Review article

eISSN 2799-8010
J Yeungnam Med Sci 2023;40(1):12-22
https://doi.org/10.12701/jyms.2022.00444

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Long-term management of Graves disease: a narrative review

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Graves disease (GD) is the most common cause of hyperthyroidism, accounting for more than 90% of cases in Korea. Patients with GD are treated with any of the following: antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, or thyroidectomy. Most patients begin treatment with ATDs, and clinical guidelines suggest that the appropriate treatment period is 12 to 18 months. While RAI treatment and surgery manage thyrotoxicosis by destroying or removing thyroid tissue, ATDs control thyrotoxicosis by inhibiting thyroid hormone synthesis and preserving the thyroid gland. Although ATDs efficiently control thyrotoxicosis symptoms, they do not correct the main etiology of GD; therefore, frequent relapses can follow. Recently, a large amount of data has been collected on long-term ATDs for GD, and low-dose methimazole (MMZ) is expected to be a good option for remission. For the long-term management of recurrent GD, it is important to induce remission by evaluating the patient's drug response, stopping ATDs at an appropriate time, and actively switching to surgery or RAI therapy, if indicated. Continuing drug treatment for an extended time is now encouraged in patients with a high possibility of remission with low-dose MMZ. It is also important to pay attention to the quality of life of the patients. This review aimed to summarize the appropriate treatment methods and timing of treatment transition in patients who relapsed several times while receiving treatment for GD.

Keywords: Graves disease; Hyperthyroidism; Long-term care; Recurrence; Review

Introduction

Graves disease (GD) is an autoimmune disease resulting from both genetic and environmental factors. GD is the most common cause of hyperthyroidism, accounting for more than 90% of cases in Korea [1]. Patients with GD are treated with any of the following: antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, or thyroidectomy. In most cases, an ATD is the preferred initial treatment, as in Korea [1]. The remission rate of GD after ATD treatment is approximately 30% to 70% [2]. Thus, approximately half of the patients experience recurrence and eventually find another treatment method despite 12 to 18 months of treatment [3,4]. Several clinical factors, such as male sex, young age, high thyrotropin receptor antibody (TRAb) levels, ophthalmopathy, and smoking, have been proposed as indicators of poor prognosis after ATD therapy [5-8].

This review aimed to summarize the appropriate treatment methods and timing of treatment transition, focusing on cases of patients who relapsed several times while receiving treatment. Furthermore, recent studies on treatment outcomes, adverse events, and quality of life (QoL) will be reviewed and compared among the different treatment modalities.

Received: June 12, 2022 • **Revised:** August 1, 2022 • **Accepted:** August 10, 2022
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Etiology

GD is caused by autoantibodies that bind to thyroid-stimulating hormone (TSH) receptors and enhance thyroid hormone function [9,10]. After T cells, which are sensitized to a peptide (antigen) of the TSH receptor, are activated by cytokines that cause inflammation, autoantibodies against the TSH receptor are produced, which subsequently activate B cells [11]. GD is affected by genetics and environmental factors, which cause an immune response in sensitive individuals when stimulated above a threshold. Risk factors for developing GD include genetic susceptibility, female sex, pregnancy, stress, viral infections, iodine overdose, and immunomodulators [12]. TRAb titers, smoking, and RAI treatment are strongly associated with Graves ophthalmopathy (GO) [12].

Diagnosis

If hyperthyroidism is suspected, thyroid hormone levels are first checked. A diagnosis of hyperthyroidism can be established by measurement of TSH levels, which will be suppressed with either elevated or normal free thyroxine (T4) and/or triiodothyronine (T3) levels (overt or subclinical hyperthyroidism). If thyroid hormone levels are elevated and accompanied by characteristic ocular disease and goiter, GD can be diagnosed based on clinical findings alone. If the diagnosis is not apparent based on clinical presentation and initial biochemical evaluation, further diagnostic testing is indicated, as recommended in the 2016 American Thyroid Association (ATA) guidelines [3]. This can include measurement of TRAb, determination of RAI uptake, or measurement of thyroidal blood flow by ultrasonography. TRAb is a sensitive (97%) and specific (98%) tool for the accurate diagnosis of GD [13]. An ^{123}I or ^{99m}Tc pertechnetate scan should be obtained when the clinical presentation suggests thyroiditis or toxic adenoma (Fig. 1A-1C). Thyroid ultrasonography can be helpful for diagnosing increased blood flow (Fig. 1D-1F).

