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Long-Term Antithyroid Drugs in Graves' Disease: A Review of the Literature

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Abstract

Graves' disease (GD), the leading cause of persistent hyperthyroidism in adults, is an autoimmune disease that primarily affects the thyroid gland and also may affect multiple other organs, including the heart, eyes, and skin. Among the currently available treatment modalities for GD are antithyroid drugs (ATDs), radioiodine ablation (RIA), and thyroidectomy. However, these treatment modalities have certain limitations. For example, ATDs are associated with a high risk of hyperthyroidism relapse, and definitive therapy, either RIA or thyroidectomy, is associated with permanent hypothyroidism, requiring lifelong thyroid hormone replacement therapy. So far, no consensus has been reached regarding the optimal treatment modality for GD. Currently, ATDs are regarded as the most preferred first-line treatment worldwide. According to the traditional standard of care, patients with GD should be treated with ATDs for 12 to 18 months. However, the relapse rate following ATD therapy is usually high (approximately 50%), and many patients require additional treatment. Therefore, whether long-term ATD (LTATD) treatment (60 months or more), relative to standard treatment for 12 to 18 months, reduces the frequency of relapse in patients with GD remains unclear. In addition, the predictive factors of remission or relapse for GD remain a matter of debate. The current paper summarizes the evidence available on LTATD treatment, focusing both on its efficacy and safety in patients with GD and on its effect on the remission rate of hyperthyroidism. The paper also presents a review of the current knowledge available regarding the predictors of GD relapse following ATD treatment.

Key Words: Graves' disease; Antithyroid drugs; Radioiodine ablation; Thyroidectomy; Relapse; Predictors.

Introduction

Graves' disease (GD) is one of the most common organ-specific autoimmune diseases. This disease is characterized by hyperthyroidism, diffuse goiter, and other extrathyroidal complications, such as Graves' ophthalmopathy (GO) and acropathy, and results from a complex interplay of genetic and environmental factors. The incidence of GD is 20-40 cases per 100000 person-years in iodine-replete populations, with a global prevalence of 2% in women and 0.5% in men[1]. Among the currently available therapeutic options for GD are antithyroid drugs (ATDs), radioiodine ablation (RIA), and thyroidectomy. However, no

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consensus has yet been reached regarding the optimal treatment modality for GD[2-4]. Furthermore, at the time of writing, no specific cure has been discovered for GD. Each of the aforementioned treatment options has its own advantages and disadvantages[5-7]. For example, although ATDs are regarded as the primary treatment modality for GD worldwide[8,9], the rates of relapse observed after their discontinuation are high (reaching 50%), even after 12 to 18 months of conservative treatment[10]. Many patients require prolonged ATD treatment or other management strategies for GD[11]. Because of the variable nature and long-term course of GD and because the predictors of remission following ATD therapy are not yet fully understood due to the limited power of each predictor, the optimal treatment regimen for GD remains a subject of debate. Identifying the risk factors for disease relapse can help improve the remission rate of GD after ATD withdrawal and the efficacy of ATDs as a treatment for GD. This paper summarizes the current evidence on long-term ATD (LTATD) treatment, focusing on its efficacy and safety in patients with GD and on its effect on the remission rate of hyperthyroidism. The paper also reviews the current knowledge regarding the factors that affect GD relapse after ATD treatment.

Conservative Treatment with a High Relapse Rate

ATDs are commonly regarded as the primary treatment modality for achieving GD remission or for preparing patients for definitive treatment modalities such as RIA or thyroidectomy[12]. Compared with definitive treatment, ATDs offer several advantages. For example, they facilitate the rapid restoration of euthyroidism, reduce the risk of severe hypothyroidism, ameliorate immune disorders, and mitigate the risk of progression into severe GO while simultaneously avoiding radiation exposure and invasive procedures[13].

Since their introduction in the 1940s, methimazole (MMI) and propylthiouracil (PTU) have been used as thionamides for the treatment of patients with GD. Carbimazole is a thionamide that exerts a pharmacological effect when it is converted into MMI, and it has similar properties to and a similar efficacy as those of MMI[14]. Thionamides function by inhibiting thyroid peroxidase, thereby blocking the synthesis of thyroid hormones. PTU also inhibits the extrathyroidal deiodination of thyroxine (T4) into triiodothyronine (T3). Compared with PTU, MMI has a longer half-life, a longer duration of action, and fewer major adverse effects (AEs)[15]. Therefore, according to the American Thyroid Association guidelines, MMI is the recommended drug for patients with GD, with the exception of those who are pregnant women in their first trimester[15,16]. Although studies have indicated that MMI is more effective and restores euthyroidism more rapidly than PTU does, the relapse rate observed after withdrawal is similar between the 2 drugs in patients with GD[17]. Currently, the mechanisms by which ATDs induce remission are not fully understood. However, research indicates they may be related to the indirect effects of ATDs on immunological regulation through the restoration of euthyroidism; the direct effects of immunosuppression on intrathyroidal T cells may also play a role in the process[18].

GD treatment involves 2 ATD-based methods: a block-and-replace method and a titration-and-block method[19]. The block-and-replace method involves the initiation of a standard dose of ATDs and the addition of levothyroxine (LT4), and the titration-and-block method involves titrating the ATD dose from the initial level to the lowest level to maintain a euthyroid state[19]. In a meta-analysis of 12 trials, Abraham et al.[19] reported that the block-and-replace method and titration-and-block method had similar relapse rates (51% vs. 54%) but the block-and-replace method was associated with a larger number of AEs (16% vs. 9%).

Because low thyroid-stimulating hormone (TSH) levels are linked to decreased TSH receptor

antibody (TRAb) production, several studies have investigated whether the administration of LT4 after successful ATD treatment can reduce the risk of GD relapse[17]. These studies have indicated that LT4 does not prevent GD relapse after successful ATD treatment[17]. Other studies have even indicated that the administration of LT4 after successful ATD treatment is associated with an increased risk of GD relapse[20,21]. Therefore, administering LT4 after successful ATD treatment is not recommended. Similarly, although the addition of selenium to ATDs has been reported to increase the rate of remission, these promising results have not been confirmed in placebo-controlled randomized clinical trials (RCTs)[22].

The major drawback of ATD treatment is the limited durability of remission following ATD withdrawal. After a single course of ATD, the remission rate of GD may reach 50%, and individual studies have reported remission rates ranging from 30% to 70%[22]. In addition, the duration of ATD treatment can affect the risk of GD relapse[17]. A meta-analysis indicated that compared with a 6-month regimen, a 12-month titration regimen was associated with a lower relapse rate; however, extending the duration of therapy beyond 18 months did not provide additional benefits[19]. Both the American Thyroid Association and the European Thyroid Association recommend that primary drug therapy last for 12 to 18 months, with this recommendation being based on the findings of RCTs conducted in the 1990s that indicated that the remission rate of GD is not influenced by the duration of primary ATD therapy as long as the initial treatment duration exceeds 6 months[23]. Given the high rate of GD relapse observed after drug withdrawal, some studies have advocated for continuous treatment with low-dose ATDs for patients with GD[24,25]. These studies have proposed that long-term maintenance of low-dose ATDs has a persistent effect in preventing relapse[24,25]. Recently, 2 meta-analyses have demonstrated the effectiveness and safety of LTATD treatment for GD[26,27].

