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Research Article

An Effective Straightforward Protocol for the Treatment of Graves' Hyperthyroidism for Primary Care Providers

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Abstract

Background: The prevalence of hyperthyroidism is very common in the United States (approximately 1.2%) with Graves' Disease (GD) being the most common non-iatrogenic cause. The limited number of endocrinologists and their concentration in larger cities means that primary care providers (PCPs) must treat a large number of these patients. This paper provides an effective, straightforward protocol for them to do so.

Material & Methods: Patients with GD hyperthyroidism were referred to a county endocrinology clinic by PCPs in clinics that cared for medically underserved, mostly minority patients, a challenging population to treat. Hyperthyroidism was diagnosed by elevated free T_4 and/or free T_4 concentrations, euthyroidism by normal concentrations of both and hypothyroidism by low free T_4 or elevated TSH concentrations. Patients were treated with methimazole with initial doses and up-titration based on free T_4 and free T_3 concentrations and down-titration by free T_4 and TSH concentrations.

Results: At the initial visit, 155 patients were, and 54 patients were not, respectively, taking an anti-thyroid drug. At the initial visit, patients either remained on methimazole, were started on the drug or were switched to it from propylthiouracil. The 209 patients were followed for up to 18 months. The protocol rapidly reversed the hyperthyroidism in most patients and at the end of the study, 72% were euthyroid, 19% were hyperthyroid and 9% were hypothyroid. Medication non-adherence probably accounted for those who were hyperthyroid at that time.

Conclusion: PCPs following this protocol will enable them to effectively treat patients with GD hyperthyroidism.

Keywords: Graves' Disease', Hyperthyroidism, Methimazole, Protocol for treatment

Introduction

The prevalence of hyperthyroidism in the United States is approximately 1.2% (0.5% overt and 0.7% subclinical) with the most non-iatrogenic common causes including Graves' disease (GD), toxic multinodular goiter and less frequently, toxic adenoma [1]. Two of the authors are endocrinologists who each receive 4-5 referrals per month from primary care providers (PCPs) from two separate medical care systems for thyroid problems, the majority of which are for hyperthyroidism due to GD. GD is the most common cause of (non-iatrogenic) hyperthyroidism with an annual incidence of 20-50 cases per 100,000 persons. The lifetime risk for women is 3% and 0.5% for men [2]. Patients with GD are typically 40 to 60 years old with a female to male ratio of 5:1 [3]. Patients usually present with the classic triad of thyrotoxicosis, goiter and ophthalmopathy (the latter occurring in about 50% of patients) [4]. GD is due to activation of the G-protein-coupled thyrotropin (TSH) receptor via binding of circulating IgG antibodies resulting in over-activation of thyroid follicles that leads to hypertrophy [3]. Thyroid hormone production increases, most often resulting in an increased ratio of serum triiodothyronine (T_3) to thyroxine (T_4) [3]. This results in a low serum TSH and high levels of serum T_3 and T_4 that are better measured as the free hormones to avoid issues with varying levels of serum thyroid binding globulins.

In addition to beta-blockers used to initially treat the adrenergic symptoms of thyrotoxicosis, the treatment options for the increased production of thyroid hormones in patients with GD include antithyroid drugs (ATDs), radioactive iodine (RAI with ^{131}I) and surgery [1], with each treatment option having advantages and disadvantages. Although the long-term quality of life following treatment for GD was the same in patients randomly allocated to one of the three treatment options [5], ATD is usually the initial treatment for GD hyperthyroidism. (RAI and surgery treatments will be discussed below.) Pharmacologic treatment of GD with ATDs, primarily methimazole (MMI) but also propylthiouracil (PTU), targets thyroid hormone synthesis by interfering with the thyroid peroxidase (TPO) enzyme. In the blood, iodine circulates in the form of the iodide ion which enters the thyroid gland. However, the iodination of tyrosines, which are the final steps of thyroid hormone synthesis, requires organification of iodide to I_2 which TPO stimulates. Hence, its inhibition by ATDs interferes with thyroid hormone synthesis.

