Relapse Rate and Clinical Risk Factors Affecting the Treatment of Graves' Disease

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ABSTRACT

Objective: To determine the relapse rate of Graves' disease (GD) and identify important clinical risk factors for relapse.

Materials and Methods: This was a 10-year retrospective cohort study. Information was collected with ICD10 E050 codes for Graves' hyperthyroidism among Thai patients of both sexes and all ages with no history of pregnancy, thyroid storm or antithyroid drug (ATD) allergy.

Results: The 286 included GD patients had a relapse rate of 35% after ATD withdrawal for one year. The clinical risk factors associated with relapse were male sex (p = 0.014), smoking (p = 0.001), serum free T4 (FT4) levels > 2 times the upper normal range at diagnosis (p = 0.005), duration for maintenance treatment < 6 and 9 months (p < 0.005) compared with remission. A TSH level < 1 mIU/L (p = 0.060) and MMI > 2.5 mg per day before ATD withdrawal (p = 0.094) trended toward associations with relapse. The clinical factors that predicted GD relapse were serum FT4 levels at diagnosis (p = 0.006) and serum free T3 (FT3) levels before ATD withdrawal (p = 0.019).

Conclusion: Male sex, smoking and serum FT4 levels at diagnosis > 2 times the normal range were significant clinical factors for GD relapse in Thai patients. To reduce the relapse rate in the first year, MMI should be used in maintenance periods for 9 to 12 months with serum FT3 levels within low-normal ranges before ATD withdrawal. This would promote future guidelines for GD management in Thailand.

Keywords: Relapse; Graves' disease; antithyroid drugs; risk factors (Siriraj Med J 2021; 73: 451-461)

INTRODUCTION

Graves' disease (GD) is the most common cause of thyrotoxicosis. There are 3 modalities for management: antithyroid drugs (ATDs), radioactive iodine (RAI) and surgery.[1] According to survey results for the management of GD conducted by members of the Endocrine Society of the USA, the proportions of respondents with ATDs, RAI therapy and thyroid surgery as the preferred modes of therapy for uncomplicated GD are 53.9%, 45% and 0.7%, respectively.[2] However, among members of the Endocrine Society of Thailand, ATDs are the preferred choice of therapy (90.8%), with RAI therapy (9.2%) being the second most preferred.[3] In a corresponding survey of the members of the European Thyroid Association, ATDs were preferred by 83.8% of respondents and RAI therapy by 14.1% of respondents.[4] ATDs have been used to treat hyperthyroidism for more than 75 years.[5] In Thailand, 2 ATD types are used: methimazole (MMI) and propylthiouracil (PTU). Generally, the guidelines suggest MMI for treatment of GD or other causes of hyperthyroidism for all patients except patients with a first-trimester pregnancy, thyroid storm or minor reaction to MMI.[1,6] The treatment goal is restoration to normal thyroid function as soon as reasonably possible even though this mode is not curative among GD patients but suppresses their autoimmunity for only a short time.[7]

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The GD relapse and remission rates vary among geographical areas due to varying in the duration of treatment and different iodine status.[8-15] In the USA, the remission rate after ATD use for at least 12-18 months is 20-30%[10], while that in Europe is 50-60% after medication use for 5-6 years.[11] In Sweden, the relapse rate is 30.2% after stopping ATDs within 1 year.[12] In Japan, the remission rate is 68% for at least 2 years after treatment with maintenance doses of MMI for a minimum of 19 months.[13] There are many clinical factors for predicting GD relapse, such as male sex, smoking, a large thyroid goiter, the FT3/FT4 ratio, and continuous TSH suppression.[16-21]