Given that GD is autoimmune-related, combining immunosuppressive drugs with standard ATDs has been associated with positive results in terms of clinical outcomes[28]. In a meta-analysis conducted in 2016, Struja et al.[29] reported a substantial reduction in the risk of relapse when immunosuppressive drugs were added to standard ATD treatment for patients with GD. They indicated that patients who received a combination of immunosuppressive drugs and ATDs had a significantly lower rate of relapse compared with those who received ATDs only (23.5% vs. 59.2%, risk ratio for relapse=0.55). Subgroup analysis revealed that this beneficial effect was independent of the type of immunosuppressive drug used and the type of study[29]. Therefore, the addition of immunosuppressive drugs may reduce the relapse rate of patients with GD after ATD withdrawal. Given the low-to-moderate quality and small number of trials and their high heterogeneity in terms of treatment modality, larger-scale RCTs are required to draw more definitive conclusions[29]. Novel TSH receptor antagonists are likely to usher in a new era of immune-based therapy for GD, and therefore, further clinical investigation is warranted[30].

LTATD Treatment with a High Remission Rate

Although many RCTs have focused on the timing of drug withdrawal in patients with GD, no gold standard has yet been reached regarding the optimal timing of drug withdrawal in GD. Typically, patients with GD undergo treatment with ATDs for 12 to 18 months and subsequently undergo an assessment for remission. However, most of the patients (approximately 70%) relapse and require prolonged treatment with ATDs[19]. LTATD treatment involves at least 24 months of therapy[31]. However, according to several RCTs, the duration of treatment does not influence the rate of relapse[32-35]. Similar results have been reported by Mohlin et al.[36] in an 11-year observational retrospective study of Swedish patients (*n*=219) with

GD. In their study, the authors reported that when the duration of ATD treatment was stratified at 6 to 12 months (10% of the participants), 12 to 18 months (44% of the participants), and >18 months (46% of the participants), no differences were observed in the risk of relapse (p=0.40). However, the presence of goiter (p=0.014) was associated with an increased risk of relapse, whereas previous smoking was associated with a reduced risk of relapse (p=0.003).[36]

In contrast to the results of the aforementioned studies, a growing body of evidence indicates that compared with short-duration treatment, LTATD treatment (up to 24 years) is associated with higher remission rates[24,37-46]. As summarized in Table 1, the majority of studies on LTATD treatment in patients with newly diagnosed GD or relapse are retrospective surveys[24,37-42], and only a few RCTs have been published[35,43-46]. Mazza et al.[24] retrospectively analyzed 249 patients with newly diagnosed GD (207 patients aged >35 years and 42 patients aged <35 years). After these patients were treated with a titration regimen of MMI, they achieved euthyroidism, which was maintained with a low of dose MMI (2.5–5.0 mg/d). Overall, the results indicated that long-term treatment with low doses of MMI was associated with a significantly lower rate of relapse compared with that for MMI therapy discontinuation in patients aged older than 35 years (25.2% vs. 43.5%) but not in those aged younger than 35 years (61.5% vs 51.7%). Laurberg et al.[38] retrospectively analyzed 108 patients with GD and severe GO who were treated with low-dose ATDs (101 patients with MMI and 7 patients with PTU) combined with LT4 replacement. They reported that 90% of the patients remained in a euthyroid state throughout the median duration of therapy (80 months). Park et al.[42] retrospectively analyzed 908 patients with newly diagnosed GD and reported that the rate of relapse decreased with extended ATD use (with relapse rates of 42.4%, 33.8%, 27.8%, and 19.1% at 1, 3, 6, >6 years, respectively), with their results revealing a significant decreasing trend (p=0.003).

Table 1. Literature review of LTATD treatment in adult patients with GD

Author, year	Country	Study design	Number of patients (F/M)	LTATD treatment duration	Comparison arm	Outcomes	AEs	Comments
Shizume et al.[37], 1970	Japan	Retrospective	86 with GD relapse after 6-12 mo of ATD Tx (NA)	2-12 y	<2 y of ATD Tx	Relapse rate after 5 y Tx: Within 1 y Tx: 76% 1-6 y Tx: 79%-91% 6-12 y Tx: 100%	NA	Low dose of LTATD Tx may be appropriate in some patients with GD.
Maugendre et al.[35], 1999	France	RCT	134 with newly diagnosed GD (115/19)	42 mo	18 mo ATD	2 y after ATD withdrawal, relapse rate did not significantly differ between 18-month group and 42-month group (36% vs 29%, p=0.38).	5 developed AEs (4 in 18-month group and 1 in 42-month group)	Tx duration greater than 18 mo did not improve remission rate determined 2 y after Tx withdrawal.
Azizi et al.[43], 2005	Iran	RCT	85 with GD relapse after 18 mo of ATD Tx (69/16)	122 mo	RIA	Higher goiter rate and higher TPOAb levels in MMI group than in RIA group	Except for minor allergic symptoms, no serious complications	Long-term continuous treatment of GD with MMI is safe.

Table 1. Literature review of LTATD treatment in adult patients with GD (Continued)

Author, year	Country	Study design	Number of patients (F/M)	LTATD treatment duration	Comparison arm	Outcomes	AEs	Comments
Mazza et al.[24], 2008	Italy	Retrospective	249 with newly diagnosed GD (NA)	Median of 48.3 mo	Median of 15.9 mo	Relapse rate: (a) Age < 35 y: 6.3% vs 12.4% (b) Age > 35 y: 22.6% vs 33.1%	1 with increased aminotransferase levels (×2) 8 with urticaria	Low doses of LTATD Tx appear to prevent GD relapse in patients aged older than 35 y.
Laurberg et al.[38], 2011	Denmark	Retrospective	108 with newly diagnosed GD and moderate-to-severe GO, including 8 undergoing RIA and 3 undergoing partial thyroidectomy (84/24)	Median of 80 mo of low-dose block-and-replace therapy	-	Relapse rate: 10%	PTU: 1 with vasculitis and minor skin ulcers MMI:5 with non-severe skin reactions, 1 with slightly elevated liver enzymes, and 1 with moderate arthralgia.	Prolonged partial block-and-replacement therapy with low-dose ATD + LT4 maintains the stability and euthyroid status of the majority of patients with severe GO and hyperthyroidism.
Konishi et al.[39], 2011	Japan	Retrospective	107 with newly diagnosed GD (92/15)	Mean of 48 mo of MMDT	-	Relapse rates of 13%, 26%, and 32% at 6 mo, 1 y, and 2 y, respectively	NA	The rate of remission increases as the duration of MMDT increases in patients who discontinue ATDs after a certain period. ATDs should not be discontinued in TRAb-positive patients who undergo MMDT for 6 months or less.
Elbers et al.[40], 2011	Netherlands	Retrospective	73 with both GD and GO (57/16)	Median of 41 mo of block-and-replace therapy	-	Relapse rate of 37% after a median of 57 mo of follow-up without GO relapse	NA	In patients with GO, long-term block-and-replace therapy for GD is associated with a reduced risk of relapse.
Villagelin et al.[41], 2015	Brazil	Retrospective	216 with GD relapse after 12-24 mo of ATDs (165/51)	Mean of 71.3 mo	RIA	Thyroid dysfunction predominant in RIA group ($p < 0.001$) Euthyroidism more common in MMI group ($p < 0.001$) GO deterioration higher in RIA group ($p < 0.0005$) Weight gain higher in RIA group ($p < 0.005$) No differences in SF-36	No notable AEs	Low doses of MMI are associated with more favorable outcomes for GO compared with RIA. Prolonged low-dose MMI treatment may be an alternative for patients with GD relapse, especially those with GO, or for patients who refuse definitive therapy

