Review Article

Updates in the Management of Graves Disease in Children

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Graves disease (GD) is the primary cause of hyperthyroidism in children. The standard management options—namely, antithyroid drugs (ATD), radioactive iodine, and surgery—have not changed for many years. Although ATD therapy is often the first-line treatment for pediatric patients, the low likelihood of spontaneous remission means that most children will require a more permanent solution. Recent clinical trials and systematic reviews have shed light on the long-term outcomes of ATD therapy, radioactive iodine, and surgical interventions in managing pediatric GD. Additionally, novel therapies aimed at B-cells or the thyroid-stimulating hormone receptor, both implicated in the pathogenesis of GD, are under investigation. However, their definitive role in treating childhood GD has yet to be established. This review will cover the latest developments in the treatment of childhood GD, including information on emerging targeted therapies.

Introduction

Graves disease (GD) is the most common cause of hyperthyroidism in children and adolescents [1]. It is characterized by autoimmune mechanisms that involve thyroid receptor autoantibodies, which stimulate the thyroid-stimulating hormone receptor (TSHR). GD is more prevalent in children who have other autoimmune disorders, such as type 1 diabetes, rheumatoid arthritis, or celiac disease [2,3]. Although the prevalence of GD in children is much lower than in adults, studies from Western countries have indicated an increasing incidence of pediatric GD [2,4,5]. Environmental factors, including exposure to endocrine-disrupting chemicals and variations in iodine status, are thought to contribute to this trend [6,7].

The primary goal of treatment for pediatric GD is to restore normal thyroid function and maintain euthyroidism, while preventing disease recurrence. The approach to managing GD in children mirrors that of adults, including antithyroid drugs (ATD), radioactive iodine (RAI) therapy, and surgical intervention [8,9]. Typically, ATD is the initial treatment modality for children diagnosed with GD. However, the likelihood of spontaneous remission following ATD therapy is relatively low. Consequently, most pediatric patients with GD eventually require a definitive treatment, such as RAI or thyroidectomy [2,8–10].

This review focuses on the management of GD in children, including ATD, RAI, and surgery, and provides updated information on the outcomes associated with these treatment modalities. Furthermore, we summarize novel targeted therapies currently under investigation for GD.

Main Text

1. Antithyroid drug treatment

1) Initiation and monitoring of antithyroid drug treatment

Methimazole (MMZ) or carbimazole (CBZ) should be used for treating GD in children. Propylth-iouracil (PTU) should be avoided due to its high risk of hepatotoxicity in pediatric patients. CBZ is a prodrug of MMZ and is rapidly converted to MMZ in the bloodstream. The initial dosing ranges from 0.15 to 0.5 mg/kg/day for MMZ and from 0.25 to 0.75 mg/kg/day for CBZ. These doses can be adjusted based on the clinical and biochemical severity of the disease [8,9]. While some clinicians prefer to divide the daily dose, MMZ can be administered once daily due to its long half-life of 3 to 5 hours [11]. Both the American Thyroid Association (ATA) and the European Thyroid Association (ETA) recommend obtaining a baseline white blood cell count with differential, as well as liver function tests, which should include measurements of transaminases, bilirubin, and alkaline phosphatase levels before starting ATD therapy [8,9]. Following the initiation of ATD treatment, thyroid function tests should be monitored at intervals of 2 to 6 weeks. It may take several months for thyroid hormone levels to normalize, and thyroid-stimulating hormone may remain suppressed for an extended period, regardless of the initial MMZ dose [12,13].

Approximately 20% of children may experience minor adverse effects from MMZ, including allergic reactions such as skin rash, pruritus, or dyspepsia, as well as myalgia and arthralgia [14]. Major side effects, which are rare, include agranulocytosis, Stevens-Johnson syndrome, vasculitis, and hepatic dysfunction [2,8,15]. Agranulocytosis is a particularly severe adverse event that requires patients on MMZ to stop the medication immediately and seek medical attention for a complete blood cell count if they present with symptoms such as fever or pharyngitis [9]. A recent systematic review found an overall prevalence of adverse effects of 17.6% in children with GD, with major side effects occurring in only 1.1% of cases [15]. Most adverse effects appear within the first three months of ATD therapy, although some may arise later [14]. The adverse effects associated with MMZ seem to be dose-dependent, which necessitates careful monitoring, particularly in children on higher initial doses [13].