Management

All three classic GD treatments began in the 1940s. Surgery was

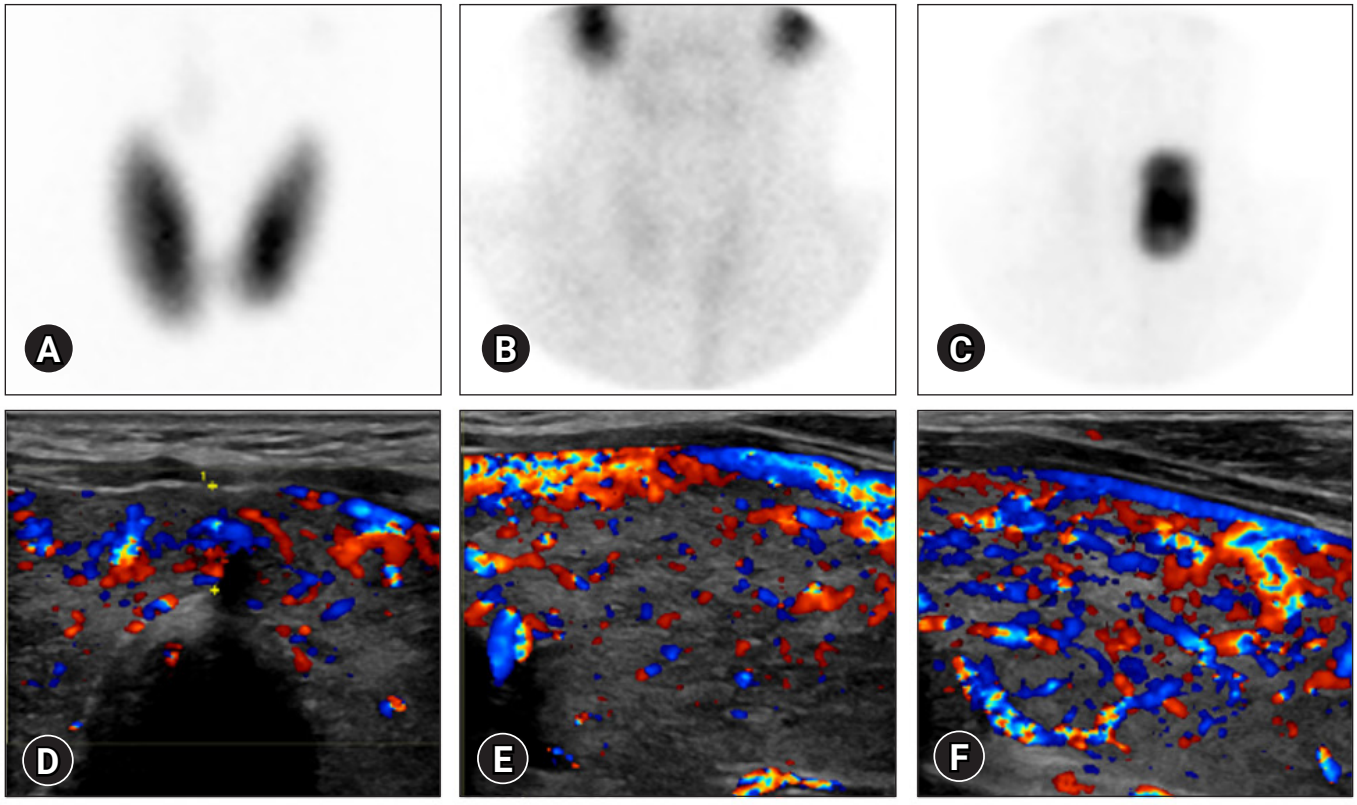

Fig. 1. (A–C) Thyroid scans can assist in the differentiation of patients with thyroid diseases. Typical appearances of ^{99m}Tc pertechnetate scans are shown in (A) Graves disease, (B) thyroiditis, and (C) toxic nodular goiter. (D–F) Doppler ultrasonography views of Graves disease show a classic finding of increased blood flow in a 28-year-old man. (D) Transverse view of isthmic area and longitudinal views of the (E) right lobe and (F) left lobe of the thyroid gland.

