

Clinical Research Article

Serum T3 Level and Duration of Minimum Maintenance Dose Therapy Predict Relapse in Methimazole-Treated Graves Disease

Yotsapon Thewjitcharoen,¹ Krittadhee Karndumri,¹
Waralee Chatchomchuan,¹ Sriurai Porramatikul,¹ Sirinate Krittiyawong,¹
Ekgaluck Wanothayaroj,¹ Siriwan Butadej,¹ Soontaree Nakasatien,¹
Rajata Rajatanavin,¹ and Thep Himathongkam¹

¹Diabetes and Thyroid Center, Theptarin Hospital, Bangkok 10110, Thailand

ORCID numbers: 0000-0002-2317-4041 (Y. Thewjitcharoen); 0000-0002-7547-648X (K. Karndumri).

Abbreviations: ATD, antithyroid drugs; FT4, free thyroxine; GD, Graves disease; MMDT, minimum maintenance dose therapy; MMI, methimazole; T3, triiodothyronine; T4, thyroxine; Tg, thyroglobulin; TPO, thyroid peroxidase; TRAb, thyroid-stimulating hormone receptor autoantibody; TSH, thyrotropin (thyroid-stimulating hormone).

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Abstract

Background: Methimazole (MMI) has been advocated as a preferred option for most Graves disease (GD) patients. However, long-term remission after a course of MMI treatment is achieved in only 20% to 40% of patients, depending on the duration of follow-up.

Objective: To evaluate clinical factors for predicting relapse of GD in Thai patients after MMI treatment.

Methods: A retrospective analysis was performed of newly diagnosed patients with GD who achieved remission of hyperthyroid GD after at least 12 months of MMI treatment. Long-term outcomes were assessed and predictive factors of early and late relapse were evaluated.

Results: A total of 443 patients with newly diagnosed GD who were treated with MMI for at least 12 months from 1985 to 2019, and were able to discontinue medication, were studied. The mean age at diagnosis was 37.0 ± 11.4 years and 81.7% were female. Of the 320 patients (72.2%) who achieved initial remission after MMI treatment for 23 months, 106 patients (33.1%) experienced late relapse during the mean follow-up duration of 9.7 years after MMI withdrawal. The remission rates decreased from 36.4% at the first year after stopping MMI to only 20.7% at 10 years. High initial serum triiodothyronine (T3) level and duration of minimum maintenance dose therapy (MMDT) of <6 months were associated with late disease relapse after remission.

Conclusion: The long-term remission rate of Graves hyperthyroidism was achieved in one-fifth of MMI-treated Thai patients. Predictive markers for late relapse included high initial serum T3 level and a duration of MMDT of <6 months.

Key Words: Graves disease; methimazole; long-term outcomes; remission

Hyperthyroid Graves disease (GD) is a common condition that requires lifelong follow-up. Antithyroid drugs (ATD) have been in use since the 1940s and represent 1 of the 3 major forms of treatment for GD [1]. ATD therapy is the preferred choice of treatment in Asia and Europe for its noninvasive nature. It is widely accepted by patients and is a favorable choice among those with Graves ophthalmopathy [2-4]. Methimazole (MMI) has been advocated as a preferred option for most GD patients due to its effectiveness in a once-daily dose and/or in small daily doses for the initial treatment period [5]. However, long-term remission after a course of MMI treatment is achieved in only 20% to 40% of patients depending on the duration of follow-up [1].

Previous studies have suggested that predictors for ATD treatment failure are age <40 years at diagnosis, the presence of moderate-to-severe Graves ophthalmopathy (GO), severe initial serum thyroid hormone levels, and persistently high serum levels of thyrotropin (thyroid-stimulating hormone; TSH) receptor antibody (TRAb) [6]. However, few studies have investigated the predictive factors for late relapse (>1 year) after ATD discontinuation. Previous studies showed that more than 50% of GD relapses occurred within 1 year after ATD cessation and more than 90% of relapses occurred within 4 years [7]. Even though negative serum TRAb level prior to ATD withdrawal could indicate higher remission rate, the re-appearance of TRAb could develop later [8]. Previous studies from Japan and Korea demonstrated that the remission rate increased with duration of minimum maintenance dose therapy (MMDT) of more than 6 months regardless of the presence of TRAb and this duration of therapy was associated with a lower rate of late relapse [9, 10]. Therefore, it would be important to explore predictive factors beyond TRAb for late relapse, especially clinical parameters and thyroid hormone levels at the time of initial diagnosis and before ATD withdrawal in order to offer other choices such as long-term ATD or ablative treatments for patients who are unlikely to achieve sustained remission.

This study aimed to investigate long-term outcomes in Thai patients with GD after a successful course of MMI treatment and to evaluate clinical factors for predicting early and late relapse of GD.

