The Longer the Antithyroid Drug Is Used, the Lower the Relapse Rate in Graves' Disease: a Retrospective Multicenter Cohort Study in Korea

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Abstract

Purpose: Current literature suggests 12 to 18 months of antithyroid drug (ATD) treatment for patients with Graves' disease, but the risk of relapse is high. Although some studies reported better outcomes of long-term ATD treatment, recent data that suggest the optimal treatment duration are limited.

Methods: We performed a multicenter retrospective cohort study of 908 patients newly diagnosed with Graves' disease between 2006 and 2013. The relapse rate according to ATD treatment duration was analyzed.

Results: After initial ATD treatment, 338 patients (37.2%) had relapsed. The relapse rate according to ATD treatment duration was 42.4% at one year, 38.5% at two years, 33.8% at three years, 31.7% at four years, 30.2% at five years, 27.8% at six years, and 19.1% at more than six years, respectively, demonstrating a significant decreasing trend ($P = 0.003$). In a multivariable Cox regression analysis, ATD treatment duration was an independent risk factor for relapse ($P = 0.043$).

Conclusions: The longer that ATD therapy is used, the lower the relapse rate is in patients with Graves' disease. Long-term ATD treatment may be considered in Graves' patients who do not show complications or an economic burden from hyperthyroidism.

Introduction

Graves' disease is an autoimmune disease caused by the continuous stimulation of thyroid glands by TSH receptor antibodies that does not exist in normal individuals. Continued stimulation of thyroid follicular cells leads to goiter and excessive thyroid hormone synthesis. Unfortunately, current treatments are aimed at inhibiting thyroid hormone synthesis or ablating the thyroid gland to induce permanent hypothyroidism rather than inhibiting TSH receptor antibodies. Current treatment modalities include antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, and thyroidectomy, all of which have their drawbacks. The main drawback of ATD treatment is a high relapse rate, ranging from 30–70%.

The remission rate following ATD treatment varies depending upon the ATD treatment duration. In the United States, remission rates of 20–30% have been reported after 12 to 18 months of ATD treatment [1], while, in Japan, rates of 60–80% were reported after five to six years of ATD treatment [2]. The current literature suggests a 12- to 18-month course of ATD treatment [3, 4], which is a relatively brief and fixed duration. Although two earlier meta-analyses have shown that ATD treatment over 18 months has no benefit [5, 6], a recent meta-analysis reports that long-term ATD treatment is effective and safe [7].

Graves' disease is associated with a 23% increase in all-cause mortality and a greater than two-fold risk of cardiovascular morbidity [8]. Adequate control of hyperthyroidism can improve survival compared with less effective control. The recommended duration of ATD treatment can adequately ameliorate thyroid hyperfunction in most patients, but the relapse rate is extremely high. Unfortunately, current recommendations are based on studies conducted in the 1990s [9, 10]. More recent studies on the

duration of ATD treatment have been very rare; therefore, there has been no recent suggestion for adequate ATD treatment duration that all physicians agree upon.

We performed a multicenter retrospective observational cohort study to gather data on real-world clinical experiences of long-term ATD treatment in patients with Graves' disease. We also evaluated the relapse rates according to the duration of ATD treatment and analyzed the clinical factors associated with relapse.

