GO by an average factor of 3.3. Cohort data from centers where early levothyroxine replacement is routinely administered following RAI therapy [1,4] suggests that this approach can decrease the risk of GO development. In addition, these data show a very low occurrence of hyperthyroidism symptoms that may present when levothyroxine is given prior to documentation of hypothyroidism. Based on these data, the recent publication of guidelines for the treatment of patients with hyperthyroidism[5] (with Drs. Bahn and Stan as task-force chair and member) recommended that hypothyroidism be avoided following RAI therapy for GD. However, no randomized trial has yet been performed to test the impact of preventing hypothyroidism through a precise protocol of early T4 administration on both GO development and QOL, a lapse that our trial intends to correct.

Completion of our current study to test the hypothesis that early initiation of levothyroxine following a precise protocol using small doses of the medication can prevent development of overt hypothyroidism without an increase in rate of symptomatic hyperthyroidism is necessary before we can design our subsequent study. That study will be a larger multi-center investigation testing the hypothesis that prevention of overt hypothyroidism after RAI using this (or a refined) protocol can prevent development or worsening of GO and at the same time improve the quality of life of these individuals.

III. Progress Report and Preliminary Studies

This project involves performing a therapeutic trial in patients with GD. I have to date participated in 3 such trials. The first trial [6] was a placebo-controlled trial that involved administration of octreotide or placebo for therapy of active GO. My participation in that trial included data collection, data analysis and drafting of the final manuscript. The second trial (Clinicaltrials.gov Identifier NCT00595335;PI:RS Bahn) is an ongoing placebo-controlled study that tests the benefit of rituximab in patients with active and moderate-to-severe GO. I was involved in designing the trial and I'm currently enrolling and following patients throughout the trial. The third trial (Clinicaltrials.gov Identifier NCT01171690) is another ongoing study testing the impact of teriparatide on the duration of hospitalization post thyroidectomy, in patients that develop postsurgical hypoparathyroidism. I am the PI in this single arm study with historical controls. We expect to complete patient enrollment by the end of 2014. In addition to these trials we have

just published our retrospective cohort results describing the development of hypothyroidism in patients with GD treated with RAI, and its impact on GO development[3]. This cohort is very similar to the group of patients that we intend to enroll in the current study. Lastly, I have completed a Masters in Clinical Research and Translational Sciences through the Mayo Clinic CTSA. This training has given me important background in clinical study protocol design to data analysis.

In our review of Mayo Clinic records, the majority (102/195;52%) of patients were overtly hypothyroid by the time of their first evaluation after RAI (Fig.1) and 36% had a TSH value > 20 mIU/L.[3] Furthermore, we found that 21% of patients are in reality seen for their first return visit after > 3 months post RAI due to practicalities of scheduling and the lack of a standardized protocol for this process. We found that the prevalence of hyperthyroidism decreased as expected between the 2 groups and dropped below 25% in groups with first follow-up after 6 weeks. We calculated the ratio between euthyroidism and hypothyroidism at each follow-up and found the ration to drop below 1.0, favoring hypothyroidism, starting from follow-up period 8-10 weeks and then to decrease linearly thereafter. It is very likely that the development of hypothyroidism in the latter groups is associated with a significant symptomatic hypothyroidism and decrease in patients' quality of life (QOL).