the only treatment before 1940, after which RAI and ATD treatments were established. Propylthiouracil (PTU) was used as the first ATD in the United States and was approved by the Food and Drug Administration. The ATDs methimazole (MMZ) and carbimazole (CBZ) were also developed. ATDs control hyperthyroidism by inhibiting thyroid hormone synthesis and preserving the thyroid gland. The medical treatment of GD using ATDs requires understanding the various responses of patients and maximizing remission, in addition to standard medical guidelines [3,4]. RAI therapy and surgery treat hyperthyroidism by destroying or removing the thyroid tissue and are considered as definitive therapies. Definitive treatment should be considered in patients with serious side effects from ATDs, poor adherence, obstructive symptoms from a large goiter, or suspicious thyroid nodules. Definitive treatment is also recommended when patients do not achieve remission with prolonged ATD therapy.

Once diagnosed, the physician and patient should discuss each treatment option, including logistics, benefits, expected speed of recovery, drawbacks, potential side effects, and costs [14]. The treatment of GD can be approached using the following steps. First, treatment with an ATD should be initiated upon diagnosis, especially when there is a high possibility of remission. Second, the following special conditions should be considered: (1) starting surgical treatment for thyroid cancer or severe goiter, (2) avoiding RAI therapy when moderate-to-severe ophthalmopathy occurs, and (3) discontinuing the ATD and considering definitive therapy if there are serious side effects, such as agranulocytosis, hepatotoxicity, or vasculitis. Finally, long-term additional low-dose MMZ could be a good option to prevent recurrence after completing 12 to 18 months of standard administration [4,15-17].

1. Antithyroid drugs

There are three types of ATDs. (1) MMZ has the longest half-life, is effective, and is used as the standard treatment. (2) CBZ is a precursor of MMZ developed in Europe, which allows quick switching to MMZ. An MMZ dose of 6 mg is approximately equivalent to 10 mg of CBZ, making it less effective than MMZ at the same dose. (3) PTU blocks the conversion of T4 to T3 in the peripheral tissues and is used in the acute treatment of thyrotoxicosis. As 80% to 90% of PTU binds to albumin in the blood and crosses the placenta less than the other drugs, it is used in the early stages of pregnancy. The starting dose of an ATD depends on the patient's weight, symptoms, signs, and biochemical severity. Thyroid status should be assessed every 4 weeks for the first 3 months, followed by assessments every 2 or 3 months thereafter. If a patient complains of mild side effects, such as rash, gastric intolerance, or arthralgia, in most cases, they will improve with symptomatic treatment without stopping the medication. However, drugs should be discontinued if they cause serious side effects, such as agranulocytosis, hepatotoxicity, antineutrophilic cytoplasmic antibody-positive vasculitis, or pancreatitis.

The European Thyroid Association (ETA) treatment guidelines recommend that patients diagnosed with GD start with MMZ or CBZ for 18 months in adults and 36 months in children [4,18]. The patient can be consulted from the beginning to decide on RAI therapy or surgery; however, except in special cases, an ATD is preferred. RAI treatment or surgery is recommended if a drug is not available or if patient's adherence is poor.

According to clinical guidelines, definitive treatment can be considered in cases where TRAb levels are positive despite a period of ATD therapy [4]. However, treatment with ATDs may be continued for an additional 12 months. Definitive therapy is again recommended if TRAb levels remain high after 12 months of additional ATD treatment. Even in patients who have relapsed after the cessation of MMZ, definitive treatment is generally recommended. However, long-term, low-dose MMZ can be an option for patients who do not want definitive treatment [4]. Sequential monitoring of serum TRAb levels can be used to determine the duration of ATD therapy [19].

