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SHORT REVIEW

Management of hyperthyroidism due to Graves' disease: frequently asked questions and answers (if any)

L. Bartalena[1] · L. Chiovato[2] · P. Vitti[3]

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Abstract Graves' disease is the most common cause of hyperthyroidism in iodine-replete areas. Although progress has been made in our understanding of the pathogenesis of the disease, no treatment targeting pathogenic mechanisms of the disease is presently available. Therapies for Graves' hyperthyroidism are largely imperfect because they are bound to either a high rate of relapsing hyperthyroidism (antithyroid drugs) or lifelong hypothyroidism (radioiodine treatment or thyroidectomy). Aim of the present article is to offer a practical guidance to the reader by providing evidence-based answers to frequently asked questions in clinical practice.

Keywords Graves' disease · Hyperthyroidism · Graves' orbitopathy · Thionamides · Methimazole · Propylthiouracil · Radioiodine · Thyroidectomy · Pregnancy · Childhood · Alemtuzumab · Agranulocytosis

Introduction

Graves' disease is the most common cause of hyperthyroidism in iodine-replete areas and is characterized by the presence in patients' serum of antibodies directed against the TSH receptor (TRAb) that produce thyroid hyperfunction [1, 2]. In addition to hyperthyroidism, extrathyroidal manifestations may be present, including Graves' orbitopathy (GO), thyroid dermopathy, and acropachy [3]. Genetic and environmental factors contribute to the occurrence of this autoimmune disorder [4, 5], which is largely prevalent in 20- to 40-year-old women [1] although may develop at any age, including childhood [6]. Medical treatment of Graves' disease relies on the use of antithyroid drugs (ATDs), thionamides [methimazole (MMI), carbimazole (CBZ), propylthiouracil (PTU)] [7, 8], but, owing to the large recurrence rate of hyperthyroidism, thyroid ablation by either radioiodine (RAI) treatment or thyroidectomy is often required.

Aim of the present article is not to provide a comprehensive review of this topic, but rather to offer a practical guidance to the reader by providing evidence-based answers to frequently asked questions in clinical practice. Some of these are summarized in Table 1.

Question 1: Are currently available therapies targeting pathogenic pathways of Graves' disease?

None of the above treatments truly targets the pathogenic mechanisms involved in Graves' disease. ATDs mainly exert their effects through inhibition of thyroid peroxidase, the enzyme involved in thyroid hormone synthesis, although they may have some immunomodulating actions [9]. Long-term restoration of euthyroidism, which is observed in about 50 % of patients after ATDs withdrawal, is better explained by spontaneous remission of the autoimmune process rather than by a specific or direct effect of ATDs. It is conceivable, however, that pharmacological control of hyperthyroidism may indirectly contribute to

✉ L. Bartalena
luigi.bartalena@uninsubria.it

[1] Endocrine Unit, Department of Clinical and Experimental Medicine, ASST dei Sette Laghi, Ospedale di Circolo, University of Insubria, Viale Borri, 57, Varese, Italy

[2] Fondazione Salvatore Maugeri and University of Pavia, Pavia, Italy

[3] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Table 1 Some questions and answers concerning the management of hyperthyroidism due to Graves' disease

	ATD treatment	RAI treatment	Thyroidectomy
Question			
Is treatment acting on pathogenic mechanisms of disease?	No	No	No
Is it the first-line treatment?	Yes[a]	Yes[a]	No
Is it a safe treatment?	Yes[b]	Yes[b]	Yes[b]
Can it be used if GO is present?	Yes	Yes[c]	Yes
Can it be used in pregnancy?	Yes[d]	No	Only exceptionally
Can it be used in children?	Yes[e]	Yes[e]	Yes[e]

ATD antithyroid drug, *RAI* radioiodine, *GO* Graves' orbitopathy

[a] ATDs are first-line treatment in Europe, Latin America and Japan; RAI is first-line treatment in North America

[b] ATDs may cause minor side effects, but major adverse events are rare; the safety profile of carbimazole/methimazole is better than that of propylthiouracil (see text). RAI may cause progression of Graves' orbitopathy, particularly in smokers. Complications of surgery are rare in the hands of a skilled, high-volume surgeon

[c] In at-risk patients (see text), a short course of low-dose prednisone (steroid prophylaxis) should be given to prevent progression of GO

[d] Propylthiouracil should be used in the first trimester, shifting to methimazole in second and third trimesters