1. Methods

A. Patients and Methods

This retrospective cohort study consisted of Thai patients with newly diagnosed hyperthyroid GD who were treated with MMI for at least 12 months between June 1985 and June 2019 at Theptarin Hospital, a tertiary endocrine center in Bangkok, Thailand. GD was diagnosed by clinical

and laboratory findings, including signs of thyrotoxicosis, diffuse goiter, the presence of GO or dermopathy, elevation of serum total triiodothyronine (T3) and/or serum free thyroxine (T4) levels, suppression of serum thyroid-stimulating hormone (TSH) concentrations, the presence of thyroid autoantibodies (TRAb, anti-thyroid peroxidase antibody [anti-TPO], anti-thyroglobulin [anti-Tg]), and/or elevated radioiodine uptake. We excluded patients from other ethnic backgrounds, age <15 years, GD in remission or GD with subclinical hyperthyroidism at the time of initial visit, propylthiouracil (PTU)-treated patients, block and replacement regimen-treated patients, and patients with MMI-treated duration less than 12 months. Palpated thyroid size determined by treating physicians was transformed into thyroid volume on the basis of goiter size compared with normal thyroid size as follows: small (barely palpable or ≤ 30 gram), medium (2-3 times when compared with normal thyroid gland), and huge (more than 3 times or ≥ 60 gram). The presence of GO was defined as an inflammatory eye disease associated with GD and was classified by disease activity and severity as mild, moderate, or severe [11]. Serum T3, FT4, and TSH concentrations were measured by electrochemiluminescent immunoassays (Roche Diagnostics, Indianapolis, USA). The reference ranges used for serum T3, FT4, and TSH levels were 60 to 177 ng/dL, 0.9 to 1.7 ng/dL, and 0.3 to 4.2 mIU/L, respectively.

The initial dose of MMI was given once daily at 15 to 20 mg/day according to the severity of the hyperthyroidism in our institute. The dose of MMI was titrated to maintain patients in the euthyroid state for at least 12 months. Serum TRAb level was measured in some patients before considering MMI discontinuation. We included the patients who had taken MMI for at least 12 months and who were then followed for ≥ 12 months after MMI discontinuation. All medical records were reviewed and analyzed with respect to their baseline clinical characteristics and laboratory data, duration of MMI treatment, and laboratory data at MMI discontinuation. Documented cases of agranulocytosis from MMI were also noted.

B. Definitions

Remission was defined as a euthyroid state with a normalized serum TSH level without medication for at least 12 months [5]. Patients who developed spontaneous hypothyroidism after MMI discontinuation for at least 12 months were also regarded as remission cases. Relapse was defined as persistently suppressed serum TSH level with or without increased serum FT4 level after discontinuation of MMI. The period of relapse was categorized as early relapse in patients who had relapse within 12 months after MMI withdrawal and late relapse for those who relapsed more than 12 months

after MMI withdrawal. Final disease status was determined based on the last clinical visit. The duration of MMDT was defined as the duration of MMI treatment with dosage of less than 5 mg/day while serum FT4 and TSH concentrations were within the reference range [9]. For example, if the patients were given MMI with an initial dose at 20 mg/day and then tapered to a dose of 2.5 mg of MMI at the eighth month after initial treatment and then discontinued MMI after 12 months, the duration of MMDT was equal to 5 months. If patients discontinued MMI abruptly while taking a dose of MMI \geq 5 mg/day, the duration of MMDT was noted as zero. The illustrated concept of MMDT is shown in Supplementary data Figure 1 [12]. This study was approved by the Institutional Review Board committee of Theptarin Hospital (EC No.4-2019)

C. Statistical Analysis

Continuous variables were described as means with standard deviations or medians with interquartile ranges (IQR) and were analyzed using the Student *t* test. Categorical variables were examined by the chi-square test and presented as frequencies with percentages. Serum T3 and FT4 values were transformed into the quartile category and the highest quartile was compared with the remaining quartiles for late relapse. A logistic regression analysis was used to identify predictive variables for early and late relapse, including age at diagnosis <40 years, female sex, medium-to-huge goiter size, the presence of GO, thyroid function tests at diagnosis and MMI withdrawal, duration of MMI treatment <24 months, and duration of MMDT <6 months. Variables with established association with a *P* value < 0.1 from univariate analysis were included in the multivariate analysis. Relapse-free survival rates were calculated using the Kaplan-Meier method and compared to the log-rank test. *P* < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS Statistical Package, version 20 (IBM Corp., Armonk, NY, USA).

2. Results

A. Baseline Characteristics of Patients

A total of 1028 adult Thai patients with ATD-treated newly diagnosed hyperthyroid GD were registered at Theptarin Hospital from 1985 to 2019. Of those, 443 patients were able to discontinue MMI treatment and 320 patients who achieved disease remission without medication for at least 12 months were included in this study, as shown in Figure 1. Early relapse of hyperthyroidism within a year after MMI withdrawal was found in 123 (27.8%) of 443 patients and the median time to relapse was 6 months. The baseline

demographic data and laboratory results of studied patients who could discontinue MMI treatment were demonstrated in Table 1. In this cohort, the mean age at diagnosis was 37.0 ± 11.4 years and 81.7% were females. MMI was initially given at the median dose of 20 mg/day and titrated to maintain euthyroidism, with the median duration of MMI treatment being 23 months (IQR 17, 30 months). The mean duration of follow-up was 114.1 ± 78.6 months after MMI discontinuation. When compared with patients who experienced initial remission (320 patients), patients who had early relapse of hyperthyroidism within a year were younger, had higher frequency of family history of thyroid disorders, and higher serum T3 and FT4 values at the initial diagnosis, as shown in Supplementary data [12]. However, only patients 40 years of age or less at the time of diagnosis and the highest quartile of serum T3 level remained statistically significant after multivariate logistic regression analysis, as shown in Table 2.