2. Radioactive iodine therapy

RAI therapy has been used extensively in patients with GD over the past few decades, especially in the United States, because it relieves thyrotoxicosis symptoms within weeks. Sufficient RAI activity is recommended, with a mean dose of 10 to 15 mCi (370–555 MBq) to make the patient hypothyroid [3]. To improve its effectiveness, an ATD can be stopped 3 to 7 days before and after therapy. It may prevent a thyrotoxicosis aggravation from a long-term perspective, especially in elderly people and patients with underlying cardiovascular disease [20,21]. Although RAI is not associated with an increased risk of cancer, it can cause or worsen ophthalmopathy. After RAI therapy, thyroid function must be monitored for life; if present, hypothyroidism should be treated. The risks of hypothyroidism and recurrent hyperthyroidism correlate with the residual thyroid tissue volume. The indications and contraindications for RAI treatment are as follows [3]. Unsurprisingly, pregnancy and breastfeeding are contraindicated, and surgery should be performed if thyroid cancer is confirmed or suspected. In patients planning pregnancy with severe hyperthyroidism who are expected to receive high doses of ATDs, RAI treatment can be attempted 4 to 6 months prior to pregnancy. For safety reasons, conception should be postponed until at least 6 months after RAI in both males and females. Young age (< 5 years), because of a greater long-term theoretical risk of malignancy, and active GO, which

 https://doi.org/10.12701/jyms.2022.00444

can be exacerbated by RAI, are also contraindicated [18,22]. RAI therapy should be considered in the absence of skilled surgeons. If hyperthyroidism persists for 12 months after RAI, a second course can be considered.

3. Surgery

Thyroidectomy is generally used in patients with a large goiter or suspected thyroid cancer, women who wish to become pregnant, and patients who do not want to receive ATD or RAI therapy. Total thyroidectomy is preferred to subtotal thyroidectomy to reduce the risk of recurrent hyperthyroidism [23]. Thyroid hormone levels should be normal before thyroidectomy to reduce the risk of complications [24]. In addition to ATDs, oral iodine (5–10 drops of Lugol's solution or 1–4 drops of saturated potassium iodide solution thrice daily) can be helpful in controlling thyrotoxicosis during 1 to 2 weeks before surgery. The indications and contraindications for surgery are summarized in the 2016 ATA guidelines [3]. The indications are as follows: patients with pressure symptoms, a large goiter of ≥ 80 g (> 50 mL in the ETA guidelines), a nodule suspected to be thyroid cancer, a large nodule, a high TRAb titer, or moderate-to-severe ophthalmopathy with concerns for aggravation with RAI therapy. Surgery is not recommended when GD is accompanied by a disease with a high expected surgical risk. In these cases, there are concerns regarding deterioration and short life expectancy.

Remission rate with antithyroid drugs

Because recurrence is common within 1 year of discontinuing an ATD, remission is defined as normal thyroid function 1 year after discontinuation of treatment. Clinical guidelines for treating GD suggest that the appropriate period of ATD treatment is 12 to 18 months based on previous meta-analyses [25,26]. Patients with severe hyperthyroidism, large goiters, or persistently high titers of TRAb are most likely to relapse when treatment is stopped [5-7]. Male sex, young age, and current smoking are also related to GD relapse [5-7]. In 2016, Vos et al. [8] conducted a prospective study to design a predictive score, called the GREAT (Graves' Recurrent Events After Therapy) score, by combining the four independent risk factors of age, free T4 level, TRAb titer, and goiter size, particularly in recurrent GD.

The long-term remission rate after ATD treatment in patients with GD is approximately 50%, ranging from 30% to 70% [2]. In the United States, the remission rate was 20% to 30% after ATD treatment for 12 to 18 months, whereas in Europe, it was 50% to 60% after 5 to 6 years of treatment [27]. However, a systematic review and meta-analysis by Azizi et al. [15-17] showed that the duration of ATD treatment was positively associated with remission rate. When comparing the usual treatment group for 1 to 2 years and the long-term administration group for 6 to 10 years, the recurrence rate was 53% and 15%, respectively. A recent Korean study also demonstrated that the duration of ATD therapy was inversely associated with relapse rate in patients with GD and that ATD treatment duration was an independent risk factor for relapse [28].

Cases in which treatment modality was inevitably changed

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Nowon Eulji University Hospital (IRB No: NEUH 2022-10-017) in accordance with the Declaration of Helsinky. The requirement for informed consent was waived by the IRB due to the use of anonymized data and the retrospective nature of the study.

In this section, I will present typical cases in our clinic where remission is difficult even with a fairly long ATD period. All of these patients had to change their treatment strategies to prevent frequent relapses and improve their QoL. The four cases described below are patients who had been treated with an ATD for 5 to 10 years.

