MANAGEMENT OF ENDOCRINE DISEASE

Arguments for the prolonged use of antithyroid drugs in children with Graves’ disease

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Abstract
Graves’ disease is an autoimmune disorder. It is the leading cause of hyperthyroidism, but is rare in children. Patients are initially managed with antithyroid drugs (ATDs), such as methimazole/carbimazole. A major disadvantage of treatment with ATD is the high risk of relapse, exceeding 70% of children treated for duration of 2 years, and the potential major side effects of the drug reported in exceptional cases. The major advantage of ATD treatment is that normal homeostasis of the hypothalamus–pituitary–thyroid axis may be restored, with periods of drug treatment followed by freedom from medical intervention achieved in approximately 40–50% of cases after prolonged treatment with ATD, for several years, in recent studies. Alternative ablative treatments such as radioactive iodine and, less frequently and mostly in cases of very high volume goiters or in children under the age of 5 years, thyroidectomy, performed by pediatric surgeons with extensive experience should be proposed in cases of non-compliance, intolerance to medical treatment or relapse after prolonged medical treatment. Ablative treatments are effective against hyperthyroidism, but they require the subsequent administration of levothyroxine throughout the patient’s life. This review considers data relating to the prognosis for Graves’ disease remission in children and explores the limitations of study designs and results; and the emerging proposal for management through the prolonged use of ATD drugs.

Introduction
Graves’ disease (GD) is much rarer in children than in adults, with children accounting for only 1–5% of all patients with GD (1). It may occur at any age during childhood, but its frequency increases with age, peaking during adolescence. The incidence of GD is thought to have risen over the last few decades (2, 3). The estimated
prevalence of GD varies between countries, from 1/100000 person-years in the United States to 1/1000000 person-years (for children aged 0–15 years) in the UK and Ireland (2). A frequency of up to 14 per 100000 person-years has been reported in Hong Kong, and differences in the frequency of this condition do not seem to depend on dietary iodine intake (4, 5). This autoimmune disorder is the major cause of hyperthyroidism in children and, similar to most other thyroid disorders in both adults and children, it is much more frequent in female than in male subjects. GD is thought to result from complex interactions between genetic and environmental factors and the immune system, although its pathogenesis remains unclear. The immune system of patients with GD produces a thyroid-stimulating hormone receptor antibody (TRAB) that triggers the production of excess thyroid hormone by the thyroid gland. The prevalence of GD is higher in first-degree relatives of patients with the disease than that in controls. Together with data from twin studies, this suggests that GD is largely determined by genetic factors (approximately 80% of the susceptibility to this disease), with environmental factors playing a lesser role (20% of susceptibility) (6, 7, 8). The frequency of GD is higher in children with other comorbid autoimmune disorders (or conditions associated with such disorders, such as Turner’s, Down’s or Di George syndrome), and in children from families with a history of autoimmune thyroid diseases (9, 10, 11).

Before discussing the pros and cons of the prolonged use of antithyroid drugs (ATDs) in children with GD, we should look at the most commonly used treatments. There is no specific cure for the disease and each therapeutic option is associated with complications. The best way to manage GD, and the pros and cons of prolonged ATD use in children with GD remain a matter of debate among pediatric endocrinologists.

As in adults, ATDs are usually the first-line treatment for GD in children and adolescents in most countries. They are used for various lengths of time, ranging from 2 to several years. Propylthiouracil (PTU) is no longer recommended for use in children due to its potential severe hepatotoxicity, and should only be used in exceptional circumstances, for short periods, with close monitoring for signs of hepatic dysfunction, before radical treatment, in patients experiencing severe side effects on carbimazole (CMZ)/methimazole (MMI) (12). CMZ and its active metabolite, MMI are, thus, the mostly widely used ATDs. They act by interfering with the iodination of thyroglobulin tyrosine residues by the thyroid peroxidase, thereby inhibiting thyroid hormone synthesis. Concerns have been raised regarding ATD toxicity, which is usually mild and reversible but may exceptionally be severe, mostly during the first 3–6 months, potentially limiting the use of ATD. It is difficult to achieve compliance in the long term and relapse rates are higher in children than that in adults. The ability of treatment with ATD to restore normal homeostasis of the hypothalamus–pituitary–thyroid axis in some cases is a key advantage, as it may allow patients to alternate periods of medical treatment with periods free from medical intervention. However, it may take some time to establish remission, and a large proportion of patients may never achieve remission (12).