2) Long-term antithyroid drug treatment

When ATD therapy is initiated as the first-line treatment for pediatric GD, the 2016 ATA guidelines recommend a duration of 1–2 years of ATD therapy [8]. However, remission rates in children are lower, ranging from 20% to 30%, compared to 40%–60% in adults, and a significant number of children experience a relapse after a median duration of 2 years on ATD therapy [16]. In clinical practice, it is common for children with GD to be treated with ATDs for extended periods, if hyperthyroidism remains well-controlled with the medication and no adverse events occur.

Several studies over the past few decades have explored the efficacy and safety of long-term ATD therapy in children [14,15,17–19]. A randomized trial comparing long-term (96–120 months) MMI treatment with short-term treatment (18–24 months) in pediatric GD found significantly higher remission rates in the long-term group: 92% at 1 year and 88% at 4 years post-MMI withdrawal, versus 46% and 33% in the short-term group, respectively [18]. A recent systematic review, which included 3,057 patients from 29 articles, reported an overall remission rate of 28.8% in children with GD treated with ATDs. The pooled remission rate increased with the duration of ATD therapy: 23.7%, 31.0%, 43.7%, and 75% after 1.5–2.5, 2.5–5, 5–6, and 9 years of

treatment, respectively [15]. In light of the latest research, the ETA has updated its guidelines to recommend a minimum treatment duration of 3 years for children with GD, extending to 5 years or more in cases with a low likelihood of remission [9].

3) Strategies for antithyroid drug treatment: dose titration vs. block-and-replacement

Given the potential for long-term ATD treatment in children with GD to increase the likelihood of remission [16], selecting an appropriate ATD treatment regimen is crucial. There are two main approaches: dose titration (DT) and block-and-replace (BR) methods. In the DT method, MMI doses are adjusted following the normalization of thyroid hormone levels to prevent hypothyroidism. In contrast, the BR method involves maintaining higher ATD doses to suppress endogenous thyroid hormone production, which is then supplemented with levothyroxine [9,10].

A previous meta-analysis reported that a higher incidence of adverse effects was associated with BR regimens than with DT, which was attributed to the higher doses of MMZ involved [20]. Although the 2016 ATA guidelines recommended against the use of BR regimens based on these findings [8], they continue to be utilized in clinical practice, particularly for patients who experience fluctuations in thyroid function with only minimal changes in MMZ dosage. A 2018 survey in the UK revealed that BR regimens were still commonly used among pediatric endocrinologists, with 29% favoring BR compared to 65% using DT [21].

Several studies have assessed the effects of DT and BR regimens in treating childhood GD [22–24]. An Italian retrospective study demonstrated favorable outcomes with the BR regimen, indicating improved control of thyroid function without an increase in adverse effects [23]. In a recent multicenter randomized trial by a British group comparing DT and BR regimens, the DT group achieved faster normalization of free thyroxine levels than the BR group within the first 6 months [24]. Over a period of 3 years, there were no significant differences in the proportion of patients with thyroid hormone levels within the reference range between the two groups, and the remission rates did not prove to be superior in the BR group [22]. The 2022 ETA guidelines suggest that while DT is generally preferred, BR may be considered in selected cases for biochemical stability, particularly for patients who frequently experience biochemical relapse during the DT method [9].

4) Outcomes of antithyroid drug treatment and predictors for remission

Recent systematic reviews have reported that the remission rate following ATD treatment ranged from 28.8% (829 out of 2,880 patients) [15] to 34.4% (850 out of 2,466 patients), while the relapse rate was 26% (551 out of 2,124 patients) [25]. Although these reviews included a few studies from Asian countries, specifically Japan and Taiwan, they did not investigate the effects of ethnicity on treatment outcomes [25].

Table 1 presents the characteristics of studies that have investigated the efficacy of ATD in Korean children with GD. All the studies were retrospective in design and included between 42 and 187 pediatric patients [26–30]. Following 2.9 to 4.5 years of ATD treatment, which consisted of one to three courses, the remission rate varied from 18.3% to 57.8%, while the relapse rate after ATD withdrawal ranged from 17.4% to 60.6%. The broad range of remission and relapse rates may be due to differences in the definition of outcomes, the duration and number of ATD courses, or the length of follow-up.