B. Factors Associated With Late Relapse and Clinical Course

Of the 320 patients who achieved initial remission, 106 patients (33.1%) experienced late relapse during the mean follow-up duration of 116.7 ± 80.0 months, and the median time to relapse was 28 months (range, 13-252 months), as shown in Table 3. The median duration of MMDT was 10 months (IQR 5, 17 months). In this cohort, 40.3% of all patients had MMDT <6 months. When compared with patients who achieved sustained remission, patients who had late relapse of hyperthyroidism had higher serum T3 level at the initial diagnosis, and the proportion of patients who had MMDT <6 months was higher in the former group (50.9% vs 35.0%, *P* = 0.008). Multivariate analysis revealed that the highest quartile of serum T3 level and duration of MMDT <6 months were independently associated with late relapse, as demonstrated in Table 4. The baseline demographic data and laboratory results of early- and late-relapsing patients were compared in Table 5. Patients with early relapse were younger at the initial diagnosis and had more positive anti-TPO.

As shown in Figure 2, the remission rates in patients who continued MMI treatment at least 12 months decreased from 36.4% at the first year to 32.6% at the second year, 30.0% at the third year, and 26.0% at the fifth year. In MMI-treated patients who had a follow-up period of at least 10 years, the percentage of patients with remission was 20.7% (103/497). In the analyzed patients who were able to stop MMI, the Kaplan-Meier survival curves and Cox proportional hazard ratios of the overall relapse rate for the highest quartile of initial serum T3 values compared with the lowest quartile values, and duration of

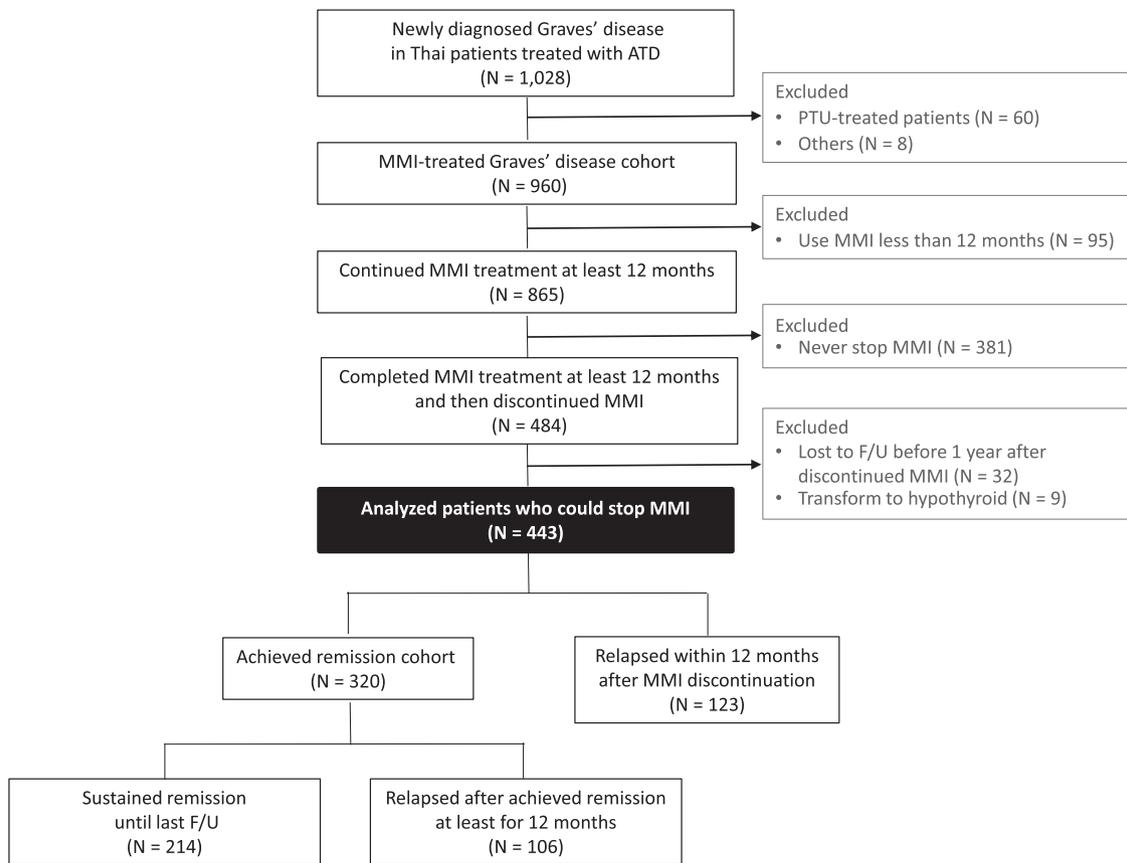


Figure 1. Flowchart illustrating the selected patients in the study.

MMDT <6 months compared with MMDT \geq 6 months, are shown in Fig. 3. Spontaneous hypothyroidism developed in 2.3% of patients who had sustained remission during the follow-up period, at a median time of 5.7 years. During the follow-up period, 17.9% of late-relapsing patients underwent RAI therapy, and none were treated with thyroidectomy. The remaining patients underwent a second course of ATD therapy. In patients who elected to continue a second course of MMI treatment, only 22.6% (24/106) were able to discontinue MMI again. There were no cases of documented MMI-induced agranulocytosis during the study period.