 Destruction of the thyroid gland through radioactive iodine (RAI) treatment or surgical ablation is frequently proposed as an alternative for second-line treatment. Such treatments frequently result in hypothyroidism, and appropriate doses of levothyroxine must therefore be administered throughout the patient’s life. However, regardless of compliance with treatment, hypothyroidism is considered preferable to hyperthyroidism, as hyperthyroidism is associated with more serious morbidities, such as cardiovascular complications, osteopenia, an increase in height velocity with advanced bone age and emotional symptoms with a neuropsychological impact (13).

Radical treatments are generally considered in children with relapse after an appropriate course of drug treatment (‘appropriate’, in such cases, remains to be defined), a lack of compliance on the part of the patient or the parents and severe ATD toxicity (12).

RAI is more frequently used than surgery. The treatment with RAI is effective and most patients can be successfully treated with a single oral dose. The use of low doses can lead to hyperthyroidism being cured without the development of hypothyroidism. However, relapse rates are high for this approach. Higher doses of 131-I (generally 220–275µCi/g, equivalent to approximately 250Gy) are therefore preferred (12). It is preferable to treat patients with ATDs to render them euthyroid before treatment with RAI. Repeat treatment with 131-I is indicated in cases of hyperthyroidism persisting 3–6 months after treatment (14). There have been no reports of reproductive dysfunction or of a higher frequency of abnormalities among the children of treated patients (15). RAI increases the risk of neoplasia and is therefore absolutely contraindicated during pregnancy and breastfeeding, and is highly inadvisable...
in very young children (aged <5 years). Concerns have been raised about its potential to cause thyroid cancers, hyperparathyroidism and death, but recent studies have shown that the excess cancer risk in adult patients can be attributed to hyperthyroidism itself and to the risk factors common to these patients, rather than to the nature of the treatment received (16, 17).

Total (or near-total) thyroidectomy is usually indicated for patients with a contraindication for RAI treatment, such as very young children or patients with high volume of goiter (>80 g). Complications, such as hypoparathyroidism, vocal cord palsy due to recurrent laryngeal nerve injury and keloid formation, may occur with an estimated incidence of approximately 15%, although such complications are less frequent if the operation is performed by pediatric surgeons with extensive experience (18). For patients with recurrent hyperthyroidism after surgery, treatment with RAI is recommended, because the risk of complications is higher for a second operation (19).

As in many rare diseases, there is currently no evidence-based strategy for the management of this disease and for the optimal duration of ATD treatment in children. GD treatment policy varies considerably within and between countries, and depends on local traditions and resources, the age and preference of the patient, the size of the goiter and the severity of the disease.

**Monitoring ATD treatment**

The initial starting dose of MMI/CMZ (CMZ is a precursor of MMI and is rapidly converted to MMI in the serum; 10 mg of CMZ is metabolized to yield approximately 6 mg of MMI) is 0.2–0.8 mg/kg/day, depending on the initial severity of the disease and the drug used (MMI or CMZ), with a maximal dose of 30 mg per day for MMI and 40 mg per day for CMZ. A complete blood cell count and liver function evaluation should be performed before starting the treatment, to check that the absolute neutrophil count is above 1000/mm³ and that the levels of liver enzymes are no more than three times the upper limit of the normal range (12). Both drugs have a long half-life and are effective when given as a single daily dose, which might improve the compliance. Beta adrenergic blockade may also be required during the first 2 weeks of the treatment, to reduce tachycardia. After 2–4 weeks, when thyroid hormone secretion is effectively blocked and free thyroid hormone levels have strongly decreased, the initial dose of MMI/CMZ is gradually reduced by 30–50%.