Table 1. Literature review of LTATD treatment in adult patients with GD (Continued)

Author, year	Country	Study design	Number of patients (F/M)	LTATD treatment duration	Comparison arm	Outcomes	AEs	Comments
Liu et al.[44], 2015	China	RCT	128 with GD relapse (107/21)	48 mo	Conventional	Relapse rate of 24%	NA	A second course of ATD treatment may result in long-term remission in patients with GD relapse. A high or high-normal TSH level at drug withdrawal may increase the likelihood of permanent remission.
Azizi et al.[45], 2019	Iran	RCT	240 with newly diagnosed GD (185/55)	Mean of 95 mo	Conventional	Relapse rate at 4 y: 15% in LTATD group and 53% in conventional group	2 with elevated liver enzymes 14 with minor cutaneous reactions No major AEs	Very-long-term, continuous, low-dose MMI courses are safe, well tolerated, and highly effective for GD, with considerably higher remission rates compared with those attained with conventional courses.
Park et al.[42], 2021	South Korea	Retrospective	908 with newly diagnosed GD (626/282)	2-6 y	Conventional	Relapse rates depending on ATD Tx duration: 42.4% at 1 y, 38.5% at 2 y, 33.8% at 3 y, 31.7% at 4 y, 30.2% at 5 y, 27.8% at 6 y, and 19.1% at >6 y	Minor AEs in 26 patients (2.9%) No serious adverse reactions with low-dose ATD therapy	The longer ATDs are used, the lower the relapse rate is in patients with newly diagnosed GD.
Lertwattanarak et al,[46], 2022	Thailand	RCT	173 with newly diagnosed GD (147/26)	36 mo	Maintenance of euthyroid status with low-dose ATDs for at least 6 mo after conventional therapy (discontinued ATD group)	Cumulative relapse rates in LTATD group significantly lower than those in discontinued ATD group at every follow-up time point (1.2% vs 11.2%, 6.8% vs 18.4%, 11.0% vs 27.2%, 11.0% vs 35.0%, and 11.0% vs 41.2% at 6, 12, 18, 24, and 36 mo, respectively; $p < 0.01$)	Neither minor nor major AEs with low-dose ATDs	Long-term treatment with low-dose ATDs beyond the recommended Tx duration of 18 mo is safe and effective in the maintenance of euthyroid status or prevention of hyperthyroidism relapse in patients with GD who have no or nonsevere GO, and its effectiveness persists as long as the ATD therapy is continued.

Note. Adapted from "Long-term thionamide antithyroid treatment of Graves' disease" by Azizi F, Abdi H, Amouzegar A, & Moeini ASH, 2023, Best Practice & Research Clinical Endocrinology & Metabolism, 37(2), 101631, p. 4-5.

Abbreviations: ATD, antithyroid drug; F, female; GD, Graves' disease; GO, Graves' ophthalmopathy; LT4, levothyroxine; LTATD, long-term antithyroid drug; M, male; mo, months; MMDT, minimum maintenance dose therapy; MMI, methimazole; NA, not available; PTU, propylthiouracil; RCT, randomized clinical trial; RIA, radioiodine ablation; SF-36, 36-item Short-Form Health Status Survey; Tx, treatment; TRAb, thyroid-stimulating hormone receptor antibody; TPOAb, antithyroperoxidase antibody; TSH, thyroid-stimulating hormone; y, years.

Azizi et al.[26] reported similar results in a meta-analysis of 6 studies on LTATD treatment. They revealed a positive association between treatment duration and remission rate, with a 16% greater chance of remission with every year of ATD treatment.

Liu et al.[44] analyzed 128 patients with GD who relapsed after 12 months of MMI therapy and were restarted on MMI at a drug dose of 2.5 mg/d. The patients were randomized into 2 groups: the first received long-term MMI therapy (with a median of 20 months), and the second received short-term MMI therapy (with a median of 15 months). After drug withdrawal, the patients were followed up for 48 months, and the results indicated a remission rate of 84.62% in the long-term MMI group and a rate of 66.67% in the short-term MMI group (p=0.024). Azizi et al.[45] conducted an RCT to compare the relapse rates of patients with GD who underwent a conventional course of MMI and long-term MMI therapy. After undergoing 18 to 24 months of MMI therapy, 258 patients were randomized into groups that either discontinued MMI (conventional group) or continued MMI for an additional 36 to 102 months (long-term group). After MMI was discontinued, the patients were followed up for 48 months. The results indicated a relapse rate of 15% in the long-term group and a rate of 53% in the conventional group (p<0.001). In a more recent RCT, Lertwattanarak et al.[46] analyzed 184 patients with GD who had been in a euthyroid state while taking MMI for at least 6 months before randomization. These 184 patients were randomly assigned to either a low-dose treatment group (92 patients) or a discontinuation group (92 patients). At the end of the 36-month study, the results indicated that the cumulative relapse rate of the low-dose treatment group was significantly lower than that of the discontinuation group at every follow-up time point (1.2% vs 11.2%, 6.8% vs 18.4%, 11.0% vs 27.2%, 11.0% vs 35.0%, and 11.0% vs 41.2% at 6, 12, 18, 24, and 36 months, respectively; p<0.01). No AEs related to low-dose MMI therapy were recorded throughout the study period. Nevertheless, 2 factors were independently associated with the risk of relapse: continuation of low-dose MMI therapy, which reduced the risk of relapse by 3.8 times (hazard ratio [HR]=0.26, p=0.007), and hyperthyroidism onset before the age of 40, which increased the risk of relapse by 2.9 times (HR=2.9, p=0.015). In summary, these findings regarding the remission of GD favor LTATD over conventional or short-term ATD treatment.

Comparison of LTATD with Definitive Treatment

Given the high rate of relapse following ATD withdrawal in GD, decisions regarding further treatment are necessary[19]. The choice of treatment strategy should account for the differences between LTATD and definitive treatment. LTATD is both safe and effective[26,27,38,43,45]. In LTATD, the lowest effective dose of MMI is prescribed to achieve euthyroidism, with regular assessments conducted every 6 to 12 months. The following section focuses on comparing LTATD with definitive treatment for GD and evaluating the available evidence across multiple aspects of effectiveness, including thyroid status; quality of life (QoL); and effect on GO, weight gain, and patient safety.