3. Discussion

The frequency of remission among patients treated with an MMI for 12 to 18 months varies from 15% to 50% [13, 14]. In this study, we found that the remission rate was only 20.7% at 10 years after drug discontinuation. Regarding predictors of late relapse following MMI withdrawal after at least 12 months, we found that the high initial serum T3 level and duration of MMDT <6 months were independently associated with late relapse while other known risk factors, including male sex, severe hyperthyroidism

pretreatment, and large goiter had no association. Based on our results, prolonged MMDT \geq 6 months or long-term MMI could be a viable option for patients who prefer to avoid ablative treatment. However, making a prediction of who would be likely to achieve remission was difficult. These findings also emphasized the role of lifelong follow-up in patients who achieve initial remission because relapse may develop many years later and a few patients may develop spontaneous hypothyroidism.

The decision to use ATD as primary treatment must be weighed against the risks and benefits of the more definitive therapy. In previous studies, the preference of Asian patients and healthcare providers repeatedly showed that ATD is the preferred option for primary treatment in hyperthyroid GD [2, 4]. Several previous studies have tried to evaluate risk factors for relapse and several risk stratifications have been devised as a tool for selection of ATD as the treatment of choice [6, 15-17]. However, few studies addressed the long-term outcomes after a successful course of ATD [9, 10]. The long-term outcomes from different genetic backgrounds and underrepresented ethnicities should be conducted. In the 1980s, the term *T3-predominate* GD had been introduced to describe a subset of GD patients who demonstrated increased T3/T4 ratio related to more active

Table 1. Baseline Characteristics of Newly Diagnosed Graves Disease in Thai Patients Treated With Methimazole at Least 12 Months and Were Able to Discontinue Treatment (N = 443)

	Total (N = 443)	Patients who achieved remission (N = 320)	Patients who experienced early relapse (N = 123)	P value
Female, n (%)	362 (81.7%)	262 (81.9%)	100 (81.3%)	0.891
Age at diagnosis	37.0 ± 11.4	38.4 ± 11.9	33.4 ± 9.1	0.000
Age <40 years	278 (62.8%)	184 (57.5%)	94 (76.4%)	
Age 40-59 years	146 (33.0%)	118 (36.9%)	28 (22.8%)	
Age ≥60 years	19 (4.3%)	18 (5.6%)	1 (0.8%)	
Family history of thyroid disorders (%)	202 (45.6%)	134 (41.9%)	68 (55.3%)	0.035
Active smoking (%)	4 (0.9%)	1 (0.3%)	3 (2.4%)	0.103
Estimated thyroid size				0.129
Small	253 (57.1%)	192 (60.0%)	61 (49.6%)	
Medium	165 (37.2%)	112 (35.0%)	53 (43.1%)	
Huge	25 (5.6%)	16 (5.0%)	9 (7.3%)	
Presence of Graves ophthalmopathy (%)	40 (9.0%)	25 (7.8%)	15 (12.2%)	0.149
Initial total T3 (ng/dL)	391.5 ± 169.2	371.4 ± 162.9	440.0 ± 175.2	0.003
Initial free T4 (ng/dL)	4.2 ± 1.9	4.0 ± 1.8	4.7 ± 2.0	0.035
Initial TSH (mIU/L)	0.013 ± 0.037	0.013 ± 0.042	0.012 ± 0.018	0.494
Positive anti-TPO* (%)	240/333 (72.1%)	162/231 (70.1%)	78/102 (76.5%)	0.289
Positive anti-Tg# (%)	211/315 (67.0%)	151/219 (68.9%)	60/96 (62.5%)	0.298
Thyroid function tests before MMI withdrawal				
Total T3 (ng/dL)	95.3 ± 21.3	94.4 ± 21.4	97.9 ± 21.0	0.255
Free T4 (ng/dL)	1.2 ± 0.2	1.23 ± 0.20	1.2 ± 0.2	0.318
TSH (mIU/L)	2.252 ± 1.840	2.291 ± 1.579	2.150 ± 2.376	0.589
Duration of MMI treatment (months)	23 (17, 30)	24 (17, 30)	22 (18, 28)	0.658
Duration of MMI minimum maintenance dose therapy (months)	10 (5, 17)	10 (5, 17)	9 (4, 17)	0.560

Abbreviations: MMI, methimazole; T3, triiodothyronine; T4, thyroxine; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH, thyrotropin (thyroid-stimulating hormone).

* Available data 333/443

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Table 2. Univariate and Multivariate Analysis of Clinical Factors and Laboratory Data for Predicting Early Relapse After a Successful Course of MMI