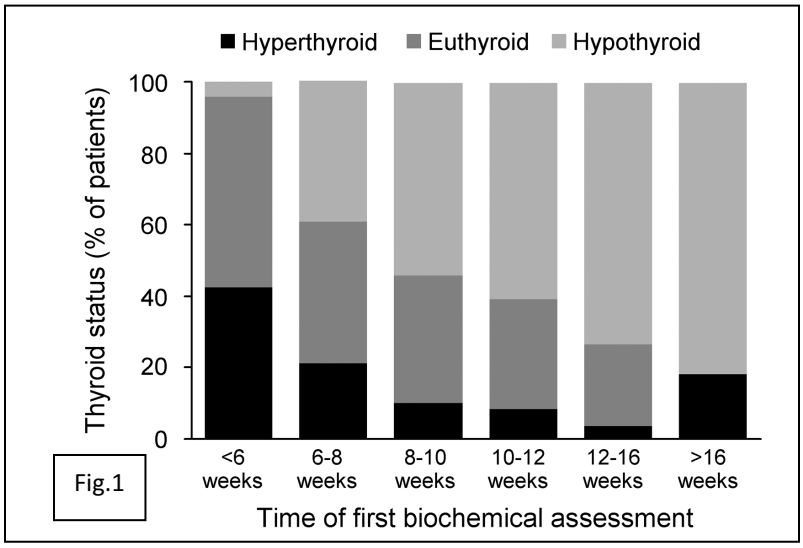

Fig.1

Table 1. Distribution of thyroid status at first biochemical follow-up

Period	Hyperthyroid – N (%)	Euthyroid/Subclinical hyperthyroid – N (%)	Hypothyroid – N (%)	Euthyroid/ Hypothyroid ratio
< 6 weeks	12 (42.9)	15 (53.6)	1 (3.6)	15
6-8 weeks	6 (21.4)	11 (39.3)	11 (39.3)	1
8-10 weeks	5 (10.9)	16 (34.8)	25 (54.4)	0.64
10-12 weeks	3 (9.1)	10 (30.3)	20 (60.6)	0.5
12-16 weeks	2 (4.1)	11 (22.5)	36 (73.5)	0.31
> 16 weeks	2 (18.2)	0 (0)	9 (81.8)	0

We found that hypothyroidism present at the first follow-up visit was strongly associated with GO development or deterioration with OR of 3.3, 95% CI:1.3-8.7,p=0.011 (Fig. 2). A multi-variate analysis was performed and included hypothyroidism status at the first follow-up, the administration of corticosteroids concurrently with RAI, smoking status, fT4 level at baseline, gender, age, 24 hr RAI uptake test results, thyroid size and dose of RAI. The factors that remained independently significant were development of hypothyroidism by the first follow-up visit after RAI therapy (OR=3.6) and preexisting GO (OR=2.8; Table 2).

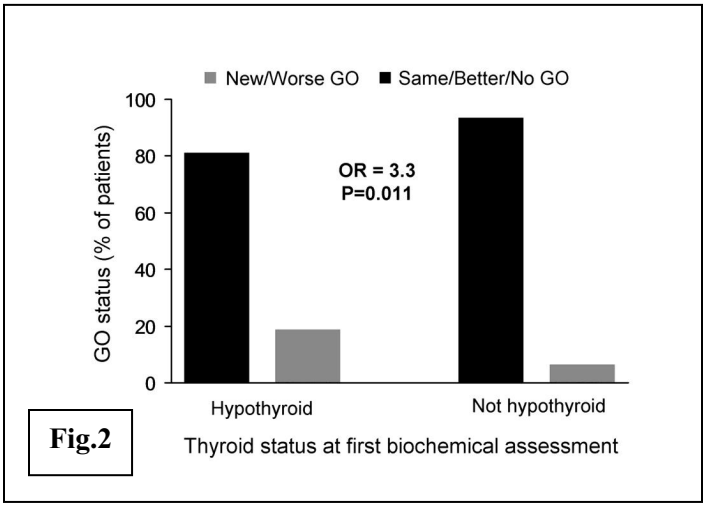

Fig.2

Table 2. GO changes correlated with thyroid status at first biochemical

Parameter	Estimate	Odds Ratio	Lower 95% CI	Upper 95% CI	P value
Hypothyroid at first follow-up (ref. - Hyper/Euthyroid)	1.2	3.32	1.26	8.72	0.015
Preexistent GO	0.91	2.48	1.03	5.99	0.043
Steroid prophylaxis (ref. – No)	-0.29	0.75	0.09	6.15	0.79
Smoker (ref. - Non-smoker)	0.47	1.60	0.59	4.37	0.36
Free thyroxine (per unit increase)	-0.08	0.92	0.75	1.13	0.44