Materials And Methods

Study subjects

We retrospectively investigated the medical data of patients who were newly diagnosed with Graves' disease at three hospitals from three cities/provinces across Korea—Samsung Medical Center (SMC), Pusan National University Hospital (PNUH), and Chonnam National University Hwasun Hospital (CNUHH)—between 2006 and 2013. A total of 4,578 patients were screened in this study, including 2,902 at SMC, 1,224 at PNUH, and 452 at CNUHH. Patients who continued ATD treatment without stopping ($n = 427$), could not take ATDs because of a serious side effect ($n = 19$), underwent RAI therapy or thyroidectomy ($n = 442$), were pregnant ($n = 120$), showed poor compliance ($n = 79$), were lost to follow-up during treatment ($n = 2,374$), or were followed for less than 12 months after ATD discontinuation ($n = 209$) were excluded. Graves' disease was diagnosed based on suppressed serum TSH levels with elevated serum T3/free-T4 levels, positive serum TSH receptor Ab (TRAb), and the presence of signs/symptoms. Discontinuing ATD treatment was considered when serum T3, free T4, and TSH levels appeared to have recovered. In most cases, ATD treatment was discontinued after the TRAb titer was normalized but, in some cases, even if the TRAb titer remained somewhat high, ATD use was discontinued. Responsible endocrinologists made the decision to discontinue ATD treatment based on TRAb titer values and patients' agreement together with the attending physician's clinical judgment as well as the patient's euthyroid status. Relapse was defined as restarting any treatment modality for Graves' disease after discontinuing ATD therapy, whereas remission was defined as not restarting any treatment again **for at least one year after ATD discontinuation.**

Data collection and outcomes

Demographics assessed and extracted from medical records included age, sex, family history, smoking status, the presence of symptoms/signs, and adverse reactions to ATDs. Goiter size at diagnosis was categorized according to the World Health Organization classification system as none, mild (palpable), moderate (visible), or severe (huge/very large goiter visible from distance). Meanwhile, the severity of Graves' orbitopathy at diagnosis was categorized according to the European Group on Graves' Orbitopathy classification system as none, mild, moderate to severe, or sight-threatening. Thyroid function test results and TRAb titer values stored in the electronic medical records system were extracted automatically. **TSH and free T4 at the laboratory of SMC were measured by a immunoradiometric assay (Beckman Coulter Immunotech, Marseille, France) and a radioimmunoassay (Beckman Coulter**

Immunotech, Marseille, France), for which the reference range was 0.3 to 6.50 IU/L and 0.64 to 1.72 ng/dl, respectively. TSH and free T4 at the laboratory of PNUH were measured by a radioimmunoassay (BRAHMS GmbH, Hennigsdorf, Germany), for which the reference range was 0.3 to 5.0 IU/L and 0.75 to 2.0 ng/dl, respectively. TSH and free T4 at the laboratory of CNUHH were measured by an electrochemiluminescence immunoassay (Cobas: Roche Diagnostics, West Sussex, UK) for which the reference range was 0.4 to 4.5 IU/L and 0.7 to 2.0 ng/dl, respectively. The measurement of TRAb at the laboratory of all three hospitals was performed by a radioimmunoassay (BRAHMS GmbH, Hennigsdorf, Germany); the normal range was < 1.5 IU/L.

Statistical analysis

All statistical analyses were performed using the SPSS Statistics version 25 software program (IBM Corp., Armonk, NY, USA). A P-value of less than 0.05 was considered to be statistically significant. **Data were presented as means (standard deviations) for parametric continuous variables, as median (interquartile range) for nonparametric continuous variables, and as numbers (percentages) for categorical variables.** Student's t-tests were performed for continuous variables and chi-squared analysis was performed for categorical variables. The Cochran–Armitage test was used to assess the trend of relapse rate over the ATD treatment duration. Cox regression analysis was used to assess the clinical factors associated with relapse, with hazard ratios and 95% confidence intervals.

Results

Patient demographics

A total of 908 patients who were newly diagnosed with Graves' disease were analyzed in this study. The baseline characteristics for the included patients are presented in Table 1. The mean age at diagnosis was 46.3 years and 626 patients (68.9%) were female. The mean levels of serum TSH and free T4 at diagnosis were 0.03 IU/mL and 3.25 ng/dL, respectively. **Total T3 or free T3 was measured in a total of 836 patients (92.1%), almost all of which were total T3 (n=829). The mean for total T3 at diagnosis was 287.1 ng/dl. Except for only 4 patients, the total T3 or FreeT3 levels were higher than the normal range. The median titer for TRAb at diagnosis was 8.46 IU/L, while 812 patients (89.4%) had positive findings for antithyroid peroxidase antibodies. Methimazole or carbimazole was prescribed for most patients (89.4%). The mean treatment duration was 23.3 (17.4) months with a mean follow-up period of 79.9 (33.7) months.**