Treatment with ATD normalizes serum thyroid hormone levels within 1 month, with thyroid-stimulating hormone (TSH) becoming detectable in the serum, usually within 2–4 months. It also leads to improvements in metabolic rates, growth velocity and body weight within 3 months, with some patients gaining more weight than expected on the basis of weight loss at presentation (20). Thyroid function tests and clinical evaluations should be carried out every 3–6 weeks during the first 3–4 months of treatment, because hypothyroidism may occur if ATD dose is not reduced, as serum free (f) T4 levels return to normal and most of the side effects of ATD occur during the first few months of the treatment. Once the ATD dose has been reduced, biochemical evaluations should be carried out every 3–4 months. However, approximately 10% of patients with fT3-predominant GD, have high serum fT3 concentrations after serum fT4 concentrations have returned to normal or subnormal levels (21). These patients therefore have a high fT3:fT4 ratio, making it necessary to determine serum free T3 concentrations in patients with long-term undetectable TSH levels, to identify cases with this presentation. These patients have larger thyroid glands and high serum titers of TRAb (21, 22, 23). They are more likely to be younger and require doses of ATD twice as high as those used in patients with classic GD, over long periods of time, although it remains unclear why the maintenance of high doses is required to overcome the resistance to ATD (21).

Two possible approaches have been discussed: the block and replace (BR) approach and the dose titration (DT) regimen. The BR approach involves the use of a high dose of ATDs together with levothyroxine, whereas the DT approach involves adjusting the dose of ATD to achieve euthyroidism, improving compliance. Compliance may also be a particularly difficult issue in adolescent patients, who may find it easier to take one ATD rather than two ATDs and levothyroxine. In most adult and child patients, no additional benefit accrues from the maintenance of a high dose of ATD together with replacement doses of levothyroxine, and there is currently no rationale for the use of levothyroxine in combination with ATDs to enhance remission rates (24). Recent studies have even suggested that high-dose treatment may be harmful, because the frequency of side effects is dose-dependent (24). Recent American Thyroid Association (ATA) guidelines suggest that the BR regimen should be avoided (12).
The use of ATDs, such as MMI/CMZ or PTU, is associated with an increase in the risk of some minor reversible adverse reactions (such as skin rash, urticaria, arthralgia and less frequently, gastrointestinal problems) in approximately 5–25% of cases, requiring concomitant transitory antihistamine treatment in some cases, and the risk of much rarer severe skin reactions (Stevens-Johnson syndrome) (25). The frequency of agranulocytosis, the most severe side effect, is between 0.2 and 0.5% for both drugs. Other major side effects are rare and are observed mostly with PTU, which should be avoided in children. They include drug-induced hepatitis, and the production of cytoplasmic anti-neutrophil antibodies (ANCA). ANCA-positive vasculitis occurs only in exceptional cases, and susceptibility to this condition seems to be higher in patients of Asian origin (26). The risk appears to increase with the duration of PTU therapy, following the opposite pattern to other adverse effects of ATDs, which typically occur during the first 3–6 months of treatment (25, 26, 27). In adults, MMI/CMZ use has also been shown to be associated with ANCA positivity, although the risk for this combination is lower than that reported for PTU (26, 28). Typical manifestations of ANCA-positive vasculitis are polyarthritus, purpuric skin lesions and occasionally, pulmonary and/or renal involvement. Discontinuation of the drug generally results in symptom resolution, but glucocorticoids or other immunosuppressive drugs may be required in more severe cases (12, 26).

The frequency of side effects is thought to be dose-related and is very low for severe side effects in patients receiving MMI at a dose of less than 10 mg/day or CMZ at a dose of less than 15 mg/day (12, 29). With the exception of dose-dependent effects at high doses of ATDs and recently identified genetic variants associated with ATD-induced agranulocytosis identified in a European population (30), no factors predictive of the development of severe, potentially life-threatening side effects have been identified. Patients and their families should be informed of the potential side effects of ATDs, preferably in writing, and should inform their physician immediately if they develop a pruritic rash, jaundice, acholic stools or dark urine, arthralgia, abdominal pain, nausea, fatigue, fever or pharyngitis, due to the need for an immediate evaluation of complete blood cell count and liver function (12). However, most adverse effects occur only rarely and, as many are minor and transient, it is not generally necessary to stop the treatment with ATD (27). Detailed physical and biochemical tests should therefore be performed in the first 3–6 months, with frequent examinations thereafter.