MMI is preferred to PTU for 2 reasons. PTU causes a higher rate of agranulocytosis and elevated hepatic transaminases and is slightly less effective in lowering initial free T4 levels that are >90.1 pmol/L [6]. Second, in doses ≤30 mg, MMI can be given once per day while PTU requires dosing 2-3 times per day [7]. An exception to preferring MMI is in the first trimester of pregnancy where MMI can cause several fetal abnormalities, the most common of which is aplasia cutis (scalp abnormality) as well as esophageal and intestinal atresias. After the first trimester, the patient should be switched to MMI [8].

Treatment with ATDs can result in durable remissions, defined as biochemical euthyroidism for at least 12 months after 1-2 years of therapy. However, hyperthyroidism may recur in approximately one-half of these pateints, and once recurrence occurs, future remissions become less likely [2].

In 2019, the American Association of Medical Colleges listed 6439 physicians involved in patient care who specialized in Endocrinology/Diabetes/Metabolism [9], many of whom are congregated in or near larger cities. These are too few endocrinologists to treat the number of patients diagnosed with GD each year, especially those not living in or near big cities. Furthermore, guidelines on how to taper patients off ATDs are scant [1]. In clinical practice, some endocrinologists rely on TSH levels that lag behind changes in free T_4 concentrations to guide ATD dosing, some stop ATDs abruptly without a taper, while others, because of concern with adverse events, recommend a shorter treatment duration than is possibly optimum [10]. For these reasons, we designed an MMI dosing algorithm in which up-titration of MMI dosing was based on elevated serum free T_3 and free T_4 levels, while down-titration was based primarily on low to normal serum free T_4 levels, although it was also guided by elevated TSH levels. Our predefined protocol was designed to rapidly bring patients to euthyroidism to shorten the symptomatic period but to keep patients on MMI for the longer term with a gradual down-titration. The protocol was carried out in an inner-city, safety-net clinic serving poor, mostly minority patients who are historically considered more difficult to treat successfully. We aimed to answer questions about the effectiveness and tolerability of the ATD protocol and provide a relatively simple, straightforward approach for PCPs to treat GD hyperthyroidism.

Methods

This prospective, observational study was submitted to 2 Institutional Review Boards; one to Charles R. Drew University at which the authors worked and the other to the Department of Health Services at Los Angeles County, the organization responsible for patient care of this medically underserved population. Both approved the study with the opinion that informed consents of the patients were not necessary because their data would be de-identified. Thyroid function tests were repeated on all patients referred for hyperthyroidism to the endocrinology clinic of the Martin Luther King Outpatient Center (MLK OC) from January, 2011 through December, 2016. Overt hyperthyroidism was diagnosed by an elevated free T_4 and/or free T_3 levels (all had a suppressed TSH level). Patients with iatrogenic hyperthyroidism were not worked up further and excluded. GD was diagnosed if one or more of the following were present; elevated levels of thyroid binding inhibitory immunoglobulin (TBII), the only thyrotropin receptor antibody test offered at the time, clinical evidence of GD ophthalmopathy and/or homogeneous distribution

of ^{99m}pertechnetate on a thyroid scan.

Free T_4 (pmol/L)	Free T_3 (pmol/mL)	Dose (mg) of MMI
>57.9	>18.5	20 bid
45.0-57.9	15.4-18.3	30 qd
34.7-43.8	12.3-15.2	20 qd
29.6-33.5	10.0-12.2	15 qd
25.7-28.3	8.0-9.8	10 qd
21.9-24.4	6.6-7.8	5 qd
<21.9	<6.6	0

Table 1: Initial dosing of MMI.

The higher dose was given if there were discrepancies between the dose based on free T_4 and free T_3.

The normal range of free T_4 was 9.9-21.8 pmol/L before November 2014 and 9.0-19.0 pmol/L after November 2014. The normal range of TSH was 0.35-5.5 µIU/mL before November 2014 and 0.35-4.94 µIU/mL after November 2014. The normal range of free T_3, was 3.5-6.5 pmol/L for all dates.