4.1 Thyroid Status

Hyperthyroidism has a widespread effect on various systems in the body, including the cardiovascular and gastrointestinal systems, as well as dermatological effects and effects on bone metabolism[47]. Cardiovascular complications are particularly common in hyperthyroidism and pose a major risk because of their high frequency of clinical presentation, and they can lead to increased mortality and morbidity[47]. In a Danish case–control study of approximately 235000 patients who were followed up for 7 years, Lillevang-Johansen et al.[48] reported that for every 6 months that a patient had a low TSH level, the HR for mortality increased by a factor of 1.11

(p<0.0001). In another Danish case–control study of approximately 215000 patients who were followed up for 7 years, Lillevang-Johansen et al.[49] reported that for every 6 months that a patient had a low TSH level, the odds ratio (OR) for the development of cardiovascular events increased by a factor of 1.10 (p<0.001). Therefore, hyperthyroidism should be promptly controlled and maintained to reduce the risk of cardiovascular complications and mortality in patients with GD.

4.1.1 Time to Euthyroidism

According to historical data, achieving euthyroidism with ATDs typically requires 4 to 12 weeks, depending on the severity of the disease and the dosing regimen[50]. Multiple studies have compared the time required to achieve euthyroidism in patients with GD who are treated with ATDs, RIA, or thyroidectomy. In a prospective study of 460 patients with hyperthyroidism, of whom 75% had GD, who were randomized into groups receiving either ATDs or RIA, Chen et al.[51] reported similar rates of normalization of thyroid hormones for the groups within 3 to 4.5 months. They indicated that ATDs were equally effective as RIA in rapidly reducing the levels of thyroid hormones. In a similar prospective study of 179 patients with GD randomized into groups receiving ATDs with LT4 (block-and-replace strategy), RIA, or thyroidectomy, Törring et al.[52] reported that all treatments were associated with a comparable decline in thyroid hormone levels, although the RIA group was slower in achieving euthyroidism. In a retrospective study of 121 patients who underwent RIA and 96 patients who underwent thyroidectomy, Davis et al.[53] compared RIA to thyroidectomy as a definitive therapy for hyperthyroidism. They reported that those who underwent thyroidectomy achieved euthyroidism faster than those who underwent RIA did (3 vs 9 months, p<0.001). In summary, these studies have indicated that ATDs and thyroidectomy are superior to RIA in terms of rapidly achieving euthyroidism. Rapid euthyroidism is crucial because sustained TSH suppression increases the risks of cardiovascular complications and mortality.

4.1.2 Risk of Hypothyroidism

Using RIA or thyroidectomy to achieve euthyroidism may result in persistent or recurrent hyperthyroidism or may lead to a delayed onset of hypothyroidism, which occurs in 2% to 3% of patients with GD every year[54]. Hypothyroidism is the ultimate goal of treatment with RIA and thyroidectomy[16]. In a study involving 104 relapsed patients with GD who were randomized to receive either long-term MMI or RIA, Azizi et al.[43] discovered that the RIA group had more abnormal TSH levels throughout the follow-up period than the MMI group did (12.8% vs 5.9% of measurements indicating hypothyroidism and 9.1% vs 7.6% of measurements indicating hyperthyroidism, respectively; p<0.01). In a retrospective analysis involving 238 relapsed patients with GD who discontinued ATD therapy for 12 to 24 months, Villagelin et al.[41] compared individuals who were prescribed long-term low-dose MMI (n=124) with those who were prescribed RIA followed by LT4 replacement (n=114). The results indicated that the long-term low-dose MMI group had a significantly higher likelihood of achieving euthyroidism during each year of the 5-year follow-up period (p<0.001), whereas hypothyroidism was more common in the RIA group at each follow-up point (p<0.001). Similar results were reported by Azizi et al.[55] in a study involving 239 patients with diffuse toxic goiter. In conclusion, current evidence indicates that achieving euthyroidism is more common with LTATD than with RIA or thyroidectomy. However, further randomized data are required to draw more definitive conclusions. Although RIA and thyroidectomy may be effective in controlling GD, the frequency of abnormal thyroid function with LT4 replacement is high, and the consequences of iatrogenic thyrotoxicosis and hypothyroidism should be carefully considered[31].

4.1.3 Risk of Hyperthyroidism Relapse

As previously mentioned, the rate of remission

varies with the duration of ATD treatment[24,37-46]. Few studies have compared LTATD with RIA or thyroidectomy in terms of the relapse risk of hyperthyroidism. In a retrospective study of 261 patients with GD, Alexander et al.[56] reported that approximately 10% to 20% of their patients developed persistent hyperthyroidism after a single dose of RIA, with this rate further decreasing when multiple doses were administered. They also identified several risk factors for persistent hyperthyroidism after RIA, including younger age (<20 years, $p<0.01$), larger thyroid glands ($p<0.01$), higher pretreatment thyroid ^{123}I uptake values ($p<0.01$), higher serum T4 concentrations ($p<0.01$), and ATD consumption before RIA ($p<0.01$). Similar results were reported by Leslie et al.[57] in a study of 88 patients with GD, in which 24% of the patients developed sustained hyperthyroidism after a single dose of RIA.

Thyroidectomy is a viable therapeutic option and can be considered the treatment of choice for many patients, such as those with aggressive hyperthyroidism or moderate-to-severe GO. After total or near-total thyroidectomy, the relapse risk of hyperthyroidism becomes less than 1%[58]. In summary, evidence indicates that the risk of relapse is highest after 12 to 18 months of ATDs, lower after LTATD and RIA, and the lowest after thyroidectomy[31]. Further studies are required to determine the optimal treatment modality for GD in terms of the risk of hyperthyroidism relapse.

4.2 Effect on GO

Unlike the gradual decrease in circulating TRAb titers that occurs during a prolonged course of ATD treatment[59], a sustained increase in TRAb titers, which may exacerbate GO by intensifying orbital autoimmune reactions, occurs with RIA treatment[41,60-63]. Tallstedt et al.[60] reported a similar frequency of GO development and worsening in a medical therapy group and a thyroidectomy group (15% vs 11%). They indicated that RIA was associated with a higher risk of GO than medical therapy and thyroidectomy were (33%, 10%, and 16%, respectively; $p=0.02$ for the comparison between the RIA subgroup and the other groups combined). Traisk et al.[61] reported that compared with medical treatment, RIA was associated with a higher risk of GO development or worsening (38.7% vs 21.3%; $p<0.001$). In a systematic review of 10 RCTs involving 1226 patients with GD, Acharya et al. [62] reported that compared with ATDs, RIA was associated with a higher definite risk of GO progression or development (relative risk [RR]=4.23, 95% confidence interval [CI]=2.04-8.77). However, unlike thyroidectomy, RIA was not associated with a statistically significant increase in the risk of GO progression or development (RR=1.59, 95% CI=0.89-2.81). Similar results were reported by Ma et al.[63] in another systematic review of 2 RCTs involving 425 patients with GD, in which RIA was more strongly associated with GO worsening or development than MMI was (38% vs 19%; RR=1.94). In summary, current evidence indicates that compared with medical treatment or thyroidectomy, RIA is more strongly associated with the development or progression of GO in patients with GD.