In addition to the duration of ATD treatment, various clinical factors have been associated with the outcomes of ATD therapy. Younger age at diagnosis, male sex, non-Caucasian ethnicity, large goiter size, and more severe thyrotoxicosis or elevated levels of thyroid receptor antibody

Table 1. Characteristics of studies investigating the effects of antithyroid drugs in Korean children with Graves disease

Reference	No. of patients	Age at diagnosis, years (mean, range)	Duration of ATD therapy, years (mean, range)	Duration of follow-up, years (mean)	ATD discontinuation rate, % (n)	Remission rate, % (n)	Relapse rate (among discontinuation group), % (n)	Predictors for remission
Lee et al., 2009 [26]	64	11.1 (3–16)	ND	8.1	67.2 (43/64)	57.8* (37/64)	37.2 (16/43)	Shorter time for TBII normalization
Song et al., 2010 [27]	113	12.6 (6–18)	4.5 (0.4–14.2)	6.6 (0.8–16.5)	66.4 (75/113)	55.8* (63/113)	20.4 (23/75)	Older age at diagnosis
Kim et al., 2012 [28]	42	11.5	4.3 (1.7–11.0) for remission group; 4.8 (2.0–9.4) for non-remission group	4.5	54.8 (23/42)	52.4* (22/42)	17.4 (4/23)	Lower TSH levels at diagnosis
Song et al., 2021 [29]	187	12.9	4.7	5.9	55.6 (104/187)	33.2* (62/187)	60.6 (63/104)	Lower FT4 at diagnosis
Rho et al., 2021 [30]	98	11.6 (2–16)	2.9 for remission group	All followed for 5 years	24.5 (24/98)	18.3 (18/98)	25.0 (6/24)	Lower TBII at diagnosis and follow-up; Shorter time for TBII normalization

ATD, antithyroid drug; ND, no data; TBII, thyroid-binding inhibitory immunoglobulin; TSH, thyroid-stimulating hormone; FT4, free thyroxine.
*Remission rate after 1–3 courses of antithyroid drug treatment.

titers have all been linked to lower remission rates [10,14,31–34]. These findings are consistent with those reported in Korean studies (Table 1) [26,27,29,30]. Although long-term ATD therapy can be effective in controlling and treating hyperthyroidism, it is not suitable for all patients, as some may ultimately require definitive treatments such as RAI therapy or surgery. Identifying children at a higher risk of relapse after long-term ATD therapy is crucial, and this can be done by evaluating their initial and follow-up clinical characteristics [19].

2. Radioactive iodine therapy

In children who do not achieve remission after ATD therapy or experience adverse events associated with ATD, RAI therapy can be chosen as the definitive treatment for GD. The goal of RAI therapy is to induce hypothyroidism through ablation because residual irradiated thyroid tissue carries an elevated risk for thyroid neoplasms [8,9].

RAI can be administered in either capsule or liquid form. There are various methods for determining the appropriate dosage. Some physicians opt for a fixed dose, while others base the calculation on the size of the thyroid gland [8,35]. Although it has not been conclusively shown which method is superior, recent guidelines recommend personalized RAI dosing that takes into account the size of the thyroid gland as estimated by ultrasound [9]. Prior to RAI treatment, ATD should be discontinued for 3 to 5 days. Thyroid hormone levels typically start to decline approximately 7 days following RAI administration, and it generally takes 2 to 3 months to reach a state of euthyroidism or hypothyroidism [8,12].

A recent systematic review, which included 1,283 pediatric patients with GD treated with RAI across 23 studies, found that the efficacy of achieving hypothyroidism after the first RAI treatment varied widely, ranging from 42.8% to 97.5% [36]. Adverse effects, both short-term and long-term, were infrequently reported, with only 1 to 6 cases for each event. Short-term side

effects included vomiting, local inflammation, and palpitations, while long-term complications encompassed benign nodules, hyperparathyroidism, multinodular benign goiter, and papillary thyroid cancer [36]. Additionally, another meta-analysis reported an RAI remission rate of 86% (164 out of 190) in children with GD [25].