A. Up-titration of MMI		
Free T_4 (pmol/L)	**Increase dose of MMI by (mg)**	
> 45	20	
32.2-43.8	10	
25.7-30.9	5 if dose ≥ 10 mg	
25.7-30.9	2.5 if dose < 10 mg	
21.9-24.4	2.5	
11.7-21.8	0	
If free T_4 is normal and free T_3 is 6.6-8.5 pmol/L, increase MMI by 2.5 mg. If free T_4 is normal and free T_3 is > 8.5 pmol/L, increase MMI by 5 mg.		
B. Down-titration of MMI if dose is ≥2.5 mg/day		
Free T_4 (pmol/L)	**TSH(mIU/L)**	**Decrease dose of MMI by (mg)**
6.4-11.6	Or TSH is > 3.0	5 if dose > 10 mg
6.4-11.6	Or TSH is > 3.0	2.5 if dose ≤ 10 mg
< 6.4	Or TSH is > 7.0	Decrease dose in half
C. Down-titration of MMI if dose is 2.5 mg/day		
Free T_4 (pmol/L)	**TSH (mIU/L)**	**Dose of MMI (mg)**
<10.3	Or TSH is >4.0	Stop MMI
10.3-12.2	Or TSH is 2.5-4.0	2.5 mg MWF

Table 2: Up- and Down-Titration of MMI

MMI - methimazole; MWF - Monday, Wednesday and Friday.

TSH, free T_3 and free T_4 levels were measured by two-step immunoassays. TBII was measured at Quest Diagnostics (San Juan Capistrano, CA, USA) using a manual FDA-cleared radioreceptor assay kit that measures the ability of TSH receptor auto-antibodies detected in the patient sample to inhibit ^{125}I-labeled TSH. The normal ranges of free T_4, free T_3, and TSH are given in Table 1. The normal range for TBII was <16% inhibition. We did not adjust the dosing protocol based on the updated laboratory values, but did base criteria for hypo-, hyper- and euthyroidism on the revised values. Hyperthyroidism was diagnosed by elevated levels of free T_3 (most common) and/or free T_4, euthyroidism by both normal free T_3 and free T_4 levels and hypothyroidism by low levels of free T_4 and/or high levels of TSH.

For patients not taking an ATD at their first visit, the initial dose of MMI was determined based on the free T_4 and free T_3 values in Table 1. If they were taking an ATD at their first visit, MMI doses were adjusted based on the free T_4 and free T_3 values in Table 2 as were changes in doses after the initial visit for all patients. Patients on doses of MMI of 30 mg/day or less were given a single morning dose while those on >30 mg/day were given MMI twice a day [7]. Twenty-five patients were taking PTU at their first visit. Of these, 12 were kept on PTU because of a history of a previous reaction to MMI and were excluded from the study, while the remaining 13 were switched to MMI at 1/10th the dose of PTU and enrolled into the study. During the study, 2 patients had a reaction to MMI, were switched to PTU and excluded from the study.

Free T_3, free T_4 and TSH levels were measured before each visit. Patients were seen approximately every 2 months if the dose of MMI was changed and every 3 months if the dose was kept constant. The outcome of using this predefined protocol to treat patients with hyperthyroidism due to GD were the proportion of patients who achieved euthyroidism. The thyroid status of these patients after enrollment into the study up to 18 months later is presented.

Results

The baseline demographics of the 209 patients enrolled into the study were as follows: 82% females, mean age (years ± SD) 56.7 ± 11.2, 76% Latino, 17% African-American, 1% White and 2 % Asian attesting to the female predominance of GD and the patient-described ethnic minority characteristics of the population served in the MLK OC. The best circumstance in which to evaluate these predefined protocols is in the 54 GD patients in whom MMI was initiated at their first visit (Figure 1A). Three patients were euthyroid at their first visit which is consistent with either remissions in some patients with mild GD hyperthyroidism without therapy [1] or sufficient time between referral and the initial visit for the patient to become euthyroid on an ATD that the referring physician had then discontinued. The protocol rapidly reversed the hyperthyroidism in most patients and in those tested at17-18 months, 81% were euthyroid, 19% were hyperthyroid and none were hypothyroid.