In principle, ATDs are used in most patients with varying characteristics and are easy to access. However, the responses to ATD treatment differ according to race and continental regions worldwide.[10-14,18] The previous study in Thailand showed the low remission rate of children with GD only 18.8% after ATD treatment about 3.5 years.[22] A recent study in adult showed the early relapse of hyperthyroidism within a year after MMI withdrawal, 27.8% of median duration of treatment being nearly 2 years.[23] However, there is no clear guideline for the treatment of such patients. Current management practices are based on those of outside countries; thus, there are variations in remedies, especially regarding treatment dosages and durations. Thus, this study aimed to evaluate the GD relapse rate in Thailand and clinically relevant factors affecting the disease that can be used as basic information to properly set treatment guidelines and reduce the cost of screening for TRAb levels before discontinuing ATDs in some groups of patients. The primary objective was to determine the GD relapse rate. The secondary objective was to identify important clinical factors for GD relapse.

MATERIALS AND METHODS

Study population

This retrospective cohort study included consecutive searches of an electronic database with ICD10 E050 for new diagnoses of GD, was 526 patients, that had been referred to and/or treated in all clinics at Charoenkrung Pracharak Hospital, Bangkok, Thailand, between 1st January 2007 and 31st December 2017. The inclusion criteria were Thai patients of any age and gender. The exclusion criteria were patients with thyroid storms, major side effects of ATDs, a history of prior RAI treatment and thyroidectomy, loss to follow-up before remission, pregnancy and death before remission. Of those, 286 patients were eligible by reviewing all documentations carefully. GD was diagnosed based on clinical diagnosis based on indicators including high serum FT4 and/or serum FT3 with suppressed TSH accompanied by one of the following clinical characteristics for at least 3 months: symptoms and signs of hyperthyroidism (pulse >100 bpm and/or fine tremor and/or warm and moist skin and/or onycholysis and/or proximal muscle weakness), diffuse goiter with or without bruit, thyroid-associated ophthalmopathy (TAO), and thyroid dermopathy (pretibial myxedema and/or thyroid acropachy). Goiter was categorized by physical examination by a physician: normal gland (10-20 gm), mild-to-moderate goiter (25-60 gm) and large goiter (>60 gm). TAO was classified according to nonspecific signs, lid lag and retraction, and specific signs, including exophthalmos.[14] An ATD titration regimen was commonly used. The duration of ATDs was divided into two periods: initial treatment and maintenance treatment. The initial period consisted of MMI > 5 mg/day or PTU > 100 mg/day followed by a maintenance period that consisted of MMI ≤ 5 mg/day or PTU ≤ 100 mg/day until withdrawal therapy. This study was approved by the Human Research and Ethics Committee of Bangkok Metropolitan Administration, Bangkok, Thailand.

Laboratory measurement

Serum FT4, FT3 and TSH levels were measured by electrochemiluminescent immunoassay (ECLIA) methods using Roche Diagnostics with normal ranges of 0.93 - 1.70 ng/dL, 2.20 - 4.40 pg/mL and 0.270 - 4.200 mIU/L, respectively. If any result value is too large or too small to measure, I will display only the highest or lowest reading for analysis.

Definitions of clinical outcomes

Remission was defined as euthyroidism with normal FT4, FT3 and TSH maintained for at least one year after ATD withdrawal. Relapse was defined as recurrence of hyperthyroidism, including low TSH with or without high FT4 and/or FT3 during follow-up after withdrawal therapy for less than one year.

Statistical analyses

The relapse rate and remission rate are presented as percentages. Continuous variables are described as means with standard deviations or medians with interquartile ranges (IQRs) and were analyzed using Student's *t* test or the Mann-Whitney U test. Categorical variables are presented as percentages and were examined with the chi-square test or Fisher's exact test. The multivariate analysis included age, sex, smoking, the presence of TAO, goiter size, serum FT4 and FT3 levels at diagnosis and after ATD withdrawal, serum TSH levels after stopping ATDs and ATD dosage before withdrawal, which were

analyzed by using logistic regression; the data are presented as the odds ratio (OR), 95% confidence interval (CI) and *p*-value. All two-sided *p*-values <0.05 were considered statistically significant. Statistical analyses were carried out using SPSS version 26.0.