4.3 Effect on QoL

The Thyroid-Related Patient-Reported Outcome (ThyPRO) questionnaire is a tool used to measure the effects of benign thyroid diseases on health-related QoL[64]. In a large Swedish cohort study, Törring et al.[65] reported that compared with the general population, patients with GD exhibited lower thyroid-related QoL scores over a period of 6 to 10 years after receiving their initial diagnosis. In addition, patients with GD who were treated with RIA had lower thyroid-related QoL scores than did those who received conventional ATD therapy (12 to 18 months) or thyroidectomy (ThyPRO score for RIA vs ATDs or thyroidectomy: 27 vs 21 or 22). However, this study had limitations related to its lack of randomization and insufficient data on comorbidities. Nevertheless,

similar results were obtained in studies using other thyroid-specific QoL questionnaires and the 36-item Short-Form Health Status Survey (SF-36) questionnaire[66,67]. Although previous randomized studies did not reveal significant differences in long-term QoL among the 3 treatment modalities, these studies were small and did not employ thyroid-specific QoL instruments[68,69].

Several studies have investigated the effect of LTATD on QoL. Azizi et al.[43] reported that patients who were treated with ATDs for up to 10 years had higher SF-36 scores than those of patients who were treated with RIA. By contrast, Villagelin et al.[41] reported no differences in SF-36 scores between patients treated with LTATD and RIA, indicating that GO may have played a major role in the QoL of the patients in Azizi et al., leading many of them to opt for LTATD.

In summary, patients with GD often experience lower QoL compared with that of the general population. This effect on QoL may persist for a long period after treatment and is greatly influenced by the presence of GO. Compared with conventional treatment and LTATD, RIA is associated with lower QoL. However, these findings should be interpreted with caution because they may be influenced by factors such as patient age, disease duration, GO presence, and baseline comorbidities. Nevertheless, according to a study[65], even when these factors are adjusted for, ATD therapy still appears to offer a more favorable QoL outcome.

4.4 Effect on Weight Gain

Multiple studies have investigated posttreatment weight gain. Dale et al.[70] conducted a study involving 162 consecutive patients with hyperthyroidism who were followed up for at least 6 months. They discovered that those who were treated with ATDs (n=87) and RIA (n=62) gained a similar amount of weight (5.16 vs 4.75 kg, p=0.645), whereas those who underwent thyroidectomy (n=13) gained more weight (10.27 kg, p=0.007). They also indicated that the development of hypothyroidism (even transiently) was associated with weight gain (no hypothyroidism, n=102, 4.57 kg; transient hypothyroidism, n=29, 5.37 kg; and LT4 consumption, n=31, 8.06 kg; p=0.014). These effects remained even after the length of follow-up was adjusted. In a retrospective review of 157 patients with GD who underwent RIA, Chen et al.[71] reported an increase in body mass index from baseline to 1 year after treatment from 9.6% to 18.5% in patients with overweight and from 6.4% to 21% in patients with obesity. Similar results were reported in patients with hyperthyroidism, indicating that RIA is associated with more significant weight gain than LTATD is[41,72]. Although transient hypothyroidism may contribute to initial weight changes, long-term data indicate that postablative therapy with LT4 may not mitigate ongoing weight changes, despite being able to maintain biochemical euthyroid status[31]. Notably, relative undertreatment of ablative hypothyroidism may play a major role in weight gain[73]. In summary, adequate treatment of ablative hypothyroidism may be associated with greater weight gain (thyroidectomy > RIA) than that associated with ongoing therapy with ATDs. Clinicians and patients should consider these factors when making treatment decisions[31].

4.5 Effect on Patient Safety

One of the key concerns when selecting between LTATD and definitive therapy is AEs, particularly major events such as hepatotoxicity, agranulocytosis, vasculitis, and pancreatitis. Major AEs typically manifest within the first 3 to 6 months of treatment, and they tend to substantially decrease with prolonged therapy[26]. The incidence of major AEs is often linked to high doses of ATDs[27]. In a retrospective analysis, Cooper et al.[74] reported an 8.6-fold increased risk of agranulocytosis with MMI doses exceeding 40 mg/d (p<0.01), with no cases being reported of agranulocytosis in patients receiving MMI doses below 30 mg/d. Azizi and Malboosbaf[27] performed a literature review

of 12 studies involving 1660 patients on LTATD treatment for a mean duration of 5.8 years. They discovered that major AEs occurred in only 0.8% of the patients, whereas minor AEs occurred in 2% to 36% of the patients, with a higher incidence associated with higher doses in pediatric patients. In another literature review, Azizi and Malboosbaf[26] reviewed 6 studies involving over 1500 patients treated for a median of 6 years. They reported an AE rate of 19.1% (95% CI=9.6-30.9, I^2=83%), with major AEs accounting for only 1.5% of the total.

Several large cohort studies have indicated that patients treated with RIA for hyperthyroidism experience increased mortality from vascular causes[75,76]. However, these studies had major limitations, such as a lack of information on comorbidities, the severity of hyperthyroidism, the underlying cause of hyperthyroidism, and the efficacy of control measures[77]. Boelaert et al.[77] reported an elevated risk of vascular-related mortality in cases in which RIA did not lead to hypothyroidism and stable mortality rates in RIA-treated patients on LT4 therapy. These findings underscore that persistent hyperthyroidism rather than RIA plays a key role in GD-related mortality. Although the majority of studies have indicated no increase in the overall risk of cancer after RIA therapy[78], some studies have reported a trend toward an elevated risk of thyroid, stomach, and kidney cancer in RIA-treated patients with hyperthyroidism[79]. Therefore, further research is required to investigate the association between the risk of cancer and the therapeutic utility of RIA in patients with benign thyroid disease.

Although the overall rate of morbidity following thyroidectomy is low, patients with GD are at an increased risk of postoperative complications. In a retrospective cross-sectional analysis of 215068 thyroidectomies, Rubio et al.[80] analyzed a large nationwide inpatient sample database and reported that 5.2% (11205) of the thyroidectomies listed on the database were performed for GD. They also reported that compared with multinodular goiter and thyroid cancer, GD was associated with a significantly higher rate of postoperative hypocalcemia (12.4% vs 7.3% and 10.3%, p<0.01), rate of hematoma requiring revision surgery (0.7% vs 0.4% and 0.4%, p<0.01), and mean length of hospital stay (2.7 vs 2.4 and 2.2 days, p<0.01). In addition, compared with multinodular goiter, GD was independently associated with a higher risk of vocal cord paralysis (OR=1.36, 95% CI=1.08-1.69), tracheostomy (OR=1.35, 95% CI=1.1-1.67), postoperative hypocalcemia (OR=1.65, 95% CI=1.54-1.77), and hematoma requiring revision surgery (OR=2.79, 95% CI=2.16-3.62). In a comparative analysis of AEs following thyroidectomy, ATD treatment, and RIA in 4661 patients with GD, Brito et al.[81] reported that thyroidectomy was associated with the highest rate of AEs (24% vs 12% vs 6%), with hypoparathyroidism being the most common complication.

Predictors for GD Relapse

Reliable predictors of relapse in GD are crucial for identifying patients who require prolonged ATD treatment or definitive therapy. In addition to the aforementioned treatment strategies, several other factors have been reported to be associated with a high risk of GD relapse. These factors include goiter size, biochemical abnormality severity, immune system parameters, age, sex, smoking habits, GO presence, and genetic and environmental factors (Table 2) [17].