1. Surgery after antithyroid drug treatment

1) A 56-year-old female who was treated with an antithyroid drug for 8 years

The first case involved a 56-year-old female who underwent surgery after long-term ATD treatment. During the 8 years from 2010 to 2018, her thyrotoxicosis symptoms improved after taking an ATD, but recurred several times despite maintaining a constant dose of 2.5 mg MMZ every other day or 2.5 mg daily. Her body weight fluctuated between 54 and 64 kg. Her TRAb levels did not fall within normal range during the treatment period. She also had a 60 g goiter with multiple thyroid nodules but preferred to continue drug treatment because there were no compressive symptoms. Eight years after the initial diagnosis, a 6 mm highly suspicious nodule was newly detected and found to be atypia of undetermined significance by fine-needle aspiration cytology. Despite long-term ATD treatment, her TRAb titer did not decrease and suspicious nodules were found; therefore, she decided to undergo thyroidectomy. The final diagnosis was nodular hyperplasia after surgery. She had normal thyroid levels while receiving levothyroxine

and her TRAb titer changed to negative. Most importantly, before the surgery, she visited our hospital four to six times per year and had blood samples drawn every visit, but now, she visits only twice a year and has a blood test once a year. This means that her QoL has improved significantly even though she has gained 4 kg over 2.5 years after the surgery. This is a case of GD where a patient with a 60 g goiter and a suspicious thyroid nodule was finally treated with surgery.

2) Surgical management in patient with a large goiter and a suspicious thyroid nodule

According to clinical guidelines for GD [3,4], patients with persistently high TRAb levels after 12 to 18 months can continue MMZ therapy and repeat the TRAb measurement after an additional 12 months, or undergo definitive therapy such as RAI therapy or thyroidectomy. In this patient, TRAb levels remained high despite long-term ATD treatment. Recurrence occurred even while taking the drug; therefore, definitive therapy was recommended several times. A large goiter was accompanied by multiple thyroid nodules, and a small suspicious nodule was newly detected during follow-up. In a recent meta-analysis by Staniforth et al. [29], the incidence of thyroid carcinoma in GD was reported as roughly 2.5 times that in the overall global population, and a coincidence of GD and thyroid nodules was found in 23% of patients with GD. Furthermore, a previous review and meta-analysis found that the presence of thyroid nodules increased the risk of thyroid cancer [29,30]. Although further research is needed, clinicians should consider screening selected patients with GD for nodules.

2. Radioiodine therapy after antithyroid drug treatment

1) A 30-year-old male who was treated with an antithyroid drug for 10 years

In the second case, RAI treatment was administered after 10 years of MMZ therapy. A 30-year-old man was diagnosed with hyperthyroidism in his early twenties. He had an irregular lifestyle and used to stay up all night playing games. He stopped taking the drug at his own judgement and visited our hospital only when thyrotoxicosis symptoms, such as weight loss, loose stools, and hand tremors, worsened. His body weight fluctuated between 56 and 66 kg. Whenever he arrived, his thyroid hormone levels were high and his TRAb titer was positive, although his goiter was not as large as expected. The patient did not have GO; therefore, RAI treatment was recommended. Initially, the patient and his mother did not want RAI treatment because of a vague sense of anxiety regarding radiotherapy. After the patient graduated from college, he finally decided to receive RAI treatment. Six months after the RAI therapy, his TRAb level normalized, and his MMZ dose was decreased from 25 to 2.5 mg daily. The patient gained 3 kg over 1.5 years. He has also halved the number of hospital visits and blood tests.

2) Radioactive iodine treatment in patient with poor adherence to medication

This patient had poor adherence with the ATD, but only had a mild goiter that did not require surgery. His TRAb titer remained positive despite long-term ATD prescription, and there was recurrence even while taking the drug because of a stressful lifestyle. The success rate of initial RAI therapy was reported to be 73.7% with 370 MBq (10 mCi) and 80.8% with 555 MBq (15 mCi) in a previous randomized controlled study [31]. RAI therapy is less invasive and more cost-effective than surgery. Therefore, many patients who fail to treat GD with an ATD only choose RAI therapy as a second-line treatment. Park et al. [32] reported that the remission rate of RAI therapy as a second-line treatment was 62.8% in Korea.