In adults, RAI is contraindicated during pregnancy and lactation, in the presence of coexisting or suspected thyroid cancer, and is not recommended for patients with active Graves' ophthalmopathy or a large goiter. RAI therapy should also be avoided in very young children under the age of 5 due to the theoretical risks of later malignancy [8,9]. For children aged 5–10 years, RAI should be considered only when surgery is not a viable option [9]. While RAI is a safe and definitive treatment for older children with GD, there are still concerns among some clinicians regarding the long-term risk of malignancy. A retrospective study that followed 116 patients treated with RAI at a pediatric age (ranging from 3.6 to 19.8 years, with a mean age of 15) found that none of the patients developed thyroid cancer or leukemia after a follow-up period of up to 36 years [37].

3. Surgery: Thyroidectomy

Thyroidectomy is a definitive and effective treatment for children with GD, particularly when performed by high-volume surgeons. In some instances, it is preferred over RAI. To prevent recurrent hyperthyroidism, a total or near-total thyroidectomy is recommended rather than a subtotal thyroidectomy [8,9]. Prior to surgery, patients should be treated with ATD to normalize thyroid hormone levels. Additionally, a potassium iodide solution may be administered for 1–2 weeks preoperatively. After thyroidectomy, patients should commence levothyroxine treatment [9].

Complications of thyroidectomy can include transient or permanent hypoparathyroidism, injury to the recurrent laryngeal nerve (RLN), or bleeding. Studies have shown that young children experience a higher rate of complications following thyroidectomy compared to adolescents or adults [8,38,39]. GD is the most prevalent cause of thyroidectomy in children with benign thyroid conditions, yet the rates of complications are similar to those associated with thyroid cancers [40]. A recent systematic review, which encompassed 1,424 pediatric patients with GD across 21 retrospective cohort studies, examined the frequency of postoperative complications in this group [41]. The review found that while transient hypocalcemia and transient RLN injury were relatively common, occurring in 6.5%–50.0% and 0.0%–10.0% of cases respectively, the incidences of permanent hypocalcemia and RLN injury were much lower, at 2.5% and 0.4% respectively. Other complications, such as infections, hemorrhage, or keloid formation, were reported infrequently [41]. The review also highlighted that better outcomes, characterized by fewer postoperative complications, were linked to operations performed by high-volume thyroid surgeons. Therefore, it is recommended that thyroidectomies in pediatric patients with GD be performed by surgeons with extensive experience in the field [8–10].

4. Comparison of each treatment modality

While numerous studies have individually examined the outcomes of ATD, RAI, and surgery in treating GD, direct comparisons of these three strategies are limited, particularly in adult populations. A multicenter study in Sweden has provided comprehensive long-term outcome data for various treatments of GD in adults [42]. This study included 1,186 patients diagnosed with GD between 2003 and 2005. After 6–10 years of follow-up, the remission rates were 45.3% (351/774) with ATD, 81.5% (264/324) with RAI, and 96.3% (52/54) with surgery. Post-remission,

hypothyroidism developed in 23%, 77.3%, and 96.2% of patients in each respective group, highlighting that only 35.7% of patients maintained normal thyroid function without the need for levothyroxine treatment. In addition, a separate review article has compiled comprehensive data on the outcomes of long-term ATD use compared to RAI and surgery. This review took into account not only thyroid status but also patient-centered outcomes such as quality of life, psychiatric morbidity, and treatment costs [43]. Long-term ATD treatment (lasting at least 24 months in adults) was found to achieve and maintain euthyroidism comparably to RAI or surgery, with the added benefits of lower financial costs and improved quality of life profiles. Currently, there are no comprehensive studies that investigate all three treatment modalities in children with GD. Further research is needed to directly compare the long-term outcomes of each treatment modality in pediatric populations.

5. Novel therapies for Graves disease

Since conventional therapeutic options for GD, including ATD, RAI, and surgery, have limited efficacy in controlling the disease, novel therapies that target the direct cause of hyperthyroidism are under investigation [44]. GD is an autoimmune disease that results from the loss of immunologic tolerance to the TSHR, and it also involves interactions between B and T lymphocytes [45]. In this context, new treatment options that target B-cells or modulate TSHR using small molecule antagonists, monoclonal antibodies, or TSHR peptides are being investigated [44].