5.1 Goiter Size

Thyroid gland enlargement correlates with the severity of GD[82]. Liu et al.[83] reported that the high relapse rate of GD observed after ATD treatment was significantly associated with goiter size at diagnosis and at the time of drug withdrawal. In a 5-year follow-up study of patients with GD with varying goiter sizes at diagnosis, Laurberg[18] reported higher remission rates in patients with normally sized or mildly enlarged goiters before treatment compared with those in patients with large goiters. Several

Table 2. Predictive factors for GD relapse and evidence supporting their role

Predicting factor	Evidence	Reference(s)
Modifiable		
Treatment duration	• Higher relapse rate in patients with GD undergoing short-term (<12-18 mo) Tx compared with LTATD (≥24 mo) Tx	19,24,37-46
Add-on immunosuppressive drugs	• Strong reduction in the risk of relapse when immunosuppressive drugs are added to standard ATD Tx in patients with GD	29
Goiter size	• High relapse rates following ATD Tx significantly associated with goiter size at diagnosis and gland enlargement at drug withdrawal	83
	• Higher relapse rates in patients with GD and large goiters before ATD Tx than in patients with normally sized or mildly enlarged goiters	18
	• High relapse rates in patients with GD without significantly decreased goiter sizes after ATD Tx	84,85
Biochemical abnormality severity	• TSH suppression after ATD withdrawal as predictor of GD relapse	83,86
	• High risk of relapse in patients with GD with high free T3 levels and free T3/free T4 ratios at disease onset	83,88-91
	• High T3/T4 ratio (>20) after ATD Tx as predictor of high risk of relapse in patients with GD	88
Immune parameters	• TRAb positivity at GD diagnosis significantly associated with increased relapse rate	17
	• High risk of relapse in TRAb-positive patients with GD at ATD withdrawal	17
	• High frequency of relapse in patients with GD with positive TSAb at ATD withdrawal	93
	• Higher sensitivity and specificity of TSAb in predicting GD relapse compared with anti-TRAb at ATD withdrawal	93
GO	• GO as risk factor for GD relapse after ATD withdrawal	86,99,100
	• High rate of relapse in patients with severe GO after ATD withdrawal	99
Environmental factors	• Iodine supplementation presumably increases rate of GD relapse	101
	• Dietary shift from low to high iodine intake increases rate of GD relapse	103
	• Stress associated with GD relapse after ATD withdrawal	17
	• Stressful events positively correlated with GD relapse after ATD withdrawal	106,107
	• Higher risk of GD relapse in smokers than in nonsmokers after ATD withdrawal	17,92
	• Patients who quit smoking have considerably low risk of GD relapse	36
Nonmodifiable		
Age	• The younger the age at GD onset, the poorer the response to ATDs, the poorer the prognosis, and the higher the risk of relapse	17,90,92,
	• Higher rate of GD relapse in younger adults than in older adults	96,97
Sex	• Higher risk of GD relapse in men than in women after ATD withdrawal	92
Susceptible genes	• Certain variants of HLA DRB1, DQA1, and DQB1 presumably serve as predictors of GD relapse	112
	• A total of 2 CTLA4 polymorphisms (rs231775 and rs231779) related to GD relapse after ATD withdrawal in Asian individuals	17
	• CD40 polymorphisms (rs745307, rs11569309, and rs3765457), T393C SNPs of the Gαs gene, and E33SNP of thyroglobulin associated with GD relapse after ATD withdrawal in patients with GD	17

Abbreviations: ATD, antithyroid drug; CTLA4, cytotoxic T-lymphocyte-associated factor 4; GD, Graves' disease; GO, Graves' ophthalmopathy; HLA, human leukocyte antigen; LTATD, long-term antithyroid drug; mo, months; SNP, single-nucleotide polymorphism; Tx, treatment; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; TRAb, thyroid-stimulating hormone receptor antibody; TSAb, thyroid-stimulating antibody.

other studies have indicated higher remission rates in patients with GD who had significantly reduced goiter sizes following ATD treatment[84,85]. These findings suggest that goiter enlargement at the onset of the disease and at the time of drug withdrawal is associated with an increased risk of GD relapse.

5.2 Biochemical Abnormality Severity

When the levels of thyroid hormones increase, the levels of TSH decrease, following a negative feedback loop[18]. Even after the normalization of thyroid hormone levels following ATD treatment, the levels of TSH in some patients with GD remain low and do not return to their normal range[18,86]. Studies have indicated that TSH suppression following drug withdrawal is a predictor of GD relapse[83,86]. Similar results were reported in a systematic review[87]. These findings highlight the importance of prolonged ATD treatment, that is, treatment until normal levels of TSH are reached, in patients with GD who experience delayed TSH recovery.

In patients with GD, the risk of relapse following ATD treatment is associated with the severity of GD at diagnosis[13,17,83]. Multiple studies have indicated that the serum level of T3 and the ratio of free T3 to free T4 at diagnosis are independent predictors of the treatment outcomes of ATDs in patients with GD[83,88-91]. Patients with higher serum T3 levels and free T3/T4 ratios are at a greater risk of relapse and thus typically require higher initial doses and a longer treatment duration[83,90,91]. Many retrospective studies have also indicated that a high serum T3/T4 ratio (>20, unitless) following drug treatment is a predictor of an increased risk of GD relapse[88]. Therefore, in patients with a high T3/T4 ratio, the duration of treatment should be prolonged, even after a conventional course of ATD therapy[17].

5.3 Immune Parameters

No consensus has yet been reached regarding which immune parameter is the most effective in predicting GD relapse. As previously mentioned, TRAb plays a key role in the pathogenesis of GD by overactivating the TSH receptor, thereby stimulating the synthesis and secretion of thyroid hormones and the growth of thyroid cells[18]. Many studies have indicated that TRAb is a useful predictor for evaluating the outcomes of ATD therapy[17,90]. At the time of GD diagnosis, TRAb positivity is associated with a significantly high rate of relapse, whereas TRAb negativity does not guarantee that no relapse will occur but is associated with long-term remission[17]. Shifting from a positive to a negative TRAb status may indicate alleviation of an immune disorder following ATD treatment in patients with GD[17]. The treatment effectiveness of ATDs may also be predicted from the titers of TRAb at the time of ATD withdrawal. At the time of drug withdrawal, the risk of relapse increases in TRAb-positive patients with GD[17]. Some of the discrepancies observed between studies in terms of the usefulness of TRAb in predicting GD relapse may be attributable to differences in the duration of ATD treatment before drug withdrawal[92]. In addition, the discrepancies observed in the detection methods used in certain studies may partially explain the negative association between TRAb levels and the relapse rate of GD after ATD withdrawal[13].

TRAb has 2 distinct properties: stimulating the TSH receptor (TSAb) and blocking the TSH receptor (TBAb) [93]. Many studies have investigated the pathogenic role of TSAb in patients with GD[94]. Relapse is more common at ATD withdrawal in TSAb-positive patients with GD than in TSAb-negative patients with GD (67% vs 17%, p=0.007) [93]. At ATD withdrawal, TSAb has higher sensitivity and specificity in predicting GD relapse compared with TBAb (63% vs 28% and 83% vs 65%, respectively)[93]. Therefore, measuring the levels of TSAb at ATD withdrawal can be valuable to clinical decision-making for patients with GD[93]. Several studies have indicated that in patients with GD who receive ATDs, TSAb values are more effective than TRAb values in predicting relapse[17].