RESULTS

Baseline and clinical characteristics of patients with GD

The mean age at diagnosis of the 286 GD patients was 43.5 ± 13.6 years (minimum, 8 years; maximum, 80 years), and 77.3% were female. Most were non-smokers (94.1%), and 48.3% had no underlying disease. Among patients with underlying disease, the most common disease was dyslipidemia, 36% (Table 1).

Regarding the clinical characteristics, laboratory results and treatments, there was no TAO in 82.5% of cases and mild-to-large goiter at diagnosis in 68.5% of cases. The mean levels of serum FT4, FT3 and TSH at diagnosis were 5.38 ± 2.14 ng/dL, 18.30 ± 8.87 pg/mL and 0.0096 ± 0.023 mIU/L, respectively. The mean serum FT4, FT3 and TSH levels after ATD withdrawal were 1.22 ± 0.29 ng/dL, 2.88 ± 0.49 pg/mL and 3.235 ± 0.289 mIU/L, respectively. In total, 92.7% were treated with MMIs. The median initial treatment duration was 7 months (IQR 4 - 14.25 months). The median maintenance treatment duration was 19 months (IQR 12 - 27.25 months). The median follow-up duration was 32 months (IQR 16 - 55 months) (Table 1).

GD patient baseline and clinical characteristics in the relapse and remission groups

The relapse rate of GD was 35% after ATD withdrawal for one year. We divided patients based on clinical features into the relapse group (n = 100) and remission group (n = 186). The baseline and clinical features, including laboratory results and treatments, are shown in Table 2. The relapse group had a mean age at diagnosis of 45 ± 15 years, most patients had no TAO (84.4%), however there were more TAO in relapse group (21%) than in remission group (15.6%) statistical insignificantly and a majority had a goiter of approximately 25-60 gm (68.5%), which was not significantly different from that of the remission group.

Clinical factors, including male sex (OR 2.01; 95%CI 1.13 – 3.53; p = 0.014) and smoking (OR 6.80; 95%CI 2.15 – 21.46; p = 0.001), were significantly different between the two groups. There was more underlying diabetes mellitus, hypertension, dyslipidemia in relapse group than in remission group but not significantly. The mean serum FT3 and FT4 level at diagnosis in the relapse group was insignificantly higher than that of remission group. The mean serum FT4 level before stopping ATDs in the relapse group (1.17 ± 0.25 ng/dL) was significantly lower than that of the remission group (1.25 ± 0.31 ng/dL) (p = 0.047). The mean dose of MMI before stopping ATDs in the relapse group (3.4 ± 2.4 mg/day) was significantly higher than that in the remission group (2.8 ± 1.7 mg/day) (p = 0.014). The median duration of remission in the relapse group was 4 months, in contrast to 1 year and 11 months in the remission group (Table 2).

Further analyses of the factors expected to influence future treatment were conducted. This was partly based on a study of a predictive model for GD recurrence based on clinical features or the Graves' Recurrence Events After Therapy (GREAT) score[25] (Table 3). The relapse group had serum FT4 levels > 2 times the normal ranges at diagnosis (OR 2.49; 95%CI, 1.30 - 4.77; p = 0.005) and intervals of the maintenance periods of ATDs < 6 and 9 months, which were significantly different from those of the GD remission group (OR 0.4; 95%CI, 0.21 - 0.78; p = 0.006 and OR 0.56; 95%CI, 0.31 - 0.99; p = 0.043, respectively). The relapse group tended to have TSH levels < 1 mIU/L before discontinuation and MMI doses > 2.5 mg/day before discontinuation in contrast to those of the remission group, but the difference was not statistically significant.