Table 1
Baseline characteristics of 908 patients with newly diagnosed Graves' disease

Age, years	46.3 (13.0)
Sex, female	626 (68.9%)
Family history	122 (13.4%)
Smoker (current and ex-smoker)	156 (17.2%)
Initial goiter	
No	344 (37.9%)
Mild	328 (36.1%)
Moderate to severe	236 (26.0%)
Initial Graves' orbitopathy	
No	818 (90.1%)
Mild	52 (5.7%)
Moderate to severe	38 (4.2%)
Initial laboratory findings	
TSH, IU/mL	0.03 (0.14)
Free T4, ng/dL	3.25 (1.54)
TRAb, IU/L	8.46 (14.27)
TPO Ab positivity (> 60 U/mL)	508 (55.9%)
ATD type, methimazole/carbimazole	812 (89.4%)
ATD treatment duration, months	23.3 (17.4)
Follow-up time, months	79.9 (33.7)
TRAb, TSH-receptor antibody; TPO Ab, thyroid peroxidase antibody; ATD, antithyroid drug.	
Data except TRAb are expressed as means (standard deviation) or numbers (percentages). TRAb is expressed as median (interquartile range)	

Relapse rate after initial ATD treatment

Among the 908 patients who were newly diagnosed with Graves' disease, 338 (37.2%) experienced relapse and 570 (62.8%) showed remission following initial ATD treatment. The mean time to relapse was 16.5 (18.7) months. **The relapse rate increased over time after the initial treatment (Figure 1).** Relapse occurred in 202 of the 338 patients (59.8%) within one year, 274 (81.1%) within two years, and 300

(88.8%) within three years, 315 (93.2%) within four years, 322 (95.3%) within five years, 329 (97.3%) within six years, 332 (98.2%) within seven years, and 335 (99.1%) within eight years after ATD withdrawal. Another two patients relapsed within nine years and one additional patient relapsed within 10 years after ATD withdrawal.

Details of the comparison of clinical characteristics between the relapsed group and remission group are described in Table 2. Patients in the relapsed group were more likely to be younger ($P < 0.001$), male ($P = 0.017$), have a family history ($P = 0.006$), and have ever smoked ($P = 0.002$) compared to those in the remission group. Goiter size and the presence and severity of Graves' orbitopathy at diagnosis did not differ between the two groups. While there was no significant difference in mean serum TSH level and TRAb titer at diagnosis ($P = 0.178$ and $P = 0.870$, respectively), the mean free-T4 level for the relapsed group was significantly higher than that in the remission group ($P = 0.022$).

Table 2
Comparison of Graves' patients with relapse to those with remission

	Relapse	Remission	P-value
Number of patients	338	570	
Age, year	44.3 (13.8)	47.5 (12.5)	< 0.001
Sex, female	217 (64.2%)	409 (71.8%)	0.017
Family history	59 (17.5%)	63 (11.1%)	0.006
Smoker (current and ex-smoker)	75 (22.2%)	81 (14.2%)	0.002
Goiter			0.552
No	120 (35.5%)	224 (39.3%)	
Mild	127 (37.6%)	201 (35.3%)	
Moderate to severe	91 (26.9%)	145 (25.4%)	
Graves' orbitopathy			0.358
No	299 (88.5%)	519 (91.1%)	
Mild	21 (6.2%)	31 (5.4%)	
Moderate to severe	18 (5.3%)	20 (3.5%)	
Laboratory findings			
TSH, IU/mL	0.04 (0.22)	0.02 (0.04)	0.178
Free T4, ng/dL	3.41 (1.66)	3.16 (1.46)	0.022
TRAb, IU/L	16.14 (27.19)	16.41 (21.84)	0.870
TPO Ab positivity (> 60 U/mL)	182 (53.8%)	326 (57.2%)	0.426
ATD type, methimazole/carbimazole	313 (92.6%)	499 (87.5%)	0.017
TRAb, TSH-receptor antibody; TPO Ab, thyroid peroxidase antibody; ATD, antithyroid drug.			
Data are expressed as means (standard deviations) or numbers (percentages).			

