Graves' disease (GD) accounts for 10%–15% of thyroid disorders in children and adolescents. The use of antithyroid drugs as the initial treatment option in GD is well accepted. An average two years remission is achieved in about 30% of children treated with antithyroid drugs. However, the optimal treatment duration and the predictive marker of remission after antithyroid drug therapy are still controversial. Additionally, $^{131}$I therapy and surgery are considered the option for treatment in children and adolescents with GD. We review the treatment options for pediatric GD and the possible determinants of remission and relapse on antithyroid drug treatment in children and adolescents.

**Keywords:** Hyperthyroidism, Graves' disease, Antithyroid agents

**Introduction**

Graves' disease (GD) occurs less frequently in childhood than in adults, affecting from 0.1 per 100,000 children and 3.0 per 100,000 adolescents per year. However, it is the most common cause of hyperthyroidism in children and adolescents1,2). GD is an autoimmune disease associated with thyroid-stimulating hormone (TSH) receptor-stimulating antibodies that stimulate the synthesis and secretion of thyroid hormone3). Treatment for GD aims at restoring normal thyroid function and avoiding the recurrence of hyperthyroidism. Three treatment options are currently available for the management of pediatric Graves' disease. These include medication, surgery and radioiodine4). Most patients are initially treated with antithyroid drugs (ATD). Subtotal or near total thyroidectomy and radioiodine therapy (RAI) are considered on relapse. However, the optimal treatment option for GD in children and adolescents remains an important controversy because of the high rate of relapse when ATD are used, and the duration of ATD therapy for the induction of remission has yet to be established.

This review focuses on the treatment of GD, and the reliable predictors of remission and relapse on ATD treatment in children and adolescents.

**Antithyroid drugs**

Thionamide derivatives such as propylthiouracil (PTU), methimazole (MMI), and carbimazole are commonly used as initial ATD therapy. These drugs inhibit thyroid hormone synthesis by disturbing the thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin5). ATD may also have an immunosuppressive effect on the thyroid gland, including apoptosis of intrathyroidal lymphocytes, although conflicting data is reported6,7).

PTU and MMI are former long standing first-line treatments in children and adolescents. PTU, unlike MMI additionally inhibits peripheral conversion of thyroxine (T4) to triiodothyronine (T3). However, PTU can cause severe, rapid onset and progressive hepatotoxicity, requiring liver transplantation8,9). MMI may be taken once daily because of its
longer half-life and 10 to 20 folds higher potency than PTU\(^5\). Furthermore, MMI improves serum concentrations of T4 and T3 more rapidly. Some studies report that MMI has greater efficacy and fewer side effects\(^3,10\). The current American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) guidelines recommend that MMI should be used in every pediatric patient as the initial treatment choice for hyperthyroidism\(^1\).

Major adverse effects of ATD include agranulocytosis (a granulocyte count <500 cells/cm\(^3\)), mild leukopenia, rash, hepatitis, jaundice, and urticaria\(^10\). Agranulocytosis is the most severe side effect of ATD and occurs in 0.2%–0.5% of treated patients\(^13,14\). However, most of the side effects are rare and many are minor and transient.

The usual starting dose of MMI is 0.2 to 0.5 mg/kg/day, with a range from 0.1 to 1 mg/kg/day\(^6\). Improvement of most symptoms generally occurs within 3 to 4 weeks after the initiation of ATD\(^5\). The dose of ATD is required to be adjusted to normalize the serum levels of T4 and T3 and eventually to maintain normal serum thyrotropin levels. Most cases are usually managed with 5 to 10 mg of MMI. Follow-up thyroid function test should be assessed every 2 to 4 weeks upon ATD initiation, until patients are euthyroid. Thereafter, follow-up intervals can be increased to every 3 to 6 months. The two possible ATD therapeutic approaches are “the titration method” and “the block and replace method”\(^15\). The titration method represents an initial high dose of MMI (e.g., 20–30 mg) followed by a gradually reduction, enough to maintain normal thyroid hormone levels. On the other hand, the block and replace method consists of continuous higher doses of ATD administered combined with levothyroxine at sufficient doses to maintain euthyroid levels. Higher doses of ATD possibly reduce the autoimmunity and help in the remission of GD. However, on systematic review, the block and replace method has a higher rate of side effects and was not advantageous, as compared to the titration method\(^16,17\). Recent ATA and AACE guidelines therefore recommend that the block and replace method should be avoided\(^11\).

**Remission rate and optimal duration of ATD treatment in children and adolescents**

The appropriate duration of ATD therapy in children and adolescents remains controversial and elusive. Recent systematic, evidence-based review in adults states that if remission does not occur after 12–18 months of therapy, there is little chance of remission on long-term therapy\(^17\). Although remission in adults is 40%–60%, less than 30% of children treated with ATD for an average of 2 years achieve remission, defined as normal thyroid function maintained for at least 1 year after termination of treatment in children and adolescent\(^18-22\). More prolonged use of ATD in children than in adults may be required to achieve remission. Some studies report that the remission rate increases by 25% for every additional 2 years of ATD treatment\(^20,23\). In one recent study on 154 children with GD, remission for at least for 18 months after completion of ATD had increasing rates with time i.e., 20% after 4 years, 37% after 6 years, 45% after 8 years, and 49% after 10 years of follow-up\(^24\). Another study shows that only 17% of prepubertal children treated for 5.9±2.8 years compared with 30% of pubertal subjects treated for 2.8±1.1 years achieve a 1-year remission after cessation of antithyroid treatment\(^25\).