3. Surgery after antithyroid drug treatment and radioiodine therapy

1) A 22-year-old female who failed to maintain euthyroidism with both antithyroid drug and radioactive iodine treatments

The third case involved a 22-year-old female who had recently undergone surgery after receiving both ATD and RAI therapy. When she was 16 years old, she received high-dose MMZ (30–60 mg) for 9 months, but her thyroid hormone levels did not improve and TRAb was positive. Owing to thyrotoxicosis symptoms such as difficulty breathing, she underwent RAI treatment at 8 mCi. Immediately after 2 months of treatment, her thyroid hormone levels normalized, and her symptoms improved. She did not visit the hospital thereafter. Five years later, she came to the outpatient clinic after her thyrotoxicosis symptoms worsened. At that time, she had lost 20 kg of body weight and had severe thyrotoxicosis symptoms, such as palpitations, heat intolerance, and insomnia. She also had a large goiter (approximately 50 mL), when estimated by ultrasonography. The patient was restarted on 30 mg MMZ. On the first day of treatment, she complained of fever and a sore throat. Her white blood cell count started to drop (absolute neutrophil count, 2,238/μL), and MMZ was discontinued to prevent further decreases in neutrophil numbers.

Considering the patient's QoL, surgery was recommended and she was hospitalized for preoperative thyroid hormone regulation. After 3 weeks of treatment with potassium iodide (starting dose of

 https://doi.org/10.12701/jyms.2022.00444

180 mg iodine/day, increasing to 480 mg iodine/day), prednisolone, and cholestyramine, her thyroid hormone levels were controlled and total thyroidectomy was performed. In this case, the treatment goal was not achieved with ATD or RAI therapy. The side effects of MMZ were also concerning, and surgery was recommended to reduce the risk of recurrence. After surgery, she had normal thyroid levels while receiving levothyroxine, and her TRAb level decreased to within the normal range. The patient also halved the number of hospital visits and blood tests. She visited our hospital more than 10 times a year before surgery; afterward, she visited the hospital three to four times a year.

2) Graves disease in the young

Graves hyperthyroidism is a relatively rare condition in children. While childhood GD accounts for 5% of all GD cases throughout life [33], its incidence before 15 years old is much lower [34]. Treatment options are similar to those in adults: ATD, RAI, or surgery. However, the risks and benefits of each modality are different from adults. The advantages and disadvantages of RAI and surgery should be carefully considered in young people planning definitive treatment and thyroid hormone replacement.

According to the 2022 ETA guideline for the management of pediatric GD [18], the treatment duration should be at least 3 years, and potentially 5 years or longer, if needed. These guidelines suggest that there are factors associated with an improved likelihood of remission following ATD treatment in children; older age, female sex, ethnicity (e.g., Caucasian), small goiter size, mild biochemical derangement at diagnosis, lower TRAb titer, history of other autoimmune conditions, and duration of ATD treatment [35-37]. The overall remission rate after 2 years of ATD treatment in pediatric patients with GD is 20% to 30% [38]. The remission rate increases with longer treatment durations. Remission rates of 24.1%, 31.0%, and 43.7% were reported after treatment durations of 1.5 to 2.5, 2.5 to 5, and 5 to 6 years, respectively [39]. There is no established role for immunomodulation with new agents, such as biologics, in young patients with GD. In recent studies, young people diagnosed and treated for GD may have a lower QoL than their healthy peers [40]. Long-term MMZ or CBZ should be the mainstay of treatment for children with GD.

4. Long-term low-dose antithyroid drug treatment

1) A 45-year-old male who maintained euthyroidism with long-term low-dose methimazole

The final case was a 45-year-old male who was diagnosed with GD 13 years prior to relapse. He was started on 30 mg MMZ, which was reduced to 5 mg every other day after 3 years of treatment. The patient did not visit the hospital as soon as his symptoms improved. One year after discontinuing treatment, he visited our clinic for thyrotoxicosis symptoms, such as weight loss of 5 kg and dyspnea on exertion. He was diagnosed with GD relapse based on high thyroid function test results and positive TRAb titers. MMZ 30 mg was restarted and the dose was rapidly reduced to 5 mg per day. But each time he overworked, his symptoms worsened despite the administration of 5 mg MMZ. After 18 months of retreatment, his thyroid hormone levels and TRAb titers decreased to normal levels and stabilized. During nine years of low-dose MMZ treatment, he visited the hospital thrice a year without recurrence, and blood tests were performed once a year.