	Univariate analysis			Multivariate analysis		
	HR	CI	P value	HR	CI	P value
Female	0.96	0.56-1.64	0.889			
Age <40 years	2.24	1.47-3.43	0.000	2.18	1.13-4.21	0.020
Medium-to-huge thyroid size	1.53	1.00-2.32	0.048	0.82	0.41-1.63	0.571
Presence of Graves ophthalmopathy	1.64	0.83-3.23	0.153			
Active smoker	5.57	0.30-101.83	0.247	4.03	0.32-50.48	0.328
Thyroid function tests at diagnosis						
High T3 (4 th quartile)	2.19	1.27-3.76	0.005	2.37	0.91-6.17	0.078
High FT4 (4 th quartile)	1.85	1.09-3.14	0.023	1.31	0.53-3.20	0.559
Duration of MMI treatment <24 months	1.27	0.84-1.93	0.256			
Duration of MMI minimum maintenance dose therapy < 6 months	1.46	0.96-2.21	0.078	1.15	0.82-2.93	0.179
Thyroid function tests before MMI withdrawal						
High T3 (4 th quartile)	1.86	0.98-3.52	0.058	2.21	1.09-4.48	0.028
High FT4 (4 th quartile)	1.43	0.76-2.67	0.269			
Low TSH (4 th quartile)	1.74	1.04-2.90	0.034	1.34	0.67-2.68	0.416

Abbreviations: FT4, free thyroxine; MMI, methimazole; T3, triiodothyronine; TSH, thyrotropin (thyroid-stimulating hormone).

Table 3. Comparison Between MMI-Treated Patients Who Experienced Sustained Remission and Patients Who Experienced Late Relapse of Graves Disease After Completion of MMI Treatment (N = 320)

	Total (N = 320)	Patients who achieved sustained remission (N = 214)	Patients who experienced late relapse (N = 106)	P value
Female (%)	262 (81.9%)	169 (79.0%)	93 (87.7%)	0.064
Age at diagnosis	38.4 ± 11.9	39.1 ± 12.1	36.9 ± 11.3	0.594
Age <40 years	184 (57.5%)	119 (55.6%)	65 (61.3%)	
Age 40-59 years	118 (36.9%)	83 (38.8%)	35 (33.0%)	
Age ≥60 years	18 (5.6%)	12 (5.6%)	6 (5.7%)	
Family history of thyroid disorders (%)	134 (41.9%)	85 (39.7%)	49 (46.2%)	0.436
Active smoking (%)	1 (0.3%)	1 (0.5%)	0	0.686
Estimated thyroid size				0.302
Small	192 (60.0%)	132 (61.7%)	60 (56.6%)	
Medium	112 (35.0%)	74 (34.6%)	38 (35.8%)	
Huge	16 (5.0%)	8 (3.7%)	8 (7.5%)	
Presence of Graves ophthalmopathy (%)	25 (7.8%)	17 (7.9%)	8 (7.5%)	0.901
Thyroid function tests at diagnosis				
Total T3 (ng/dL)	371.4 ± 1.6	343.5 ± 146.1	428.2 ± 181.1	0.001
Free T4 (ng/dL)	4.0 ± 1.8	3.8 ± 1.8	4.2 ± 1.8	0.143
TSH (mIU/L)	0.013 ± 0.042	0.010 ± 0.015	0.021 ± 0.073	0.211
Positive anti-TPO*(%)	162 (70.1%)	113 (72.4%)	49 (65.3%)	0.504
Positive anti-Tg#(%)	151 (68.9%)	103 (69.6%)	48 (67.6%)	0.885
Thyroid function tests before MMI withdrawal				
Total T3 (ng/dL)	94.4 ± 21.4	94.9 ± 22.9	93.2 ± 18.0	0.593
Free T4 (ng/dL)	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.4	0.388
TSH (mIU/L)	2.291 ± 1.579	2.270 ± 1.640	2.350 ± 1.440	0.692
Duration of MMI treatment (months)	24 (17, 30)	24 (17, 32)	22.5 (17, 29)	0.275
Duration of MMI minimum maintenance dose therapy (months)	10 (5, 17)	11 (6, 17)	9 (3, 16)	0.079

Abbreviations: MMI, methimazole; T3, triiodothyronine; T4, thyroxine; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH, thyrotropin (thyroid-stimulating hormone).

* Available data 231/320

Available data 219/320

Table 4. Univariate and Multivariate Analysis of Clinical Factors and Laboratory Data for Predicting Late Relapse After a Successful Course of MMI

	Multivariate analysis			Multivariate analysis		
	HR	CI	P value	HR	CI	P value
Female	1.91	0.98-3.71	0.058	1.83	0.93-3.60	0.081
Age <40 years	1.27	0.79-2.04	0.331			
Medium-to-huge thyroid size	1.23	0.77-1.98	0.383			
Presence of moderate-to-severe GO	0.95	0.40-2.27	0.901			
Thyroid Function Tests at diagnosis						
High T3 (4 th quartile)	1.98	1.00-3.94	0.050	2.11	1.05-4.24	0.037
High FT4 (4 th quartile)	1.48	0.77-2.84	0.239			
Duration of MMI treatment <24 months	1.11	0.69-1.80	0.670			
Duration of MMI minimum maintenance dose therapy < months	1.93	1.20-3.09	0.007	1.96	1.21-3.16	0.006
Thyroid function tests before MMI withdrawal						
High T3 (4 th quartile)	0.64	0.30-1.39	0.260			
High FT4 (4 th quartile)	0.50	0.22-1.18	0.114			
Low TSH (4 th quartile)	0.82	0.43-1.54	0.534			

Abbreviations: FT4, free thyroxine; MMI, methimazole; T3, triiodothyronine; TSH, thyrotropin (thyroid-stimulating hormone).