Relapse rate according to ATD treatment duration

The relapse rate according to the ATD treatment duration showed a significant decreasing trend over time (**P for trend = 0.003**) (**Figure 2**). Among 908 patients who were followed for more than one year after ATD withdrawal, the relapse rate according to the ATD treatment duration was 42.4% for the one-year treatment group, 38.5% for the two-year treatment group, 33.8% for the three-year treatment group, 31.7%

for the four-year treatment group, 30.2% for the five-year treatment group, 27.8% for the six-year treatment group, and 19.1% for the more-than-six-year treatment group, respectively. Then, when we analyzed the relapse rate according to the ATD treatment duration in 774 patients who were followed for more than two years after ATD withdrawal, similar results were obtained (P for trend = 0.008) (Supplementary Figure 1).

Factors associated with relapse

In a multivariable Cox regression analysis, ATD treatment duration was an independent risk factor for relapse ($P = 0.046$) (Table 3). The serum free-T4 level at diagnosis ($P = 0.043$), age at diagnosis ($P = 0.002$), and smoking status ($P = 0.012$) were also significantly correlated with the relapse of Graves' disease. Conversely, sex ($P = 0.099$), goiter size at diagnosis ($P = 0.626$), the presence and severity of orbitopathy at diagnosis ($P = 0.366$), and TRAb titer at diagnosis ($P = 0.491$) were not correlated with the relapse of Graves' disease.

Table 3
Risk factors associated with relapse

Characteristics	Multivariable Cox regression analysis			
	P-value	HR	95% CI	
Age at diagnosis, year	0.002	0.986	0.977	0.995
Gender, male	0.099	1.271	0.956	1.689
Goiter	0.626			
No vs. mild	0.544	1.086	0.831	1.420
No vs. moderate to severe	0.755	0.952	0.697	1.299
Graves' orbitopathy	0.366			
No vs. mild	0.451	1.191	0.756	1.878
No vs. moderate to severe	0.206	1.387	0.835	2.303
Smoking (current and ex-smoker)	0.012	1.518	1.096	2.101
ATD treatment duration,	0.046			
1 year vs. 2 year	0.055	0.767	0.585	1.005
1 year vs. 3 years	0.008	0.602	0.415	0.874
1 year vs. 4 years	0.020	0.575	0.361	0.915
1 year vs. 5 years	0.330	0.746	0.413	1.347
1 year vs. 6 years	0.128	0.490	0.196	1.227
1 year vs. 7 years	0.045	0.351	0.127	0.975
Free-T4 level	0.043			
≤ WNL vs. 1–1.5 WNL	0.725	0.930	0.621	1.393
≤ WNL vs. 1.5–2 WNL	0.719	1.079	0.713	1.633
≤ WNL vs. 2–3 WNL	0.277	1.269	0.825	1.951
≤ WNL vs. > 3 WNL	0.025	1.833	1.079	3.113
TRAb, tertile	0.491			
1st tertile	0.684	0.935	0.675	1.294
2nd tertile	0.381	1.160	0.832	1.616
3rd tertile	0.863	0.967	0.660	1.417
ATD, antithyroid drug; WNL, within the normal limit; TRAb, TSH-receptor antibody				

Discussion

Until now, the optimal duration of ATD therapy as an initial treatment modality for patients with Graves' disease was recommended to be 12 to 18 months, but the risk of relapse is as high as 50% to 70% [6,11]. Intriguingly, this study reveals that long-term ATD treatment over 18 months could reduce the risk of relapse by as low as 20%. The results show that, the longer the ATD treatment duration, the lower the relapse rate, and this finding was statistically significant. **This large cohort study also demonstrates the duration of ATD treatment as an independent risk factor for relapse in Graves' disease patients.**