The remission rate varies between geographical areas. Remission rates are approximately 50% to 60% in Korean children and adolescents with GD. Lee et al.\(^26\) show that of 64 subjects with GD, remission rates increased with time and were 6.3%, 16.4%, 29.4%, and 55.8% after 3-, 4-, 5-, and 6-year follow-up, respectively. Another study indicates that 56.6% were in remission after a mean 4.3±2.9 years of ATD therapy\(^27\). However, Kim and Hwang\(^28\) report that of 41 children with GD, only 5 (12.2%) were in remission during the follow-up period (mean, 3.6±2.3 years).

**Predictors of relapse after discontinuation of ATD treatment**

Factors that are associated with relapse and remission in children and adolescents with GD are reported by several earlier studies. The results from studies on the development of more effective ATD treatment strategies have heterogeneous and conflicting results. Younger age, large goiter size, low body mass index, and higher initial thyroid hormone concentrations are independently and significantly associated with a higher probability of relapse\(^19,20,23,25,29\). Thyroid stimulating hormone receptor antibodies (TRAb) titers at the onset and end of treatment is one of the predictive markers of relapse\(^22,26\). Some studies have failed to assess these findings. A meta-analysis in adults reports that TRAb is not an effective predictor of relapse post-ATD treatment\(^31\). A recent review cites the variability in assay methodology, population characteristics, and study design in published data, as reasons why TRAb titers are insufficient predictors of relapse\(^32\).

The findings on the risk of relapse are also inconclusive and variable in Korean studies. The predictive markers of GD relapse are age at diagnosis, serum thyrotropin concentration at presentation, and rapid achievement of TRAb normalization in Korean children and adolescents\(^26,28,33\).

**Radioiodine therapy**

Radioiodine therapy (RAI) is an effective nonsurgical option for the definitive therapy for GD. Most clinical RAI experience is in children and adolescents from the United States, while it is still very uncommon in other geographic areas\(^4\). The goal of RAI is to prevent the recurrence of GD by inducing hypothyroidism, rather than euthyroidism. \(^131\)I doses are typically calculated to deliver radiation based on the estimated amount of the thyroid gland and the 24-hour uptake (50 to 200 µCi radioiodine per gram of thyroid tissue), although some researchers deliver a fixed dose of radioiodine.
without measuring uptake\textsuperscript{35,36}. The risk of thyroid cancer and nodules is greater with exposure to low level thyroid irradiation, and not with the higher doses used to treat pediatric GD\textsuperscript{37,38}. Furthermore, low administered activities of \textsuperscript{131}I result in a high relapse rate\textsuperscript{39}. Larger doses (usually >150 µCi of \textsuperscript{131}I per gram of thyroid tissue) are hence preferred over smaller doses of radioiodine\textsuperscript{40}. Hypothyroidism is achieved in approximately 60\%–95\% patients with a dose of radioiodine 150–200 µCi/g of thyroid\textsuperscript{41,42}. The thyroid gland begins to shrink at 6–8 weeks after RAI, and hypothyroidism typically develops by 2–3 months posttreatment\textsuperscript{43}.

The most common adverse effects of RAI include vomiting and radiation-induced thyroiditis, characterized by anterior neck pain\textsuperscript{44}. No serious complications occur for as long as 23 years on follow-up, according to a recent review on RAI in children and adolescents\textsuperscript{45}. Although the major concern of RAI is the long-term risk of malignancy, there is no increased incidence of cancer in adults treated with radioiodine in childhood or adolescence\textsuperscript{46}. However, RAI should be avoided in very young children (<5 years) because of an increased risk of neoplasia\textsuperscript{47}. RAI causes new or worsening of Graves’ ophthalmopathy in about 15\%–20\% of adult patients, although there are rare reports of pediatric patients with worsening Graves’ ophthalmopathy after RAI\textsuperscript{48}.

**Surgery**

Surgery is a valid and acceptable treatment option of GD in children and adolescents, but is selected less often than ATD and RAI because of the risks of surgery. Thyroidectomy is indicated in patients with a large goiter causing compressive symptoms, relapse of hyperthyroidism after ATD, low uptake of radioactive iodine, or when associated cancer is suspected\textsuperscript{49}.

Total or near-total thyroidectomy is the recommended procedure, since subtotal thyroidectomy increases the risk of relapse of hyperthyroidism more than total or near-total thyroidectomy\textsuperscript{50}. Furthermore, near-total or total thyroidectomy does not increase the complication rate\textsuperscript{51}. Surgical complication rates are higher in children than in adults, with higher rates in younger than older children. Transient hypocalcemia occurs in 10\% of patients and permanent hypothyroidism in 2\% of children\textsuperscript{52}. Furthermore, hypoparathyroidism, palsy of the recurrent laryngeal nerve and wound infections can occur after thyroidectomy\textsuperscript{53}.

**Conclusions**

GD is the most leading cause of autoimmune hyperthyroidism in the pediatric population. ATD is considered the first-line therapy of pediatric GD. MMI should be selected for the treatment of GD in children and adolescents, because PTU can cause severe hepatotoxicity. The optimal duration of ATD treatment to remission, and the predictive factors for remission are not established. Children and adolescents may require more prolonged ATD treatment than adults. While there is no single marker that provides 100\% predictability, there are several markers that are associated with a decreased likelihood of achieving and maintaining remission, such as high TRAb titers, large thyroid gland size, and younger age. Surgery and RAI are considered as the treatment option for GD. However, many patients and their guardians have an extreme fear of radiation and surgery, hence RAI and thyroidectomy is rarely used in Korea.

Prospective, multicenter studies are needed to identify the long-term risks and benefits of therapeutic options including ATD, RAI and surgery and also, to determine the appropriate duration of ATD and the predictive markers with high sensitivity and specificity.

**Conflict of interest**

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

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