IV. Research Design and Methods

a. Study Design/Overview –The design for this study was developed based upon the findings of our retrospective cohort study described above. We propose a randomized trial with 2 arms, intervention and control, as depicted in Figure 3. The randomization will be done in blocks of 6 patients. In the intervention arm patients will start levothyroxine therapy 4 weeks prior to return evaluation with Mayo Endocrinologist, approximately 4 weeks after RAI therapy. The initial dose of levothyroxine will be 25 mcg/day. It will be increased to 50 mcg/day 2 weeks later and then adjusted at 8 weeks post RAI based on a full face-to-face clinical and biochemical evaluation. At the 8 weeks visit the treating physician can be informed about the randomization status (actual levothyroxine dose received by the patient). This will be done only if requested by the treating physician for optimal clinical care and the information will be delivered through the secretarial staff or the study coordinator, after communication with the research pharmacy. Both the active capsules and the placebo will be provided by Mayo Research Pharmacy, who will also coordinate the randomization process. In the control arm patients will receive placebo capsules and be evaluated for levothyroxine therapy during a full face-to-face evaluation at 8 weeks, following currently accepted clinical practice. Patients in both groups will have blood drawn at 4 and 6 weeks (in Rochester if agreed by the patient or by mail-in kit to maximize the percent of data collection), stored and analyzed at a later time (batch processing for limiting costs) for free thyroxine and TSH. The study

coordinator will follow on this process to ensure that the patients perform these interim studies. Development of hypothyroidism will be assessed using these tests at 4, 6 and 8 weeks using the cutoffs for free thyroxine and TSH values as described previously[3]. For the 8 weeks visit all patients will be asked to bring their medication bottles and the study coordinator will perform a pill count to assess compliance with the protocol. Final evaluation for both groups will be at 6 months after RAI at which time patients will undergo a phone questionnaire which will assess the rate of recurrence of hyperthyroidism and test the feasibility of screening for changes in GO status over the phone. In both groups a quality of life instrument will be used at baseline, 4, 6 and 8 weeks and at 6 months. We will use the hypothyroid-Health Related Quality of Life (hypothyroid-HRQL)[7] and also the Thyroid Specific Questionnaire (TSQ)[8]. These questionnaires are disease-specific for hypothyroidism. A major advantage to our study is also their ability to be self-administered. These last 2 interventions will be used to assess the feasibility of using them in the larger, multi-center trial where GO prevention and QOL benefit will be the primary outcomes.