The preferred duration of ATD treatment as well as the preferred initial treatment modality vary geographically [12, 13]. As a result, remission rates are considerably different between geographical regions. In the United States, it has been recommended to continue ATD treatment for approximately 12 to 18 months and then cease drug use if the serum TSH level is normal at that time, although a recent guideline also recommended considering TRAb levels at the end of ATD treatment [3]. A European guideline also recommended the same duration of ATD treatment [4], but some data in Europe have indicated a high remission rate of 50–60% may exist after five to six years of ATD treatment [14]. On the other hand, a Japanese guideline recommended to maintain ATD treatment for a certain period with minimum maintenance dose after restoring the euthyroid state, noting a remission rate as high as 81% after five to six years of ATD treatment [2, 15]. According to a 2013 Korean survey of clinical practice patterns, the normalization of TRAb was considered more important than the fixed duration of ATD treatment as a criterion for ATD discontinuation; thus, the average duration of ATD treatment was longer in Korea than in other countries [16, 17].

Two systematic review articles published in 2005 and 2010 concluded that there was no clear benefit that accrued to longer duration ATD treatment over 18 months [5, 6], but this finding was based on the data of only two studies performed in the late 1990s [9, 10]. Since few studies were conducted in the early 2000s, currently, most guidelines still recommended a 12- to 18-month course of ATD treatment [3, 4]. There have been several reports that long-term ATD treatment might be effective for adolescents or patients with Graves' orbitopathy, but this consideration has not been generally adopted [18, 19]. Recently, considerable new reports have been published, suggesting long-term ATD treatment induced a higher remission rate than a fixed treatment duration [14, 2, 7, 20, 21]. A recent randomized clinical trial reported a significantly lower relapse rate with a 60- to 120-month course of low-dose ATD treatment compared to a conventional 12- to 18-month course of ATD treatment (15% vs. 53%) [20]. The results of these recent studies are consistent with our findings. In particular, the relapse rate of this study, which was less than 20% in patients treated for six years or more, was similar to that from the randomized clinical trial study [20].

This study is distinctive in that it shows a significant relationship between relapse rate and duration of ATD treatment—that is, the longer the treatment duration, the lower the relapse rate. A recent meta-analysis revealed that long-term ATD treatment was effective and safe, with a remission rate of 16% per year of treatment [7]. This meta-analysis suggested the positive relationship between treatment duration and remission rate but it was just calculated based on only a small number of studies. Our study is

meaningful because it reports clinical experience that supports the results derived from recent meta-analyses.

Several factors associated with relapse, including male sex, young age, past or current smoker, large goiter size, high level of free T4, and high titer of TRAb, have been reported [22–25]. In this study, the duration of ATD treatment is suggested as an independent risk factor for relapse after adjusting for other risk factors for relapse. The possible mechanism is associated with establishing and maintaining the euthyroid state for a long period [26]. Although still controversial, remission during ATD treatment seems to be primarily related to the restoration and maintenance of the euthyroid state rather than the direct immunosuppressive effects of ATD therapy itself [26–29]. A number of reports have suggested that remission is not related to ATD type, ATD dose, or the additional use of levothyroxine [30, 31]. The fall in serum TRAb is similar in patients treated by ATD or by thyroid surgery [32, 33]. The hyperthyroid state worsens autoimmunity and leads to increases in TRAb titer [34, 35]. Once this vicious cycle is broken by either ATD or surgery, most patients gradually enter the remission state. Conversely, if ATD is stopped without sufficient time to improve autoimmunity, it can be easy for the patient to return to the hyperthyroid state. In most previous studies of patients treated with ATD for 12 to 18 months, approximately 75% of relapses occurred within the first three months after ATD withdrawal [22]. However, considerable instances of relapse occurred after one year in this study. This result suggested that a relatively prolonged course of ATD treatment could reduce the number of early relapses that happen within one year after ATD withdrawal.