[e] ATDs are first-line treatment and can be given for many years; RAI should be avoided before 10 years of age; thyroidectomy is associated with a higher rate of complications than in adults

remission by reducing autoantigen exposure by the resting thyroid gland. The commonly observed decrease in serum TRAb concentration during ATD treatment might reflect either mechanism [10]. Thyroidectomy and radioiodine cure hyperthyroidism (not Graves' disease) by removing or reducing thyroid tissue, but deliberately cause permanent hypothyroidism requiring lifelong L-thyroxine replacement therapy. Total thyroid ablation (thyroidectomy followed by RAI treatment), although proposed as thyroid treatment in patients with GO (see below), does not represent an established treatment for Graves' hyperthyroidism [11].

Answer to Question 1: Current treatments are not effective on the pathogenesis of Graves' disease and are imperfect because they are bound either to a high rate of relapses (ATDs) or to lifelong hypothyroidism (RAI and thyroidectomy).

Question 2: Is there a general consensus on the first-line treatment for newly diagnosed hyperthyroidism?

There are regional differences in the choice of the first-line treatment for newly diagnosed hyperthyroidism [2]. In a recent survey of clinical practice among North American thyroidologists, ATD treatment was indicated as the first-line treatment by only 40 % of North American respondents [12], whereas in a European survey ATDs represented the first-line treatment for 84 % of respondents [13]. Radioiodine treatment was indicated as first-line treatment by approximately 60 % of North Americans [12] and only 14 % of European [13] experts. Interestingly, these continental differences have not substantially changed in the last 25–30 years [14–16]. It should, however, be noted that the proportion of North American thyroidologists using ATDs as first-line treatment seems to be increasing, because of the steadily increasing number of thionamide (mainly MMI) prescriptions in the period 1991–2008 [17]. ATDs constitute the first-line treatment also in Asia, Oceania and Latin America [12]. The role of thyroidectomy as first-line treatment is modest worldwide (0.9 % in North America [12], 2.1 % in Europe [13]), but it may be important in countries where facilities for RAI administration are not easily available [18] or direct and indirect costs of long-term ATD treatment (hormone assays, repeated visits, loss of working hours) cannot be afforded [19].

Answer to Question 2: ATDs represent the first-line treatment in most countries. Although RAI treatment is still preferred in North America, an increasing use of ATDs has been observed even there. The role of thyroid surgery as first-line treatment is limited worldwide.

Question 3: Are there differences in the outcome of various regimens of ATD treatment?

There are two major regimens of ATD treatment, the *titration method*, which is based on the use of the lowest ATD dose maintaining euthyroidism, and the *block-and-replace method*, in which the high starting dose of thionamides is kept, but L-thyroxine is added to avoid hypothyroidism [20]. A systematic review of randomized clinical trials published some years ago failed to show a superiority of either regimen in terms of relapse rate, which was around 50 %

irrespective of the method used [21]. The number of patients withdrawing treatment because of side effects appeared to be slightly higher using the block-and-replace method [21]. The 2011 American Thyroid Association/American Association of Clinical Endocrinologists guidelines state that the block-and-replace is generally not recommended because of this reason [22]. In a recent European survey, the titration method was used by 36 % of respondents, the block-and-replace by 26 %, while the remaining 38 % would use the block-and-replace method only in selected cases [13].

Duration of ATD treatment is extremely variable in the literature. Using the block-and-replace method, there seems to be little advantage, in terms of recurrence rate, to prolong treatment beyond 6 months [23]. Even after a prolonged block-and-replace course (median duration 41 months; range 24–132 months), relapse occurred in 37 % of patients [24]. Using the titration method, ATDs are usually given for 12–18 months, because shorter treatment courses are associated with a higher rate of recurrences [21]. Prolonged treatment (up to 42 months) apparently does not provide a substantial advantage in terms of permanent remission after drug withdrawal [20]. However, this view is not shared by all authors [25–27]. In a recent European survey, two-thirds of respondents treated patients for 12–18 months, whereas only about 4 % gave ATDs for >24 months [13]. A very prolonged treatment (with low/very low doses of ATDs) may represent a possible option under particular conditions, such as in the elderly with important comorbidities or in patients who do not want to be treated with lifelong thyroid hormone replacement after thyroid ablation.