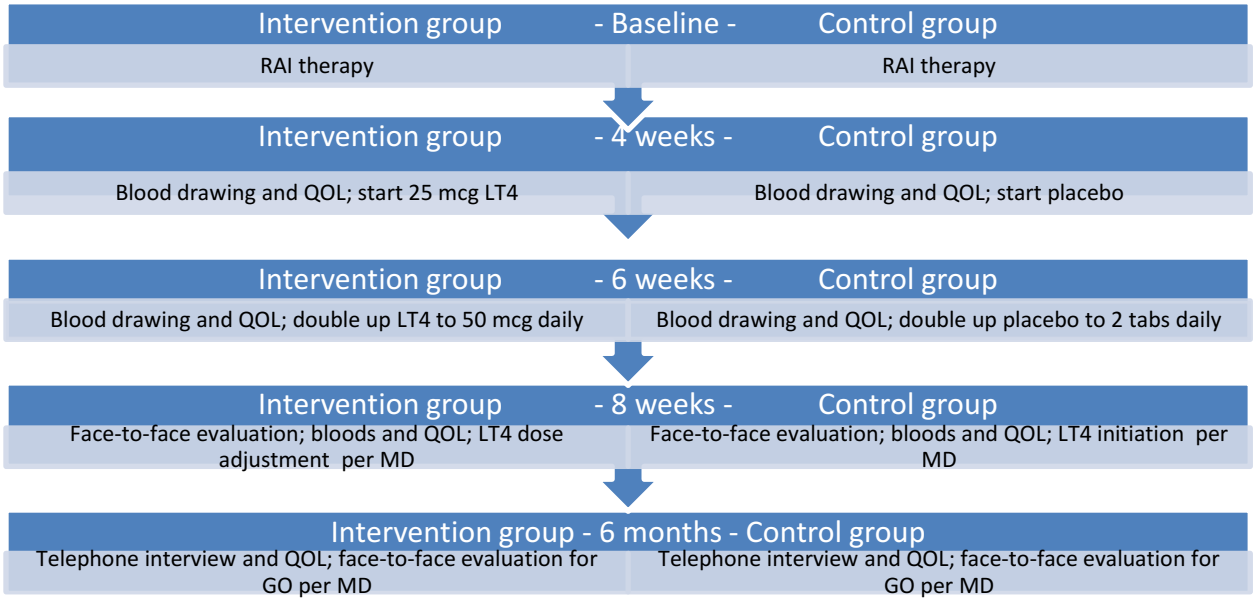

Figure 3 – Trial flow chart

b. Study Subjects - Inclusion criteria target all adult patients (ages 18-70 years) with GD who will receive RAI for treatment of GD. We plan to have 60 individuals complete the study. For that up to 90individuals may need to be screened. Exclusion criteria - Patient with clinically manifest GO will be excluded from the study. We will also exclude patients with recent (<1 yr.) history of arrhythmias or any history of ventricular arrhythmias, those with preexistent cardiomyopathy, those with malnutrition and those with psychiatric history that could get worse if patient remains persistently hyperthyroid. Patients unlikely to return for the planned follow-up visits, to comply with the blood drawing schedule and with the completion of the hypothyroid-HDQL and TQS questionnaires will also be excluded. If a medical examination was performed within the last 4 weeks by an endocrinologist we can discuss the study over the phone. The consent material can be exchanged by mail or fax.

d. Data Collection **-** The data will be collected prospectively and stored in an electronic database. Baseline assessment will include demographic data, thyroid size, thyroid functional parameters (TSH, T4 and T3 levels), RAI uptake and dose, smoking status and history of therapy with corticosteroids or methimazole (pre and post RAI) . The development of hypothyroidism is defined as TSH > 3.0 mIU/L or free thyroxine (fT4) < 0.8 ng/dL. The methodology for thyroid functional parameters will be the currently used clinical assays. We will offer blood collection for all the required samples here in Rochester. For

those patients that are not local the blood drawing will be organized with the help of mail-in kits. This will maximize the likelihood of the tests being completed and the study coordinator will follow with the patients over the phone to ensure that this process will happen.

g. Feasibility and Time Frame - Our own data indicate that every year 150 patients with Graves' hyperthyroidism who are evaluated at Mayo Clinic Rochester by RSB, MNS or one of other members of the Endocrinology Division and Thyroid Core Group. This group of physicians collaborates closely on clinical studies and would in all likelihood refer their patients with GD for participation in this study. We would therefore expect to be able to enroll at least 30% of this patients group and complete enrollment in 1.5 years' time. Analysis and drafting of the manuscript will likely take an additional 6 months. Compliance with the study planned follow-up time frame should be acceptable for the vast majority of patients as the protocol remains close to the current standard of care while the early thyroid testing will be done utilizing mail-in kits for patients' convenience.

h. Statistical Considerations

Outcomes:

Primary endpoint:

Incidence of overt hypothyroidism at 8 weeks post RAI (TSH > 3.0 mIU/L or fT4 < 0.8 ng/dL)

Exploratory endpoints:

Quality of Life measured by the hypothyroid-HRQL and the TSQ at 8 weeks and 6 months

Development of GO at 6 months

Safety Endpoints

New development/deterioration of symptoms of hyperthyroidism.

Sample Size

The sample size for this study is based on the incidence of hypothyroidism primary endpoint using an alpha=0.10 (two-sided), beta=0.10. The proportions of participants that develop hypothyroidism in the placebo and experimental groups are assumed to be 60% and 20%, respectively. A sample size of 30 per group will provide 90% power to detect a difference between the group proportions of 40% using the two-sided Fisher's Exact test.