Table 5. Comparison Between MMI-Treated Patients Who Experienced Early Relapse of Graves disease (N = 123) With Patients Who Experienced Late Relapse After Completion of MMI Treatment (N = 106)

	Patients who experienced early relapse (N = 123)	Patients who experienced late relapse (N = 106)	P value
Female (%)	100 (81.3%)	93 (87.7%)	0.178
Age at diagnosis	33.4 ± 9.1	36.9 ± 11.3	0.005
Age <40 years	94 (76.4%)	65 (61.3%)	
Age 40-59 years	28 (22.8%)	35 (33.0%)	
Age ≥60 years	1 (0.8%)	6 (5.7%)	
Family history of thyroid disorders (%)	68 (55.3%)	49 (46.2%)	0.173
Active smoking (%)	3 (2.4%)	0	0.083
Estimated thyroid size			0.419
Small	61 (49.6%)	60 (56.6%)	
Medium	53 (43.1%)	38 (35.8%)	
Huge	9 (7.3%)	8 (7.5%)	
Presence of Graves ophthalmopathy (%)	15 (12.2%)	8 (7.5%)	0.238
Initial total T3 (ng/dL)	440.0 ± 175.2	428.2 ± 181.1	0.704
Initial free T4 (ng/dL)	4.7 ± 2.0	4.2 ± 1.8	0.100
Initial TSH (mIU/L)	0.012 ± 0.018	0.021 ± 0.073	0.302
Positive anti-TPO* (%)	78/102 (76.5%)	49/75 (65.3%)	0.028
Positive anti-Tg# (%)	60/96 (62.5%)	48/71 (67.6%)	0.063
Thyroid function tests before MMI withdrawal			
Total T3 (ng/dL)	97.9 ± 21.0	93.2 ± 18.0	0.189
Free T4 (ng/dL)	1.2 ± 0.2	1.2 ± 0.4	0.454
TSH (mIU/L)	2.150 ± 2.376	2.350 ± 1.440	0.498
Duration of MMI treatment (months)	22 (18, 28)	22.5 (17, 29)	0.842
Duration of MMI minimum maintenance dose therapy (months)	9 (4, 17)	9 (3, 16)	0.525

Abbreviations: MMI, methimazole; T3, triiodothyronine; T4, thyroxine; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH, thyrotropin (thyroid-stimulating hormone).

* Available data 177/229

Available data 108/229

TRAb-mediated cAMP stimulation of type 1 5'-deiodinase and were associated with higher rate of relapse [18-20]. However, this concept has largely disappeared from the literature. Based on our present study, the initial serum T3 values could be a valuable simple marker to identify a subset of patients who are unlikely to achieve long-term remission after drug discontinuation. In GD patients, a higher fraction of T3 is secreted into plasma from its higher content inside follicular cells and deiodination of T4 to T3 is enhanced by deiodinase enzyme [21]. The initial serum T3 elevation which reflects higher in vivo TRAb activity could serve as a surrogate marker for serum TRAb level. As a result, the T3/FT4 ratio at both initial treatment and at the time of ATD withdrawal might indicate the disease activity of GD. In contrast with other proposed risk stratification tools, which included serum FT4 level as one of the predictive factors [6], our study in Thai patients found that total serum T3 rather than serum FT4 level was associated with early and late relapse.

Our results were also in accordance with a recent study from Korea showing that prolonged MMDT (≥6 months)

was associated with a lower relapse rate after ATD withdrawal [10]. However, unlike the Korean study, serum T3 and FT4 values at the time of ATD withdrawal were not predictors of late relapse. Serum TRAb level could not be included as a predictive risk factor in our study because not many of them were available. Based on a Japanese cohort regarding the pattern of serum TRAb [22], up to 50% of patients whose serum TRAb level converted to negative after treatment became positive again (fluctuating pattern) and this pattern correlated with lower remission rate when compared with persistent negative serum TRAb level (37.2% vs 88.9%). In contrast, up to 20% of their patients demonstrated smoldering pattern of serum TRAb level which is defined as conversion from positive TRAb to negative TRAb after long-term ATD for at least 5 to 10 years. Therefore, the likelihood of sustained remission remains difficult to predict precisely in clinical practice.

Seven decades after its introduction, ATD continue to be important in the management of hyperthyroid GD and ongoing strategies to minimize relapse rate has been proposed [12, 23]. Some previous studies advocated alternative ATD