2) Effects and safety of long-term low-dose antithyroid drug treatment

This case was considered to have a high possibility of remission with long-term low-dose ATD treatment; therefore, drug treatment was maintained rather than using definitive treatment. Indications for ATD are simply those cases with a high likelihood of remission and should be considered even if hyperthyroidism persists or relapses. The most important contraindications are the serious side effects of ATD treatment. According to a recent large amount of data on long-term ATD treatment for GD, it is expected that low-dose MMZ maintenance will have few side effects and can reduce the risk of recurrence. Azizi et al. [15-17] reported that 60 to 120 months of MMZ treatment may be safe and effective. Comparing the normal-treatment group (1–2 years) and the long-term administration group (6–10 years), the recurrence rates were 53% and 15%, respectively. There was no significant difference in the frequency of side effects between the two groups. The authors suggested that after administering low-dose MMZ for 12.8 years, when the discontinuation and maintenance groups were observed for 6 years, there was no recurrence in the maintenance group. Meanwhile, recurrence occurred in 19% (6 of 32) of the discontinuation group [41]. A recent Korean study also demonstrated that the duration of ATD therapy was inversely associated with the relapse rate in patients with GD and that ATD treatment duration was an independent risk factor for relapse [28]. The authors showed that the relapse rate according to ATD treatment duration was 42.4% at 1 year, 38.5% at 2 years, 33.8% at 3 years, 31.7% at 4 years, 30.2% at 5 years, 27.8% at 6 years, and 19.1% at > 6 years.

According to a recently published study by Bandai et al. [19], the time for the remission rate to reach a certain level in adults after long-term administration of ATDs was approximately 6.8 years (4.0–10.9 years). When patients were classified based on the pattern of changes in TRAb levels during long-term ATD administration, a positive antibody result after 5 years of treatment reflected a

19.8% remission rate. The remission rate was 88.9% when the antibody titers were reduced and maintained over 5 years of medication but was only 37.2% when the antibody titers fluctuated repeatedly. Therefore, if long-term administration of ATDs is planned, changes in TRAb levels for at least 5 years should be observed.

Comparison of each treatment modality

Regarding the choice of treatment, therapeutic guidelines recommend that physicians and patients decide after discussing the mechanism, strengths and weaknesses, duration, side effects, and costs of each choice. More than 90% of patients with GD depend on their doctors when choosing treatment modality, thus requiring extensive consultation.

1. Treatment outcome

Surgery is more advantageous because it significantly improves biochemical tests faster than other treatments, and there is little risk of hyperthyroidism recurrence. Meanwhile, the incidence of hypothyroidism is significantly high even when taking levothyroxine. The risk of hypothyroidism during ATD treatment was approximately 9%, which is lower than that with other treatments; however, the risk of hyperthyroidism recurrence was 30% to 70%, even if it was reduced to 15% during long-term treatment [16,42-44]. RAI treatment was at the midpoint between the two treatments; the occurrence of hypothyroidism was 7% to 28% and reported even after 14 years of levothyroxine treatment [42,43,45,46]. The recurrence of hyperthyroidism after RAI treatment was 10% to 20%, comparable to that of long-term ATD treatment [16,42-44].

2. Adverse events

Considering the trend of choosing long-term treatment with ATDs over definitive therapy, it is important to compare the major side effects of ATDs to those of other treatments. Adverse events (AEs) associated with ATDs can be subdivided into major events, such as agranulocytosis, hepatotoxicity, pancreatitis, or vasculitis, and minor events, such as rash, gastric intolerance, and arthralgia.

When comparing ATD treatment and RAI therapy, major AEs were more likely to occur during ATD treatment, particularly at high doses of MMZ. A retrospective analysis found an 8.6-fold increased risk of agranulocytosis with MMZ doses greater than 40 mg/day, but no cases were reported in patients receiving MMZ doses less than 30 mg/day [47]. Azizi and Malboosbaf [15] recently reported 19.1% AEs and 1.5% major AEs in a systematic review of six studies with over 1,500 patients treated with an ATD for a median of 6 years. They reported that major AEs occurred within the first 3 months of treatment and decreased significantly with long-term therapy. These data suggest that long-term ATD treatment is safer than expected if the lowest dose is administered and the patient is monitored well.