Primary Endpoint Analysis*:*

The difference in the incidence rates of hypothyroidism at 8 weeks will be tested using Fisher's exact test.

Exploratory Endpoint Analysis*:*

Change in quality of life is measured serial over the course of the study follow-up. Change from baseline will be assessed using a hierarchical linear model ("growth curve"). The primary parameter of interest from the model will be the treatment by time interaction term. Time, for this study, will be a collection of indicator variables representing each assessment point. The incidence of GO will be tested using Fisher's exact test.

Safety Analysis:

Frequency tables of adverse events by treatment groups at the patient level will be tabulated. The relative risk of developing a serious, and at least potentially related, adverse event will be estimated along with the 90% confidence interval for relative risk.

Additional Statistical Considerations

The primary analysis will be conducted according to the intention to treat principle. Efforts will be made to ascertain the incidence of hypothyroidism even in participants that are lost to follow up. In the event the data cannot be obtained, the primary analysis will assume these participants are positive for hypothyroidism. Sensitivity analysis will be conducted on the per protocol data set.

Missing data for the primary endpoint is addressed through the intention to treat analysis. Missing data in exploratory endpoints could occur. The analysis plan for the QOL endpoint include maximum likelihood estimation that allows for missing data, provided the data are missing at least missing at random.

A P-value < 0.10 will be considered significant for the primary endpoint and exploratory analyses.

i. Strengths - The design for this study was developed based upon the findings of our retrospective cohort study described above. This trial design will compare an active intervention with the current practice using the benefit of blinding and randomization for eliminating a placebo effect and differences in known and unknown confounders between the groups. It is also minimally disruptive of patients schedule while providing potential benefit for both quality of life and decreasing the risk of GO. By having the free thyroxine values at 0, 4, 6 and 8 weeks it will provide us with the ability to better predict the development of euthyroidism/hypothyroidism, to decide on the best levothyroxine dose and to adjust the therapeutic sequence accordingly. We have allowed for a low recruiting percentage to avoid the possibility of extending the study beyond the planned funded time frame.

j. Limitations - There may be patients that will report increase/recurrence of hyperthyroidism-like symptoms. Those cases are rare and in the literature early T4 therapy (started at 50 mcg daily 2 weeks after RAI) required discontinuation due to symptoms of thyrotoxicosis in only 7/314 patients (2.2%)[1,4]. In that case we will decrease the dose of levothyroxine x 2 weeks and if the symptoms persist the medication will be discontinued. Beta-blockers will be used liberally at the discretion of the treating physician.

k. Regulatory aspects – We have discussed extensively and consulted with the Office of Research Regulatory Support on the issue of applicability for an IND application. The intention of the study is to treat with levothyroxine patients that are in the very early stages of developing hypothyroidism. The timing of the therapy is based on data that documents onset of hypothyroidism well before the usual 8-12 weeks follow-up. We have proposed to start at a very conservative dose (25 mcg) which represents 25% of the median dose used in the therapy of hypothyroidism. This is quite safe as mentioned above, with only 2.2% of patients required discontinuation of therapy in similar studies in Europe. In addition the patients will be evaluated 4 weeks later and the dose adjusted as clinically indicated. Given all these considerations we have concluded that we are not outside of the scope of the FDA-approved indication for levothyroxine in hypothyroidism management and we have decided against submitting an IND application.

Table 3 – Schedule of Events

Schedule of Events					
Study Activity	Wk 0	Wk 4	Wk 6	Wk 8	Wk 24
Study Agent(s)		X	X	X	
Informed consent	X				
History	X			X	X[c]
Concurrent meds	X	X		X	X[c]
Physical exam (Ht, Wt, BSA, VS)	X			X	
Goiter size	X			X	
RAI uptake/dose	X				
Serum chemistry [a]	X	X	X	X	
Adverse event evaluation		Ongoing			
B-HCG	X[b]				
QoL instruments		X	X	X	X[c]

a: Free thyroxine, TSH; total T3 will be obtained at the discretion of the treating physician.
b: Serum pregnancy test (women of childbearing potential).
c: Phone interview.

V. References

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