**Outcome**

Studies in adults and children have taught us that the initial severity and course of the disease are highly variable and that relapse rates are higher in children than that in adults, with remission occurring in 20–30% in children and 40–60% of adults after a first course of treatment lasting a median of 2 years (3, 24, 31, 32, 33, 34, 35, 36, 37, 38, 39). Relapse occurs within 6 months of the end of drug treatment in 75% of patients, whereas only 10% of patients present a relapse more than 18 months after the end of the treatment (36, 40, 41). However, the definition of remission differs between studies, with patients being considered to be in remission if they display euthyroidism for a period of 0.5–2 years after the end of the ATD therapy, although most studies have reported the recurrence of hyperthyroidism after at least 1 year off ATD treatment (Table 1) (12, 24, 27, 31, 32, 33, 34, 35, 36, 38, 39, 40).

**Recent findings from adult studies**

Early studies in adults provided no evidence to suggest that the prolongation of the treatment with ATD beyond 2 years was of any benefit (24). Remission rates vary between geographic areas and seem to be better in Europe and in Japan than those in the USA, where RAI was, until recently, favored as the first-line treatment or used within 1 year of the start of the ATD treatment (12, 42, 43). Lower remission rates have been reported for men, smokers (especially men) and those with severe biochemical disease with high serum TRAb levels and large goiters (≥80 g) (12, 44). However, some patients prefer to prolong treatment with low doses of ATD (2.5–7.5 mg/day, MMI or CMZ) over several years (45) and two recent studies have even suggested that prolonged ATD treatment yielded better results (46, 47). A better outcome with the treatment with ATD was demonstrated particularly for patients with severe ophthalmalopathy, which is likely to be aggravated by the treatment with RAI, and TSH receptor antibody levels were found to decrease more rapidly after the treatment with ATD than after RAI treatment (45). The prolonged use of low doses of MMI/CMZ was safe in these studies (45, 47) and thyroid function seemed to remain more...
stable in the low-dose MMI group, with subclinical and overt hypothyroidism more frequently observed in the RAI + levothyroxine group than in the MMI group (45). An individual approach based on a predictive score at the time of diagnosis for the risk of recurrence after a first 2-year course of ATD has recently been described, with genetic background also modulating individual responsiveness in adults (48).

Recent findings from studies in children

Pediatric GD studies are scarce, due to the rarity of this disease in children. They also tend to present the biases inherent to observational design, with most studies retrospective, with a limited number of patients enrolled, many of whom are lost to follow-up, and large amounts of missing data. The main pediatric cohort studies are summarized in Table 1 (3, 27, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 49). The comparative effectiveness of treatment with ATD, as characterized by the remission rate (the definition of which differs between studies), varied from 11 to 49% with treatment most effective for the longer duration of treatment with ATD in two large independent cohorts, with no fatal side effects reported (27, 40).

Methods for identifying patients unlikely to achieve remission after the drug treatment would greatly improve patient management, by making it easier to tailor treatment more effectively in newly diagnosed patients. Age, goiter size, decrease in body mass index and severity of biochemical hyperthyroidism at onset, TRAb levels at onset and at the end of treatment, and duration of medical treatment have all been evaluated as predictive markers for GD relapse during childhood (32, 33, 34, 35, 37). However, these studies were subject to major limitations: all but one (35) was retrospective, with most patients receiving ATDs for approximately 2 years, and none of these studies has led to widespread changes in the clinical practice. Our prospective study (36) showed that the risk of relapse after a first course of ATD for an intended duration of 2 years was higher in very young patients and patients of non-Caucasian origin, and that this risk increased with disease severity at diagnosis, as assessed on the basis of serum TRAb and free thyroid hormone levels.