Other factors considered included age < 40 versus > 40 years, the thyroid gland abnormality at diagnosis, serum FT3 three or more times the normal value, and an ATD maintenance period duration less than or equal twelve months, but the comparisons between relapse and remission groups revealed no statistically significant differences.

As shown in Table 4, there were three clinical factors that predicted the likelihood of GD recurrence, namely, serum FT3 levels at diagnosis, serum FT4 levels at diagnosis and serum FT3 levels prior to discontinuation, and differences were statistically significant (p <0.05). It was found that when serum FT3 at diagnosis was reduced by 1 pg/mL, there was a chance of reducing GD relapse by 0.84 (OR 0.84; 95%CI, 0.71 - 0.99; p = 0.036). When serum FT4 at diagnosis was increased by 1 ng/dL, there was an increased risk of GD relapse by 2.35 (OR 2.35; 95%CI, 1.28 -4.32; p = 0.006). When serum FT3 levels before discontinuation increased by 1 pg/mL, there was an increased risk of relapsed GD by 3.85 (OR 3.85; 95%CI, 1.24 – 11.93; p = 0.019), so serum FT3 was considered the most important variable. If the serum FT3 value changed, it might also change the course of the disease.

TABLE 1. Baseline and clinical characteristics, including laboratory results and treatments, of 286 patients with GD.

Characteristics	Total, *N* = 286 (%)
Baseline characteristics	
Age at diagnosis (years), min–max	43.5 ± 13.6, 8–80
Sex	
Female	221 (77.3)
Male	65 (22.7)
Smoking	
Never smoker	269 (94.1)
Smoker	15 (5.2)
Former smoker	2 (0.7)
Coexisting disease	
None	138 (48.3)
Hypertension	90 (31.5)
Diabetes mellitus	42 (14.7)
Dyslipidemia	103 (36.0)
Cardiac diseases	11 (3.8)
Cerebrovascular diseases	8 (2.8)
Renal diseases	2 (0.7)
Liver diseases	4 (1.4)
Others	57 (19.9)
Clinical characteristics	
Thyroid-associated ophthalmopathy at diagnosis	
Absent	236 (82.5)
Lid lag and/or lid retraction	25 (8.7)
Exophthalmos	25 (8.7)
Goiter at diagnosis	
Normal (10–20 gm)	83 (29.0)
Mild to moderate (25–60 gm)	196 (68.5)
Large (> 60 gm)	7 (2.5)
Laboratory results and treatments	
Mean levels of thyroid function at diagnosis, min–max	
FT4 (ng/dL)*	5.38 ± 2.14, 1.16–7.77
FT3 (pg/mL)**	18.30 ± 8.87, 3.40–32.55
TSH (mIU/L)	0.0096 ± 0.023, 0.002–0.300
Mean levels of thyroid function at ATDs withdrawal, min–max	
FT4 (ng/dL)#	1.22 ± 0.29, 0.25–2.94
FT3 (pg/mL)##	2.88 ± 0.49, 1.21–4.39
TSH (mIU/L)###	3.235 ± 0.289, 0.032–84.960
Type of ATDs	
MMI	265 (92.7)
PTU	21 (7.3)
Median initial duration of treatment (months), IQRs	7, 4–14.25
Median maintenance duration of treatment (months), IQRs	19, 12–27.25
Median total duration of treatment (months), IQRs	27.5, 24–38
Median follow-up duration of treatment (months), IQRs	32, 16–55
Median duration of remission (months), IQRs	14, 5–31

*N = 277, **N = 261, #N = 239, ##N = 202, ###N = 284 due to missing data or data not obtained
GD, Graves' disease; ATDs, antithyroid drugs; MMI, methimazole; PTU, propylthiouracil; IQR, interquartile range

TABLE 2. Baseline and clinical characteristics, including laboratory results and treatments, of the relapse group versus the remission group of patients with GD.