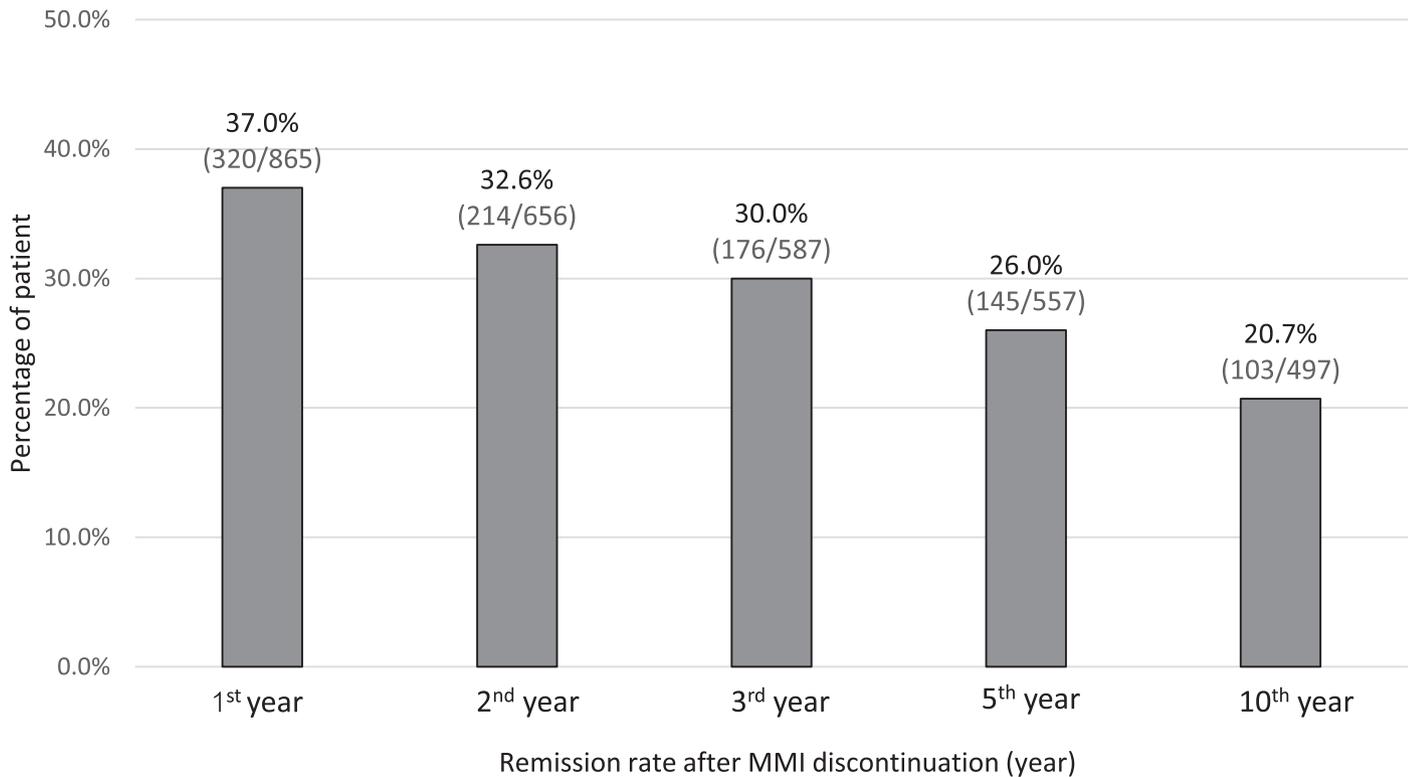


Figure 2. Remission rate after completed course of MMI treatment at least 12 months.

regimens such as block-replace regimen, prolonged low-dose ATD beyond 24 months, combined with various immunosuppressants, to improve therapeutic efficacy and reduce the relapse rate [24-27]. The high relapse rate seen with ATD treatment necessitates prolonged low-dose ATD for at least 4 years of therapy as an alternative option for patients who would like to avoid hypothyroidism from definitive treatments [28]. Unfortunately, most studies to date remain inconclusive with mixed results [29]. In our routine practice, block-replacement regimen was used in less than 2% of our ATD-treated patients. This regimen might be useful in exceptional cases, such as patients with unstable thyroid function tests, patients who are unable to come to frequent follow-up, avoidance of hypothyroidism in patients who required high dose of ATD, and so forth [3]. However, there are several drawbacks to this option, especially risks from over- or undertreatment and most prospective data have revealed no advantages in term of prolonged remission [12]. Remission of GD might be associated with the recovery of immunologic regulation with restoration of the euthyroidism [30]. Therefore, the concept of prolonged MMDT of ATD had been suggested in East Asian studies [9, 10]. Our present study also supported this concept. However, the heterogeneity of GD patients should be considered. Some patients with only a mild disease might

take an unnecessary extended course of ATD instead of a fixed period of 12 to 18 months.

Regarding the dosages of MMI, our data strongly suggest that low dosages of MMI (such as 10-20 mg/day) among Asians [31-33], rather than higher dosages (such as 30 mg/day or more) which are currently recommended in the initial treatment of hyperthyroidism in the American Thyroid Association guideline [5] are equally effective in restoration of euthyroidism and induction of initial remission. Asian GD patients seem to have greater sensitivity for the initial dosage of MMI than Caucasian patients. When comparing our present data with the previous study in Thai patients in 1970s [14], the initial remission was seen to have decreased from 50% to 36.4% and the overall rate of remission up to the time of last follow-up had decreased from 34% to 24.7%. The introduction of iodine supplementation in Thailand over the past 3 decades [34] could be one of the possible factors in explaining the less effectiveness of ATD as observed in several studies [35-37]. After salt iodization, absolute iodine uptake by the thyroid gland was higher in GD patients and might affect alteration in the response of GD to treatment with ATD [38]. However, a study from China showed no effect on the outcomes of treatments following universal salt iodization [39].