Figure 1B shows the results of the protocol in the 155 patients who were taking an ATD on their initial visit started by their referring provider. Euthyroidism or hypothyroidism in patients on their initial visit were due to the effects of the ATD between referral and when first seen at the MLK OC endocrinology clinic. The pattern in these patients also showed a reversal of hyperthyroidism with 80% being euthyroid, 14% hyperthyroid and 6% hypothyroid in those tested at the 17-18 month visit. These results confirm the effectiveness of the protocol in bringing hyperthyroid patients already under treatment with an ATD to euthyroidism, maintaining euthyroidism in those who had achieved it by the first visit on the previous ongoing treatment and reversing those who were initially hypothyroid to euthyroidism.

Figure 1C shows the combined results in patients in whom protocol MMI treatment was either started or adjusted for those already receiving ATD treatment. Regardless of the initial therapeutic situation, in patients tested at 17-18 months, 80% were euthyroid, 16% were hyperthyroid and 4% had hypothyroidism.

The mean duration that patients were followed was 15 months. At their last visit (whenever that may have been), of the 209 patients,72% were euthyroid, 19% were hyperthyroid and 9% were hypothyroid. However, in the 73 patients who failed to keep their appointments and left the study before 18 months, only 4% were euthyroid when they dropped out and 69% remained hyperthyroid which certainly contributed to the 19% of the total cohort who were hyperthyroid at their last visit.

Discussion

Figure 1A (patients started on protocol MMI treatment), Figure 1B (patients receiving an ATD on their initial visit) and Figure 1C (all patients combined) show a rapid reversal of hyperthyroidism with 80% achieving euthyroidism if followed up to 18 months. Although not systematically tracked, medication non-adherence was frequently anecdotally noted in progress notes when patients stated that they had delayed refilling their prescriptions to avoid an extra trip to the pharmacy at MLK OC. Since ATDs are very effective in treating hyperthyroidism [1], one would expect that once euthyroidism was achieved, it would continue as long as ATDs were taken. The increase in the nadir prevalence of hyperthyroidism at 8-10 months compared with 17-18 months (Figure 1) suggests that medication non-adherence may have accounted for many of these patients being hyperthyroid at study end.

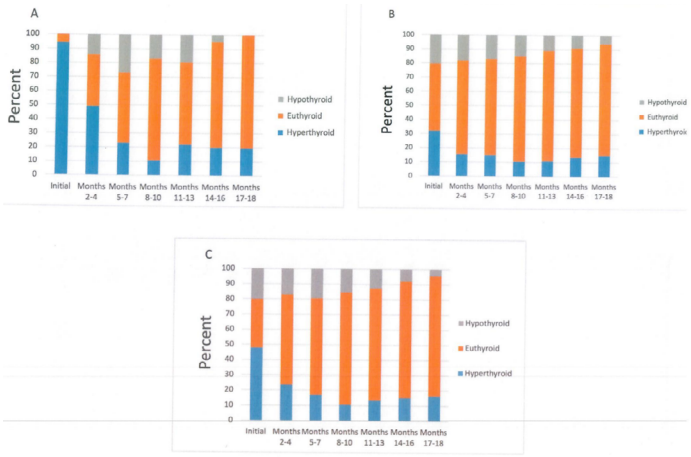

Figure 1: Thyroid function in patients with Graves' Disease hyperthyroidism up to 18 months after the initial visit: A) 54 patients not receiving anti-thyroid drugs (ATD) at the initial visit; B) 155 patients receiving ATD at the initial visit; C) All 209 patients.

The American Thyroid Association (ATA) recommends treatment with an ATD for 12-18 months [1]. After ATDs were stopped, relapse rates ranged from 33% to 82% [11-16]. Figure 2 describes the therapeutic options when discontinuation of ATDs might be considered. One approach is simply to continue them at the dose that is maintaining the patient euthyroid [17-19]. Safe, effective long-term treatment up to 25 years has been described [20]. A potential disadvantage of long-term therapy is that patients need to be evaluated relatively frequently to ensure that they remain euthyroid. They would have to be monitored at their regular visits every 3 months or so.