Characteristics	Relapse group, *n* = 100 (%)	Remission group, *n* = 186 (%)	*p*-value, odds ratio (95% CI)
Baseline characteristics			
Age at diagnosis (years), min–max	45.0 ± 15.0, 12–80	42.7 ± 12.7, 8–76	
15 or under	2 (2.0)	6 (3.2)	
16–25	10 (10.0)	15 (8.1)	
26–35	11 (11.0)	27 (14.5)	
36–45	30 (30.0)	60 (32.3)	0.187§
46–55	24 (24.0)	49 (26.3)	
56–65	15 (15.0)	23 (12.4)	
Over 65	8 (8.0)	6 (3.2)	
Sex			
Female	69 (69.0)	152 (81.7)	**0.014**†, 2.01 (1.13–3.53)
Male	31 (31.0)	34 (18.3)	
Smoking			
Never smoker	87 (87.0)	182 (97.8)	
Smoker	11 (11.0)	4 (2.2)	**0.001**†, 6.80 (2.15–21.46)
Former smoker	2 (2.0)	0 (0.0)	
Coexisting disease			
None	42 (42.0)	96 (51.6)	
Hypertension	40 (40.0)	50 (26.9)	
Diabetes mellitus	22 (22.0)	20 (10.8)	
Dyslipidemia	40 (40.0)	63 (33.9)	
Cardiac diseases	3 (3.0)	8 (4.3)	0.121†, 1.47 (0.90–2.41)
Cerebrovascular diseases	4 (4.0)	4 (2.2)	
Renal diseases	2 (2.0)	0 (0.0)	
Liver diseases	1 (1.0)	3 (1.6)	
Others	24 (24.0)	33 (17.7)	
Clinical characteristics			
Thyroid-associated ophthalmopathy at diagnosis			
Absent	79 (79.0)	157 (84.4)	
Lid lag and/or lid retraction	12 (12.0)	13 (7.0)	0.348†, 1.44 (0.77–2.68)
Exophthalmos	9 (9.0)	16 (8.6)	

TABLE 2. Baseline and clinical characteristics, including laboratory results and treatments, of the relapse group versus the remission group of patients with GD. (Continue)

Characteristics	Relapse group, *n* = 100 (%)	Remission group, *n* = 186 (%)	*p*-value, odds ratio (95% CI)
Goiter at diagnosis			
Normal (10–20 gm)	28 (28.0)	55 (29.6)	
Mild to moderate (25–60 gm)	69 (69.0)	127 (68.3)	0.882†, 1.08 (0.63–1.85)
Large (> 60 gm)	3 (3.0)	4 (2.2)	
Laboratory results and treatments			
Mean levels of thyroid function at diagnosis			
FT4 (ng/dL)*	5.66 ± 1.94	5.24 ± 2.24	0.155‡
FT3 (pg/mL)**	18.79 ± 8.48	18.06 ± 9.08	0.548‡
TSH (mIU/L)	0.01 ± 0.03	0.01 ± 0.02	0.372‡
Mean FT3/FT4 ratio at diagnosis (pmol/L)	0.38 ± 0.10	0.41 ± 0.10	0.317‡
Mean levels of thyroid function at ATD withdrawal			
FT4 (ng/dL)#	1.17 ± 0.25	1.25 ± 0.31	**0.047**‡
FT3 (pg/mL)##	2.94 ± 0.54	2.84 ± 0.47	0.423‡
TSH (mIU/L)###	4.45 ± 10.64	2.58 ± 1.83	0.317‡
Type of ATD			
MMI	93 (93.0)	172 (92.5)	0.871†, 0.93 (0.36–2.37)
PTU	7 (7.0)	14 (7.5)	
Mean dose of ATDs at diagnosis (mg/day)			
MMI	37.1 ± 9.7	49.5 ± 10.9	0.962‡
PTU	158.2 ± 107.9	204.3 ± 89.2	0.219‡
Mean dose of ATDs before withdrawal (mg/day)			
MMI	3.4 ± 2.4	2.8 ± 1.7	**0.014**‡
PTU	67.9 ± 42.6	41.1 ± 12.4	0.091‡
Median initial duration of treatment (months), IQR	8, 5–16	7, 4–13.25	0.249‡
Median maintenance duration of treatment (months), IQR	19, 8–31	19, 14–25.25	0.804‡
Median total duration of treatment (months), IQR	28, 24–43.5	27, 24–37	0.445‡
Median duration of remission (months), IQR	4, 3–7.75	23, 14.75–40.25	**<0.001**‡