Table 1 Summary of studies on remission rate after antithyroid drug treatment for Graves’ disease in children (studies included if ≥50 studied patients with a follow-up period after discontinuation of treatment ≥6 months).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study design</th>
<th>Number of patients</th>
<th>ATD treatment duration (years; median or range)</th>
<th>Remission rate</th>
<th>Follow-up period*, years</th>
<th>Pronostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>(30) USA</td>
<td>Retrospective</td>
<td>182</td>
<td>2</td>
<td>20%</td>
<td>2</td>
<td>ND</td>
<td>Prepubertal children appear to require longer periods of treatment than pubertal children to achieve remission</td>
</tr>
<tr>
<td>(31) USA</td>
<td>Retrospective</td>
<td>60</td>
<td>Up to 6</td>
<td>25%</td>
<td>&gt;1</td>
<td>ND</td>
<td>BMI (SDS), goiter volume</td>
</tr>
<tr>
<td>(32) USA</td>
<td>Retrospective</td>
<td>100</td>
<td>2–6</td>
<td>PP: 17%; PC: 30%</td>
<td>1</td>
<td>ND</td>
<td>Initial severity (FT4), age, euthyroidism by 3 months on ATD</td>
</tr>
<tr>
<td>(33) USA</td>
<td>Retrospective</td>
<td>106</td>
<td>2</td>
<td>25%</td>
<td>6 mo</td>
<td>ND</td>
<td>Age, ethnicity, initial severity (FT4, TRAbs), duration of treatment</td>
</tr>
<tr>
<td>(34) USA</td>
<td>Prospective</td>
<td>51</td>
<td>2</td>
<td>29%</td>
<td>1</td>
<td>ND</td>
<td>Initial severity (FT4), other autoimmune conditions</td>
</tr>
<tr>
<td>(35) France</td>
<td>Prospective</td>
<td>154</td>
<td>2</td>
<td>30%</td>
<td>2 years</td>
<td>ND</td>
<td>Duration of ATD treatment</td>
</tr>
<tr>
<td>(36) Italy</td>
<td>Retrospective</td>
<td>115</td>
<td>1.5–2</td>
<td>33%</td>
<td>ND</td>
<td>Initial severity (TRAbs), time required for TRAb level normalization, goiter volume</td>
<td></td>
</tr>
<tr>
<td>(37) Australia</td>
<td>Retrospective</td>
<td>65</td>
<td>2</td>
<td>11%</td>
<td>≥4</td>
<td>ND</td>
<td>Remission not affected by ethnicity or sex</td>
</tr>
<tr>
<td>(38) USA</td>
<td>Retrospective</td>
<td>291</td>
<td>ND</td>
<td>15%</td>
<td>&gt;1</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

PP, prepubertal; PC, pubertal children; mo, months.

*Follow-up period for defining remission after discontinuation of treatment; †25% every 2 years of treatment for up to 6 year.
(high levels being associated with severity). Conversely, relapse risk decreases with increasing duration of the first course of ATD. In this study, a prognostic score was generated, allowing the identification of three different risk groups at diagnosis, defined on the basis of clinical and biological characteristics and intended duration of ATD treatment: a low-risk group with a score between 0 and 3 (38% of cases); an intermediate-risk group with a score between 4 and 7 (47% of cases); and a high-risk group with a score between 8 and 11, (15% of cases). The patients in the low-risk group have a predicted 2-year relapse rate of 46%, those in the intermediate-risk group have predicted relapse rate of 77%, whereas those in the high-risk group have relapse rates as high as 98% 2 years after the end of treatment with ATD (36). It could be argued that definitive treatment should be considered earlier in the management of patients in the high-risk group (score >8), because almost all these patients suffer relapses after 2 years of treatment with ATD, but these patients are often younger (<5 years old), and it is prudent to avoid RAI and thyroidectomy in such young patients. These patients should, therefore, preferably be offered prolonged treatment with ATD without the need for re-evaluation after the ‘classic’ period of 2 years of medical treatment, as they are likely to present relapses after 2 years of treatment. However, little is known about the long-term outcome, because there have been few studies of the relationship between duration of treatment with ATD and remission rate or relapse risk in pediatric patients, although it is widely accepted that there is a need to prescribe longer courses of treatment for children than that for adults. Our study was the first to investigate the effect of long-term treatment with ATD prospectively. In this cohort, after three consecutive courses of treatment, each lasting about 2 years, and a median follow-up period of 10.4 years, approximately half of the patients achieved remission after the discontinuation of ATD treatment with CMZ (40). Less severe forms of hyperthyroidism at diagnosis and the presence of other associated autoimmune conditions were associated with an increase (by a factor of about 2.2) in the predicted remission rate achieved with ATD treatment. In contrast to our previous report concerning the risk of relapse after the first course of treatment (36), we observed no independent effect on long-term remission rate of age, ethnicity or serum TRAb levels at diagnosis (40). Other factors, such as sex, iodine intake, smoking and genetic background are thought to modulate individual responsiveness in adults (44, 48). This study was subjected to several limitations: a relatively small number of boys were included, possibly preventing the detection of male sex as a determinant of GD relapse, a lack of serum TRAb determinations during the follow-up and a lack of information about genetic background, precluding evaluations of the association of these factors with relapse rate (37). Our findings suggest that children with GD displaying good compliance with treatment and with no major adverse effects of ATD could be offered several years of treatment with ATD, to increase the chances of remission, before definitive ablative treatment is envisaged (40).