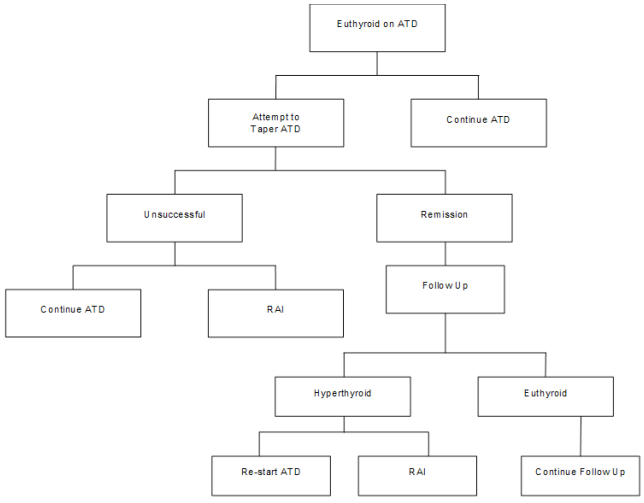

Figure 2: Therapeutic options after 12-18 months of anti-thyroid drugs treatment; ATD – anti-thyroid drugs; RAI – radioactive iodine.

Alternatively, one could attempt to discontinue ATD therapy. If this proved unsuccessful, ATD could be reinstituted or a more definitive therapy, RAI or surgery, could be considered. The ATA lists several circumstances in which surgery might be considered, e.g., active Graves' ophthalmopathy (RAI contraindicated), suspected or confirmed thyroid malignancy, one or more large thyroid nodules or coexisting primary hyperparathyroidism [1]. Except for the first one, these will be very unusual circumstances. The advantage of RAI is that it almost always permanently reverses hyperthyroidism. One disadvantage is that the majority of patients subsequently develop hypothyroidism [1]. However, once a stable dose of levothyroxine replacement has been achieved, the annual evaluation of that dose compares favorably with the more frequent evaluations of patients remaining on ATDs. On the other hand, up to 15% of appropriately treated hypothyroid patients fail to achieve a sense of well-being on levothyroxine and continue to have hypothyroid symptoms [21] which is often helped by adding a small amount of liothyronine. Other disadvantages of RAI therapy are the unavailability of nuclear medicine specialists, and if available, the near-term challenge of treating patients after receiving it because RAI treatment may release thyroid hormone and there is a several months delay in starting to reverse hyperthyroidism. Additionally, many female patients have young children and RAI therapy is contraindicated if the patient cannot be completely separated from their children during the week after treatment because of radiation exposure to the latter.

If remission occurs after discontinuing ATDs, continued follow up is necessary. After patients remained euthyroid off of MMI for 2 months, we typically evaluate them every 3 months for the remainder of the first year. If euthyroid at that time, we refer them back to their PCPs with the recommendation that they be evaluated for recurrent hyperthyroidism every 6 months. If they become hyperthyroid again, an ATD could be re-started or RAI considered. Note that once a recurrence occurs, future remissions become less likely [2].

In conclusion, GD hyperthyroidism is common and the lack of endocrinologists may force many PCPs to treat this autoimmune disease. This effective, straightforward protocol will not only enable PCPs to effectively treat the acute hyperthyroidism, but provides an approach to follow these patients long-term.

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Ethical Considerations

This prospective, observational study was submitted to 2 Institutional Review Boards; one to Charles R. Drew University where the authors worked and the other to the Department of Health

Services at Los Angeles County, the organization responsible for patient care of this medically underserved population. Both approved the study with the opinion that informed consents of the patients were not necessary because their data would be de-identified. The study was carried out in accordance with the guidelines in the Declaration of Helsinski.

Conflict of Interests

The authors declare that they have no conflicts of interests and that there was no outside source of funding for this study.

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