§Independent t-test, †chi-square test, ‡Mann-Whitney U-test

*N = 277, **N = 261, #N = 239, ##N = 202, ###N = 284 due to missing data or data not obtained

GD, Graves' disease; 95% CI, 95% confidence interval; IQR, interquartile range

TABLE 3. Specific clinical risk factors that are expected to influence future treatment in the relapse group versus remission group of patients with GD.

Characteristics	Relapse group, *n* = 100 (%)	Remission group, *n* = 186 (%)	*p*-value, odds ratio (95% CI)
Baseline and clinical characteristics			
Age at diagnosis			
< 40 vs ≥ 40 years	39 (39.0) vs 61 (61.0)	74 (39.8) vs 112 (60.2)	0.897†, 1.03 (0.63–1.70)
Goiter at diagnosis			
Normal vs abnormal glands	28 (28.0) vs 72 (72.0)	55 (29.6) vs 131 (70.4)	0.780†, 1.08 (0.63–1.85)
Laboratory results and treatments			
Level of thyroid function at diagnosis			
FT4 < 2 vs ≥ 2 times the normal range	14 (14.6) vs 82 (85.4)*	54 (29.8) vs 127 (70.2)*	**0.005**†, 2.49 (1.30–4.77)
FT3 < 3 vs ≥ 3 times the normal range	23 (26.4) vs 64 (73.6)*	64 (36.8) vs 110 (63.2)*	0.095†, 1.62 (0.92–2.86)
Level of thyroid function at ATDs withdrawal			
TSH ≤ 1 vs > 1 mIU/L	22 (22.2) vs 77 (77.8)	25 (13.5) vs 160 (86.5)	0.060†, 0.55 (0.29–1.03)
Dose of MMI before withdrawal			
≤ 2.5 vs > 2.5 mg/day	63 (63.9) vs 37 (37.0)	135 (72.6) vs 51 (27.4)	0.094†, 1.56 (0.93–2.61)
Duration of maintenance treatment			
≤ 6 vs > 6 months	23 (23.0) vs 77 (77.0)	20 (10.8) vs 166 (89.2)	**0.006**†, 0.40 (0.21–0.78)
≤ 9 vs > 9 months	28 (28.0) vs 72 (72.0)	33 (17.7) vs 153 (82.3)	**0.043**†, 0.56 (0.31–0.99)
≤ 12 vs > 12 months	31 (31.0) vs 69 (69.0)	41 (22.0) vs 145 (78.0)	0.096†, 0.63 (0.36–1.86)

*Missing data or data not obtained, †chi-square test
GD, Graves' disease; 95% CI, 95% confidence interval; ATDs, antithyroid drugs

TABLE 3. Demonstrated clinical factors for prediction of relapsed GD by Wald (forward stepwise) logistic regression.