Two retrospective studies reported that using low doses of MMZ offers better outcomes and fewer side effects for GO than RAI treatment [48,49]. A systematic review and meta-analysis of two randomized controlled trials involving 425 adults with GD identified that thyroid eye disease developed or worsened in 38% of cases treated with RAI and 19% of those treated with MMZ, giving a relative risk of 1.94 [50].

3. Quality of life

The incidence and progression rate of ophthalmopathy are reported to be significantly higher with RAI treatment than with ATD treatment. ThyPRO is a questionnaire on thyroid-related QoL that is responsive to the treatment used for benign thyroid diseases [51]. According to a recent study by Törring et al., [52] regardless of treatment modality, patients with GD had worse thyroid-related QoL over 6 to 10 years after diagnosis than the general population. They also reported that patients receiving RAI therapy had worse thyroid-related QoL than those with 12 to 18 months of ATD therapy or thyroidectomy (ThyPRO score: RAI vs. ATD or thyroidectomy, 27 vs. 21 or 22). Although previous studies have found no significant differences in long-term QoL among the three treatment modalities, these studies were small and did not use thyroid-specific QoL [53,54]. Therefore, further research in Korea is required. In terms of posttreatment weight gain, RAI-treated patients were at a disadvantage compared to long-term ATD-treated patients [55]. This difference could be explained by the higher frequency of hypothyroidism in the RAI-treated group than in the ATD group despite taking levothyroxine after treatment.

Antithyroid drugs under development

Although classic treatments control the disease quite well, they are not based on the pathological mechanisms of GD, an immune disorder [9]. Several factors, such as genetics, interactions between endogenous and environmental factors, and immune system dysregulation, have been implicated in the pathogenesis of GD [10]. TRAb is a pathogenesis determinant of GD and its extrathyroidal manifestations.

With this in mind, new treatments are under development. There are ways to prevent the proliferation of T and B cells, which play a central role in the immune response, or to block the connection between T cells and B cells. A treatment may block inflamma-

 https://doi.org/10.12701/jyms.2022.00444

tory substances that activate T cells, such as tumor necrosis factor-α (TNF-α) or interleukin-6 (IL-6), or inhibit antibody production in B cells. A treatment can also block TSH receptor antibodies or insulin-like growth factor type 1 receptor (IGF-1R) antibodies, which are involved in newly discovered mechanisms of ophthalmopathy development [56,57]. ATX-GD-59, an immunotherapeutic agent specific for the TSH receptor peptide antigen, has been shown to have positive effects against GD in a phase 1 clinical study [58]. A chimeric antibody against CD20 (rituximab) showed some therapeutic effects in GO but not in GD [59,60]. Drugs for treating GO that target cytokines, such as anti-IL-6 (tocilizumab) or anti-TNF-α (etanercept), have been developed [61]. The immunosuppressant (Ki-70), which antagonizes the action of TRAb, has been shown to be effective in animal experiments [62]. Teprotumumab, a human monoclonal anti-IGF-1R blocking antibody, is very effective in patients with GO [63,64].

Conclusion

GD recurs and worsens repeatedly, affecting the patient's QoL. Current treatments for GD are inadequate for completely restoring thyroid function to a normal state. Based on the cases in the text, there is a significant gap between the current guidelines and the conditions encountered by patients in clinical practice.

In conclusion, to treat GD, it is important to induce remission by appropriately evaluating the patient's response to the drug, sometimes stopping ATD treatment at an appropriate time, and actively recommending a switch to a definitive therapy, such as RAI or surgery, in addition to standard clinical guidelines. It is sometimes encouraged to continue drug administration for an extended time, because more remission is expected with longer ATD use. If long-term administration of ATD is planned, the lowest possible dose should be used to avoid side effects. The ATD must be finely adjusted to improve the patient's QoL, reduce a recurrence, and prevent progression to hypothyroidism. As remission rates are predicted by the pattern of changes in TRAb titer, it is necessary to carefully monitor it and to consider RAI or surgery if required.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

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 https://doi.org/10.12701/jyms.2022.00444