**Strategies for managing GD involving the prolonged use of ATDs in children**

It is widely accepted that the remission of GD in patients treated with ATDs is linked to the restoration of euthyroidism, rather than the immunosuppressive effects of the drugs. Hyperthyroidism has been shown to aggravate autoimmune problems, and autoimmunity leads to the generation of more TSH receptor antibodies and a worsening of hyperthyroidism. Once this cycle has been broken by treatment with ATD rendering the patient euthyroid, the patient may experience gradual remission of the disease (13, 50). This hypothesis and our results, together with those of a Japanese study of the largest pediatric cohort investigated to date (27), highlight the positive impact on outcome of a long period of first-line treatment with ATD, to minimize thyroid autoimmunity and disease recurrence. The use of ATDs for longer periods, of at least 3–6 years, depending on initial disease severity, may be required to achieve a better rate of remission in children (27, 32, 40, 49). Continuous treatment, rather than 2-year treatment cycles, may be more effective for achieving a gradual remission of GD, and should, therefore, be considered in future clinical trials. The use of prolonged low doses of MMI/CMZ may also yield better outcomes by triggering a faster decrease in serum TRAb levels than that by treatment with RAI, particularly in the rare children presenting severe ophthalmopathy (45, 51, 52). Compliance is, therefore, an important issue in the management of these children, and should be improved by educational strategies.

**Conclusion**

The major advantage of ATD therapy is that normal homeostasis of the hypothalamus–pituitary–thyroid axis may be restored, with periods of medical treatment
followed by freedom from medical intervention. However, remission may take a long time to achieve, and may never be achieved in a substantial proportion of patients (approximately 50–60%), regardless of ethnicity and age at diagnosis. In patients who are not cured by the treatment with ATD and experiencing recurrences of hyperthyroidism after prolonged ATD treatment, the RAI therapy may be safer than near-total thyroidectomy and can be used for definitive treatment. However, both these radical treatments entail a high risk of permanent hypothyroidism.

As recommended in recent guidelines (12), the treatment with ATD should be proposed as the initial therapy in all children with GD, to bring the disease under control as soon as possible. Careful discussion with the parents and the child is then required, to determine the best choice of treatment, long-term ATD or more definitive options, such as treatment with RAI and thyroidectomy, as large prospective randomized trials with long-term quality-of-life assessment have not yet been carried out to address this issue in children. The long-term treatment with the lowest MMI/CMZ dose resulting in euthyroidism should be offered to all patients, to increase the likelihood of remission. This new strategy requires optimization through educational strategies, to improve compliance with treatment and medical care, particularly during the transition from pediatric to adult services.

Further prospective randomized studies are required in children to confirm the efficacy of a prolonged conservative approach and to compare the efficacy and side effects of long-term ATD treatment with those of RAI and surgical ablation.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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J Léger and J-C Carel

Grave’s disease in children

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