A recent systemic review demonstrated that long-term ATD treatment has few adverse events and that any major adverse reactions will occur in the first few months of treatment [36]. This study also showed that long-term ATD treatment is safe. Among a total of 4,578 patients who were initially screened in this study, only 19 patients (0.4%) were unable to complete the ATD treatment due to serious side effects including agranulocytosis and hepatic damage. Among a total of 908 patients who completed the initial ATD treatment, only 26 patients (2.9%) experienced minor side effects, most of which were pruritus or rash, and all were tolerable without stopping ATD treatment. Serious adverse reactions were not observed with low-dose ATD treatment that continued after restoring hyperthyroidism at an initial dose. Graves' disease is associated with a significant adverse impact on the quality of life (QoL) [37]. Some reports have found that patients who take a thyroid hormone for their remaining lifetime after thyroid surgery continue to experience worse QoL than the general population [38–40]. Remaining in a state of euthyroidism for a longer ATD course may be a better choice for patients who do not experience adverse events of ATD treatment, or who may have a poorer QoL after thyroid surgery or RAI therapy.

Although this is a multicenter and large cohort study reflecting real-world experience, there are several limitations because of the retrospective nature of the study. **Because there was no consensus protocol for ATD discontinuation, TRAb titers were not routinely taken prior to ATD discontinuation.** In addition, this study was conducted in an iodine-replete area, which is a well-known risk factor for relapse. **Since the hospitals participating in this study were tertiary referral hospitals, some patients were referred to the primary care centers, which caused an increase in follow up loss.** Further studies will be necessary to

evaluate the effectiveness of long-term ATD treatment and to clarify how it can be applied in patients with Graves' disease, especially in countries where medical costs are high.

Over the last century, there have been several changes in Graves' disease treatment strategies, including a shift away from RAI therapy to ATD and a near-elimination of the use of propylthiouracil [41]. Because of the fears of worsening Graves' orbitopathy and increasing the radiation-induced malignancy rate, ATDs are increasingly used worldwide. However, current recommendations of ATD treatment lead to high relapse and need improvement. Since long-term ATD treatment has not proven to be effective until recently, a 12- to 18-month course of ATD treatment is consistently recommended based on expert opinion and cost-effectiveness. Especially in countries where medical costs are not high, it may be more cost-effective to improve the remission rate with long-term ATD treatment rather than risk relapse after short-term treatment. These findings included in our study should be considered seriously to revise future practice guidelines.

In conclusion, this large multicenter retrospective study demonstrated that, the longer ATD was used, the lower the relapse rate in patients with newly diagnosed Graves' disease. ATD treatment lasting longer than 18 months should be considered as an initial treatment modality. Long-term ATD treatment may be considered in Graves' patients who are at a high risk of relapse, who are concerned about the side effects of hyperthyroidism such as cardiac arrhythmia, or who do not have complications or an economic burden of ATD treatment.

Declarations

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Conflict of Interest:

The authors have no conflicts of interest to declare.

Ethics approval:

This study protocol was approved by the Institutional Review Boards of SMC (no. 2019-02-106), PNUH (no. 1907-009-080), and CNUHH (no. 2019-123).

Consent to participate:

Patient consent was waived in some instances by the Institutional Review Boards committee, because of the retrospective chart review study design and use of only deidentified clinicopathological information.

Availability of data and material:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions:

S.Y.P and B.H.K analyzed data and wrote the first draft of the manuscript, and contributed equally to this work. M.K, A.R.H, J.P, and H.P were involved in the data collection. M.S.C analyzed the data. T.H.K and S.W.K revised the manuscript for important intellectual content. H.C.K and J.H.C designed the study and analyzed data, and contributed equally to this work. All authors contributed to the interpretation of the results and approved the final version of the manuscript.

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Figures

Figure 1

Cumulative relapse rate after ATD withdrawal (per year).

Relapse rate according to ATD treatment duration (per year)

Figure 2

Relapse rate according to ATD treatment duration (per year) among 908 patients who were followed up with for more than one year.

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