5.4 Age and Sex

GD is rare in children; its incidence gradually increases from early puberty and remains stable after the age of 30 years[95]. Studies have indicated that a younger age at GD diagnosis is associated with a poorer response to ATDs, a less favorable prognosis, and a higher risk of relapse[17,90]. Several long-term follow-up studies of children and adolescents with GD have indicated remission rates of less than 25% after more than 2 years of ATD treatment[90]. In adults, reports on the influence of age after medical treatment vary[17,92]. However, several studies have reported a higher relapse rate in young adults than in older adults[96,97]. For instance, Allahabadia et al.[96] reported that younger patients with GD (younger than 40 years) had a lower remission rate than that of older patients with GD (32.6% vs 47.8%; OR=0.53; 95% CI=0.32-0.87; $p < 0.01$).

GD is 4 to 5 times more common in women than in men, although men are at a higher risk of relapse after ATD treatment cessation[92]. The reason underlying this sex-related disparity remains unclear and may be related to sex hormone variations[17]. Estrogen indirectly regulates the immune system, and the increased estradiol levels in patients with GD are associated with TRAb positivity, which is considered to be a useful predictor of ATD treatment outcomes[17]. The high risk of relapse observed in male patients with GD may be associated with factors such as goiter enlargement and genetic background[17]. Goiter enlargement correlates with severe immune and biochemical disorders, and the presence of a family history of autoimmune thyroid disease is more common in male patients with GD[17]. Nevertheless, this topic continues to be debated, with studies reporting conflicting results[17].

5.5 Presence of GO

GO is the most frequent extrathyroidal manifestation of GD. The severity of GO strongly correlates with immune system dysfunction[98]. At the time of diagnosis, 25% to 30% of patients with GD develop GO[36,98]. Several studies have indicated that the presence of GO is a risk factor for the relapse of GD after ATD withdrawal[86,90,99,100]. In patients with severe GO, the relapse rate of hyperthyroidism following ATD withdrawal may reach 93%[99]. Despite being associated with a high relapse rate, ATDs remain a favored therapeutic option for patients with GO because they improve the outcomes of GO and therefore may lead to stable euthyroidism and decreased inflammatory and TRAb titers[17]. Multiple retrospective studies have suggested the use of extended LTATD therapy for patients with GO to achieve satisfactory results[38,40]. Notably, Shi et al.[13] reported the absence of a clear correlation between GO and an increased relapse rate of GD. They indicated that the symptoms of GO were not consistently in line with the symptoms of thyrotoxicosis and that variations in clinical practice may have contributed to these inconsistent results[13]. Further research is required to analyze the association between GO and GD relapse.

5.6 Environmental Factors

Environmental factors may play a role in influencing the relapse rate of GD after medical treatment. Iodine is a key substrate required for the synthesis of thyroid hormones. Previous research has indicated that iodine supplementation increases the risk of GD relapse[101]. Patients with GD who achieve a state of euthyroidism after ATD withdrawal may experience hyperthyroidism relapse if they are exposed to pharmacological doses of iodine[102]. Therefore, controlling dietary intake of iodine may be necessary. Several epidemiological studies have indicated that in areas with sufficient iodine intake, the relapse rate among patients with GD after medical treatment is not higher than that in areas with insufficient iodine intake[17]. Transitioning from low to high iodine intake in the diet may increase the risk of GD relapse and thereby lead to negative outcomes after ATD therapy[103]. These results indicate that a sudden increase in iodine intake

triggers GD relapse. However, a prospective study indicated that excessive iodine intake does not influence clinical outcomes after ATD withdrawal, and therefore, strict dietary control with iodine restriction may not be necessary in the management of GD[104]. Further large-scale interventional studies are required to better understand the association between iodine uptake and the risk of relapse in patients with GD after ATD withdrawal.

Because stress has a profound effect on the immune system, it may play a key role in precipitating GD in patients predisposed to autoimmune thyroid disorders[105]. Previous research has established a connection between negative life events preceding the onset of GD[105]. The majority of studies have indicated that stress is associated with GD relapse after ATD withdrawal[17]. For example, in a prospective study, Vita et al.[106] reported that patients who experienced a relapse encountered more stressful events compared with those who achieved remission. They also indicated that the overall number of stressful events correlated with the frequency of GD relapse. Similar results were reported in another prospective study[107] indicating that 4 personality traits, namely hypochondriasis, depression, paranoia, and mental fatigue, positively correlated with the rate of relapse. This prospective study also indicated that the total stress score of major life events positively correlated with the rate of GD relapse after ATD withdrawal. Therefore, reducing stress through positive psychological interventions is a crucial step in lowering the rate of GD relapse in patients with euthyroidism.

Smoking may alter the structure of the TSH receptor or increase the activity of the sympathetic nervous system, thereby promoting the development of thyrotoxicosis in predisposed individuals[108]. Smoking may also increase the levels of TRAb[17]. Several studies have indicated that compared with nonsmokers, smokers have a higher risk of relapse after ATD withdrawal[17,92]. For instance, Quadbeck et al.[109] reported that compared with nonsmokers, smokers exhibited significantly higher TRAb titers at 4 weeks after ATD withdrawal. Mohlin et al.[36] reported a notably low rate of relapse in patients who had quit smoking. These findings highlight the role of smoking as a risk factor for GD. Notably, some studies have reported no clear association between smoking and an increased rate of GD relapse[83,110,111]. Therefore, further large-scale studies are required to investigate the association between smoking and the rate of GD relapse.

5.7 Genetic Factors

Familial forms of GD have a major genetic component. Individuals with a genetic predisposition tend to produce TRAb when they are exposed to specific environmental factors. These factors include excessive iodine intake, smoking, stress, and postpartum conditions, which have a definitive effect on the development and relapse of GD[112].

GD's autoimmune-relatedness is linked to the human leukocyte antigen (HLA) complex, which plays a key role in immune response. Both protein tyrosine phosphatase nonreceptor type 22 C/T polymorphism and HLA subtypes (DQA1*05, DQB1*02, and DRB1*03) are predictors of GD relapse in White individuals[112]. In addition, both rs231775 and rs2317792, which represent cytotoxic T-lymphocyte-associated factor 4 polymorphisms, are associated with GD relapse after ATD withdrawal in Asian individuals but not in White individuals[17]. Multiple studies have investigated the association between polymorphisms and the risk of relapse in patients with GD after ATD withdrawal. These polymorphisms include CD40 polymorphisms (rs745307, rs11569309, and rs3765457), T393C single-nucleotide polymorphisms (SNPs) of the Gαs gene, and E33SNP of thyroglobulin[17]. With the continual advancements being made in the field of genetics, genotyping may become an even more reliable method for predicting GD relapse, and more susceptibility genes may be identified in the future.