Several therapies targeting B-cells are currently under investigation in clinical trials to determine their effectiveness in treating GD (Table 2). Rituximab, an anti-CD20 monoclonal antibody, is pivotal in the management of various autoimmune disorders due to its B-cell-depleting action. A recent phase 2 study assessed the efficacy of Rituximab as an adjunctive treatment in young patients with GD aged 12–20 years. The study reported a remission rate of approximately 50% at 24 months following a single dose of Rituximab in combination with 12 months of ATD therapy [46]. Iscalimab, another monoclonal antibody that targets CD40, works by inhibiting B-cell activation via blocking the CD40-CD154 co-stimulatory pathway [45]. In a recent phase 2 trial, 47% of adult patients with GD (7 out of 15) achieved normal thyroid hormone levels without the need for ATDs during the 24-week period after receiving five doses of iscalimab over 12 weeks [47]. Furthermore, clinical trials are in progress to assess the potential of other therapies that either block immunoglobulin recycling or inhibit B-cell proliferation and differentiation [48].

Treatments that directly target TSHR signaling, including small molecules, TSHR-blocking antibodies, and TSHR-specific immunotherapy, are currently under development (Table 2). These approaches offer a more specific form of intervention compared to the B-cell targeted therapies mentioned earlier and, theoretically, do not result in global immunosuppression [44]. A recent phase 1 trial of the monoclonal TSHR-blocking antibody K1-70 has demonstrated a safe and tolerable profile, as well as clinical improvement in symptoms of hyperthyroidism [49]. In the context of other autoimmune diseases, immunotherapy strategies have been devised that involve administering small and gradually increasing doses of antigens to elicit a tolerogenic immune response. An example of this in GD is the TSHR peptide mixture ATX-GD-59 [44]. A recent phase 1 study has shown that 50% of adult patients with GD (5 out of 10) achieved normalization of hyperthyroidism, and 70% (7 out of 10) experienced improvements in free thyroid hormone levels [50]. For these emerging therapies, randomized clinical trials of extended duration are necessary to evaluate their potential impact on long-term outcomes.

Table 2. Novel therapeutic approaches for Graves disease under investigation in clinical trials

	Mechanism	Drug	Stage of development	Outcome
B-cell target	B-cell depletion	Rituximab (anti-CD20 monoclonal antibody)	Phase 2 trial in young patients (12–20 years old) [46]	13/27 (48%) in remission at 24 months after a single dose of rituximab and 12 months of ATD
	Blocking CD40 receptor interactions (attenuating B-cell activation)	Iscalimab (anti-CD40 monoclonal antibody)	Phase 2 trial [47]	7/15 (47%) showed normal free T4 and free T3 levels without ATD at 24-week after 5 doses of iscalimab over a 12-week period
	Blocking immunoglobulin recycling (targeting FcRn)	RVT-1401 (rozanolixizumab, Efgartigimod), IMVT-1401 (batoclimab)	Phase 2 trial for thyroid eye disease (batoclimab) [48]	3/7 showed responses in both ptosis and clinical activity score
	Inhibition of B-cell proliferation and differentiation (blocking BAFF)	Belimumab (anti-BAFF monoclonal antibody)	Ongoing phase 2 trial (EudraCT 2015-002127-26)	ND
TSHR target	TSHR-blocking antibodies	K1-70 (anti-TSHR monoclonal antibody)	Phase 1 trial [49]	Tolerable pharmacodynamics effects (decrease in free T4 and T3) and safety profile
	TSHR-specific immunotherapy	ATX-GD-59 (TSHR peptide)	Phase 1 trial [50]	After 10 doses in treatment-naïve patients over an 18-week period, 5/10 showed normalization of hyperthyroidism; 7/10 showed improvement in hyperthyroidism

ATD, antithyroid drug; T4, thyroxine; T3, triiodothyronine; TSHR, thyroid-stimulating hormone receptor; FcRn, neonatal immunoglobulin Fc receptor; BAFF, B-cell activating factor; ND, no data.
Modified from Lane et al. [44] with CC-BY.

Conclusion

The management of GD in children presents some challenges, including a lower rate of spontaneous remission with ATD therapy and an increased risk of complications from treatment options compared to adults. It is crucial to educate patients and their families about the disease trajectory, the effectiveness of treatment options, and potential drawbacks, as well as the long-term outlook. While recent guidelines advocate for extended ATD therapy in pediatric GD management, some patients may still need definitive therapy. Ongoing research is necessary to pinpoint risk factors. Emerging treatment strategies that target the root causes of GD are in development and expected to become part of future clinical practice, though their role in treating pediatric GD requires more research.

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

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