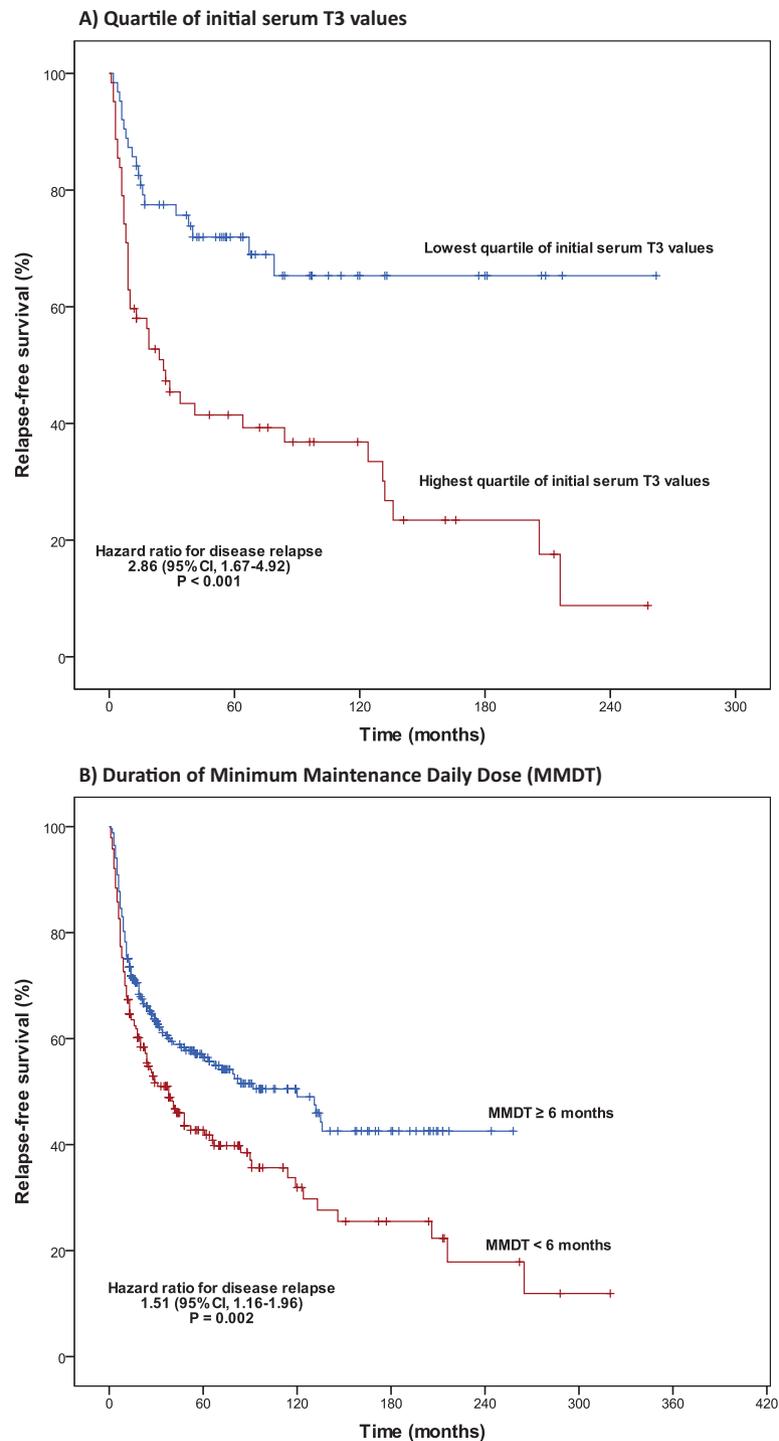


Figure 3. Kaplan-Meier (KM) curves. **A**, KM curves of relapse-free survival between patients with the highest initial serum T3 values compared with the lowest initial serum T3 values. **B**, KM curves of relapse-free survival between patients with duration of MMDT <6 months compared with MMDT ≥6 months.

There were several limitations which could have influenced our results. First, the retrospective nature of the study and a single data source from a tertiary endocrine center in Bangkok should be acknowledged. There were many relevant missing data in medical records, including biochemical data (particularly serum TRAb level before

MMI withdrawal), anti-TPO titers, accuracy of GO assessment, patients' preference, and documented various MMI side effects. However, our present report is one of the largest cohort studies in Southeast Asian patients with long-duration follow-up based on a real-world practice. Moreover, MMI is a safe and effective option [13]. Second,

selection bias from the strict inclusion criteria in the definition of remission needs to be interpreted with caution in comparison with other studies. Most relapse develops within 6 to 12 months after ATD discontinuation but previously described risk factors might include patients with persistent disease rather than recurrent of GD. Third, low serum TSH level with normal levels of thyroid hormones could be caused by the lag phase in TSH response to ATD treatment of up to 2 years. Therefore, our cohort of relapsed disease might include some patients with delayed recovery of pituitary axis after GD remission. Finally, other well-known factors, such as the effect of pregnancy or stressful events on relapse, could not be evaluated.

4. Conclusions

The present study indicated that the long-term remission rate of GD could be achieved in one-fifth of MMI-treated Thai patients, which is consistent with other reports. More than 40% of relapses occurred more than 1 year after MMI withdrawal. Predictive markers for late relapse included high initial serum T3 level and MMDT duration of <6 months. Patients with high risk for relapse may require different treatment approaches, and lifelong follow-up after ATD withdrawal is mandatory.

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Additional Information

Correspondence: Dr. Yotsapon Thewjitcharoen, Theptarin Hospital, 3850 Rama IV road, Klongtoey district, Bangkok, 10110, Thailand. E-mail: kamijoa@hotmail.com

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