Conclusions

Although since the 1940s, ATDs have been primarily used for the treatment of GD worldwide, the high rate of relapse associated with ATDs, even with the traditional standard of 12 to 18 months of treatment, underscores the importance of patient-centered therapy selection (Figure 1). When a treatment

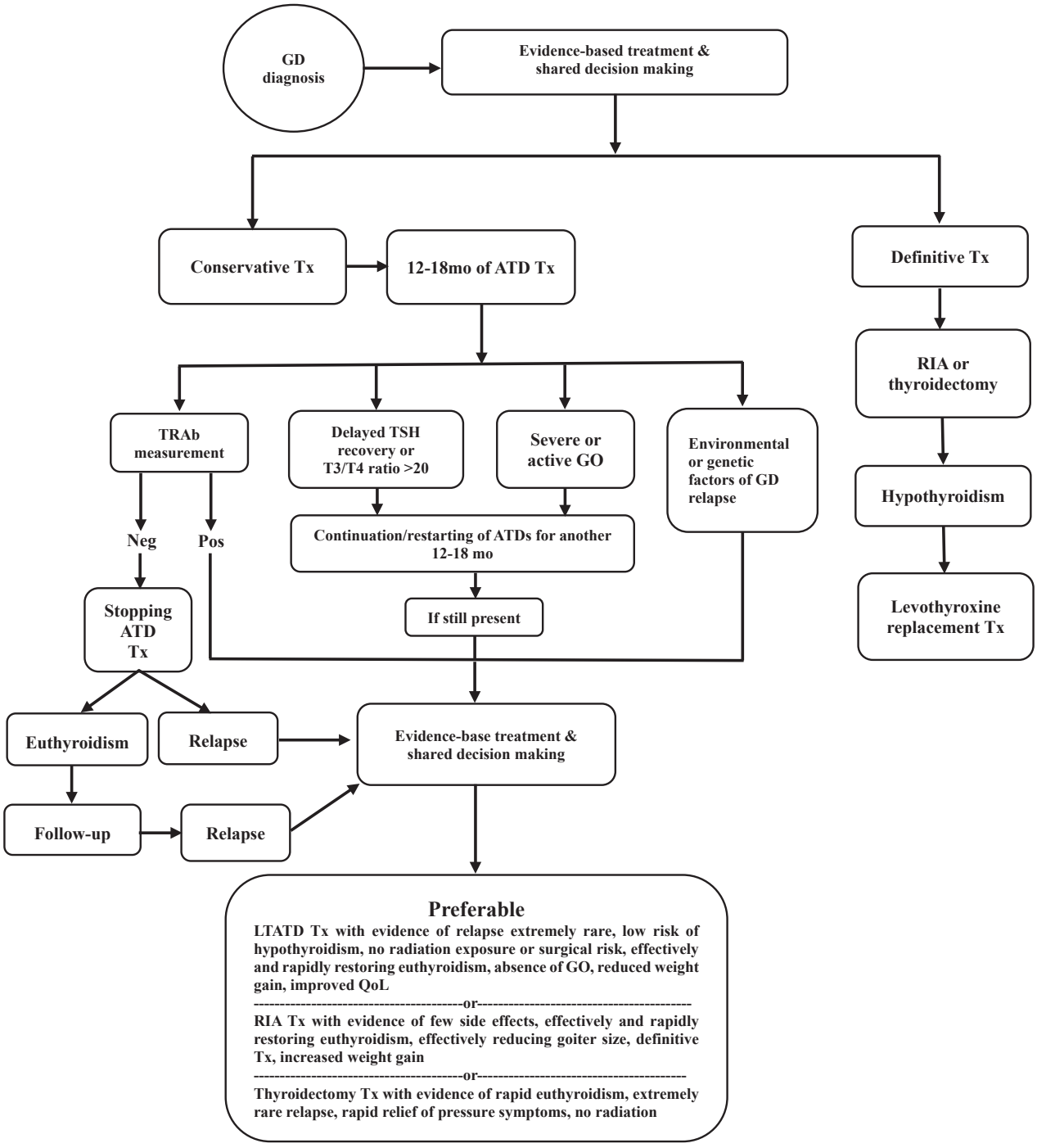

Figure 1. Algorithm of GD management.

Abbreviations: ATD, antithyroid drug; GO, Graves' ophthalmopathy; LTATD, long-term antithyroid drug; mo, months; Neg, negative; Pos, positive; QoL, quality of life; TSH, thyroid-stimulating hormone; TRAb, thyroid-stimulating hormone receptor antibody; RIA, radioiodine ablation; Tx, treatment; T3, triiodothyronine; T4, thyroxine.

modality is selected, specific patient factors should be considered, such as cardiovascular comorbidities, pregnancy, sex, age, the presence or absence of GO, and patient choice. According to the findings of this literature review, LTATD is associated with a higher rate of GD remission compared with that of short-term treatment. Therefore, LTATD should be considered a viable option for patients with GD whose hyperthyroidism is well controlled with a stable dose of ATDs and for patients who prefer this treatment over definitive therapy. LTATD offers advantages over definitive therapy, such as avoiding lifelong hypothyroidism, improving QoL, achieving a more rapid return to a state of euthyroidism, and exerting a favorable effect on other biological outcomes, and therefore, it has potential as treatment for most patients with GD. Identifying risk factors for predicting disease relapse can aid in enhancing the remission rate of GD and the efficacy of ATDs as a treatment modality for GD after ATD withdrawal. Notably, managing GD with ATDs, especially in terms of optimal treatment duration, remains a subject of debate because of the considerable variation in disease presentation among patients. In addition, the potential predictors of GD relapse after ATD therapy require further investigation because each known factor has limited predictive power.

Conflicts of interest

No conflicts of interest associated with this manuscript to declare.

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長期抗甲狀腺藥物在葛瑞夫茲氏病的治療：文獻回顧

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摘要

葛瑞夫茲氏病 (Graves' disease) 是導致成年人持續性甲狀腺機能亢進的主要原因，它是一種自體免疫性疾病，主要影響甲狀腺，也可能影響多個其它器官，包括心臟、眼睛和皮膚等等。目前主要治療葛瑞夫茲氏病的方式包括有抗甲狀腺藥物、放射碘消融術和甲狀腺切除術。然而，這些治療方式都各存有某些的局限性。例如，抗甲狀腺藥物的治療存有高度甲狀腺機能亢進復發的風險，而決定性的治療 (definitive therapy)，無論是放射碘消融術還是甲狀腺切除術，容易造成永久性甲狀腺功能低下，需要終身接受甲狀腺素補充的治療。到目前為止，關於葛瑞夫茲氏病的最佳治療方式尚未達成共識。目前，抗甲狀腺藥物被認為是全球最受歡迎的首選治療方式。根據傳統的治療標準，甲狀腺機能亢進患者應該接受抗甲狀腺藥物治療 12 至 18 個月。然而，抗甲狀腺藥物治療後的復發率通常很高（約略 50%），許多患者需要接受額外的治療。因此，長期服用抗甲狀腺藥物（60 個月或以上）治療相對於標準治療 12 至 18 個月是否能減少甲狀腺機能亢進患者的復發頻率仍不清楚。此外，對於葛瑞夫茲氏病的緩解或復發的預測因子仍存在有爭議。本文綜論有關長期服用抗甲狀腺藥物治療來治療葛瑞夫茲氏病，主要舉證該治療方式在患者之中是有其有效性和安全性，以及其對甲狀腺機能亢進緩解率的影響。此外，本文也針對目前抗甲狀腺藥物治療後關於葛瑞夫茲氏病復發預測因子做進一步文獻探討。