Influencing clinical risk factors (variables)	β	S.E.	Wald	*p*-value	Odds ratio	95% CI for odds ratio	
						Lower	Upper
Constant	-4.252	2.510	2.869	0.090	0.014		
Age	0.021	0.016	1.689	0.194	1.021	0.989	1.055
Sex	-0.136	0.549	0.061	0.805	0.873	0.297	2.562
Smoking	1.116	1.077	1.074	0.300	3.052	0.370	25.187
TAO	0.411	0.721	0.325	0.569	1.508	0.367	6.199
Goiter size	-0.543	1.221	0.198	0.656	0.581	0.053	6.360
Serum FT3 level at diagnosis	-0.181	0.086	4.399	**0.036**	0.835	0.705	0.988
Serum FT4 level at diagnosis	0.855	0.310	7.602	**0.006**	2.352	1.281	4.321
Serum FT3 level before ATDs withdrawal	1.349	0.577	5.465	**0.019**	3.852	1.243	11.933
Serum FT4 level before ATDs withdrawal	-2.141	1.326	2.607	0.106	0.117	0.009	1.581
Serum TSH level before ATDs withdrawal	0.000	0.050	0.000	1.000	1.000	0.907	1.103
Doses of ATDs before withdrawal	0.072	0.064	1.254	0.263	1.075	0.947	1.219

GD, Graves' disease; 95% CI, 95% confidence interval; TAO, Thyroid-associated ophthalmopathy; ATDs, antithyroid drug

DISCUSSION

This 10-year retrospective study of 286 first-diagnosed Thai patients with GD focused on ATD therapy only. The relapse rate was 35% among patients with GD after first-year ATD withdrawal therapy. Overall, this study had a median follow-up of 2 years and 8 months, the relapse group was found to comprise males and smokers, and the mean MMI doses before discontinuation were greater than those in the remission group (Table 2). From which the mean serum FT4 level before stopping ATDs in the relapse group was significantly lower than that of the remission group while the mean serum FT3 and FT4 level at diagnosis in the relapse group was higher than that of remission group but insignificantly (Table 2), probably due to T3 toxicosis was predominated in the relapse group. When subgroup analysis for each factor that was expected to affect future treatment was performed, the relapse group had a serum FT4 level at diagnosis ≥ 2 times the normal range, and the maintenance treatment duration, less than 6 and 9 months, was significantly different from that of the remission group. However, there was no significant difference in use of this treatment for up to 12 months compared with more than 12 months. Additionally, the relapse group tended to have serum TSH levels ≤ 1 mIU/L and doses of MMI before discontinuation of more than 2.5 mg/day compared with the remission group, but the difference was not statistically significant (Table 3). When important clinical factors were used in relation to GD relapse during the first year after discontinuation, elevations in serum FT4 levels at diagnosis of 1 ng/dL and elevations in serum FT3 levels before discontinuation of 1 pg/mL increased the risk of GD recurrence by 2.35 and 3.85, respectively (Table 4).

Compared to previous studies in Asia, the relapse rate was 32 - 52% after one to two years of ATD discontinuation.[13,14,23,26,27] The clinical factors related to relapse were younger age[27], large thyroid gland[14,27], TAO after drug treatment[14], higher serum FT3 and FT4 levels[27], FT3/FT4 (pmol/l) ratio[14], continued TSH suppression levels[14], TRAb levels[14] and a duration of ATD use in the maintenance period of less than 6 months.[26] The clinical factors related to remission were older age (45.6 ± 10.3 years)[14] and a minimum dose of MMI of 5 mg every other day for at least 19 months.[13] Compared with rates from previous studies in Europe and Africa, the relapse rate was 30 - 49% after one year of discontinuation.[28-30] The clinical factors related to relapse were < 40 years of age; smoking; TAO; thyroid size by ultrasound; serum FT4, FT3, and TRAb levels; and total T4 levels ≥ 2 times the upper normal range.[30] The clinical factors related to remission were female sex, nonsmoking status, no TAO and duration of treatment of more than 2 years.[28] This study showed a relapse rate similar to that of previous studies and confirmed that some clinical risk factors influence relapse in both Asian and Western countries. However, we found that ATDs should be taken as maintenance treatment for more than 9 months and a trend toward having TSH > 1 mIU/L before discontinuation medications to reduce relapse.

In Thailand, a recent study showed the relapse rate 37% within first year of ATD withdrawal as well as this study (35%). However, the factors associated with early relapse in that study showed patients 40 years of age or less and the highest quartile of serum T3 level at the time of diagnosis[23], in contrast with this study showed no statistically significant of those factors.

When statistically significant clinical factors associated with relapsed GD after one year of ATD withdrawal were assessed in the context of previous studies, we made several observations. First, male sex: many previous studies have shown that male sex was a factor associated with the GD relapse. One study showed that men usually have a larger thyroid gland and more of a family history of autoimmune thyroid disease than women.[31] Another study found that men have a larger thyroid gland and still smoked more than women.[32] This was consistent with the results of our study showing that males smoked more cigarettes (24.6%) than females (0.5%), but there was no difference in thyroid size in our study. Second, smoking: in addition to being a major risk factor for developing GD[33], studies comparing smokers to nonsmokers found that elimination of serum FT4, serum FT3 and TRAb among smokers was slow, causing antibodies to be present longer, leading to disease progression.[34] This support the results of our study showing that smoking is associated with relapse. Third, serum FT4 levels at diagnosis ≥ 2 times the normal range: a previous study showed a positive correlation between FT4 and TRAb levels, indicating that higher FT4 levels were also associated with a high TRAb level[35], thus promoting disease recurrence. This was consistent with our study results. Fourth, higher mean serum FT3 levels before discontinuation: a previous study found that the remission phase is related to normal thyroid hormone levels regardless of the doses received.[36] This supports the results of our study, which show that more of such factors are associated with a higher risk of relapsed GD. Fifth, administration of more than 2.5 mg/day MMI prior to discontinuation and a maintenance treatment duration less than 6-9 months: these findings are consistent with a recent study showing that a 2.5-mg daily dose of MMI for periods of less than 6 months is associated with relapse[28] and that treatment with MMI

5 mg every other day for no longer than 6 months has a higher rate of relapse.[13]

According to the American Thyroid Association[1] and the European Thyroid Association[37], it is recommended that the total dose of ATDs is given for approximately 12 to 18 months and discontinued after the TSH and TRAb levels are normal; the consequent remission rate is 20-30%. Based on studies in 1994[38] and 2004[39], treatment with ATDs for 18 months versus 6 months has lower rates of recurrence. However, in a meta-analysis published in 2005[40], the remission rate did not increase after taking ATDs for more than 18 months. Consistent with the results of this study, the median total duration of ATDs was 28 months, and no difference was found between the relapse and remission groups. However, this study provides additional data showing that low-dose ATDs should be taken for 9-12 months before stopping medications to reduce the relapse rate.

Benefits

1. Knowledge of the relapse rate and the important clinical factors for GD relapse in Thai patients.
2. Ability to provide ATD treatment with appropriate dosages and durations of administration to minimize the likelihood of GD relapse in Thai patients.
3. Usefulness as the basis for planning suitable guidelines in the management of GD in Thailand that lead to a reduction in costs associated with measuring TRAb levels before discontinuation of ATDs for patients among whom these measurements are unnecessary, such as females, nonsmokers, those with serum FT4 levels at diagnosis < 2 times the normal range, and those with low serum FT3 levels before discontinuation.

Limitations

This is a 10-year retrospective study using data from past medical records. Patients were examined by physical examination, which might lead to inaccuracies regarding certain clinical features. Some information was considered missing data, namely, in cases in which data was lost or cases that were not fully investigated, with data including serum FT4, FT3 and TSH levels at diagnosis and before ATD withdrawal. However, these cases were rare and comprised missing data for only select hormones in a few patients but not all hormones at once. Therefore, only the information contained in the dataset was analyzed.

Suggestions

Further studies should include a prospective trial with physical examination by any internist or endocrinologist and set the protocol for the laboratory test. For further reliability, a Hertel ophthalmometer and ultrasound may be used for the measurement of thyroid gland size and additional TRAb levels to help provide more accurate data.

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