Measurement of serum TRAb concentration represents a useful tool to decide whether ATD treatment can be withdrawn or should be continued [28]. Patients with positive TRAb test at the end of treatment will almost invariably recur, while patients with negative TRAb tests have higher chances (but not certainty) to remain in remission [28, 29]. Relapses usually occur in the first year after ATD discontinuation [29].

Answer to Question 3: Both main regimens of ATD therapy (block-and-replace and titration methods) are bound to a high rate of relapsing hyperthyroidism, with no significant differences between the two of them.

Question 4: Are there predictive factors of ATD treatment outcome?

As illustrated in Table 2, in addition to TRAb positivity, several other factors have been proposed to increase the risk of recurrence after drug withdrawal [29, 30]. While for some of them (age, gender, severity of hyperthyroidism, presence of GO) the evidence is not unequivocal, relapses appear to be certainly more frequent in patients with large goiters [29, 31–33] and in smokers [31, 32, 34, 35]. Refrain from smoking seems to reduce the risk of relapse [33]. The postpartum period is a risky period for women with Graves' disease, even if in remission after long-term ATD withdrawal [36]. A Dutch group has recently proposed a predictive model, called Graves' Recurrent Event After Therapy (GREAT) score, based on clinical markers or clinical and genetic markers (GREAT+) which might help to identify at diagnosis patients who are more prone to have a recurrence of hyperthyroidism after ATD treatment [37]. This model needs to be validated by further studies.

Table 2 Factors negatively influencing the outcome of antithyroid drug treatment

Factor	Negative effect on outcome of therapy
Thyroid volume	Yes
TSH receptor antibody persistent positivity	Yes
Smoking	Yes
Postpartum period	Yes
Presence of Graves' orbitopathy	Uncertain
Severity of hyperthyroidism	Uncertain
Age and gender	Uncertain

Answer to Question 4: Large goiter, smoking habit, postpartum period, positive TRAb tests at the end of treatment seem to be the most important risk factors associated with failure of ATD treatment.

Question 5: Are ATDs safe?

ATDs are usually well tolerated and cause either no side effects or minor side effects. Pruritus, itching, and skin reactions usually occur at the beginning of treatment course and when using (at least for MMI) large doses of the drug [9]. These minor side effects, which usually do not require ATD withdrawal or switching from one thionamide to the other, may be treated with antihistamine drugs. The most threatening adverse events are agranulocytosis, liver toxicity, and vasculitis. Agranulocytosis, defined as a granulocyte count $<0.5 \times 10^9$/L, occurs rarely, with an incidence ranging from 0.2 to 1.2 % [38, 39], is usually observed within 3 months after initiation of ATD therapy [40], seems to be, at least for methimazole, dose-related [41], and is more frequent in the elderly [38]. Agranulocytosis may develop abruptly, thus reducing the relevance and usefulness of periodical controls of white blood cell counts, and may even occur during a second or third course of ATD treatment [42]. The mean recovery time of agranulocytosis may not be shortened by the administration of granulocyte

colony stimulating factor [39]. Frequently, patients are not properly informed about this serious adverse event [43]. They should be advised to have an urgent differential white blood cell count done in case of high fever, severe sore throat, or other signs/symptoms of infection [9]. Because cross-reaction between MMI and PTU is common, switching from one drug to the other is not recommended.

Liver toxicity may rarely occur during treatment with MMI (0.03 %) and usually has cholestatic features [44]. Hepatocellular damage, heralded by a marked increase in serum liver transaminases, occurs in 0.07 % of PTU-treated patients (although it may be observed also with methimazole) [44, 45]; it is not dose-related and may be as severe as to cause death or require liver transplantation [45, 46]. MMI or PTU withdrawal should be immediate, as well as the referral to specialized centers. It is unsettled whether periodical assessment of liver function tests, in the absence of suspicious symptoms/signs (jaundice, acolic feces, dark urine, abdominal pain, arthralgias, anorexia, nausea, fatigue), is useful. Noteworthy to recall is that hyperthyroidism per se may cause a slight and transient increase of liver enzymes. Thus, obtaining liver function tests at the time of initial evaluation is useful to avoid misinterpretation of increased serum transaminase levels during ATD treatment.

Vasculitis associated with positivity for antineutrophil cytoplasmic antibody (ANCA) tests occurs in less than 1 % of patients treated with PTU and is even rarer during treatment with MMI [9]. It is characterized by fever, polyarthritis, purpura, renal and lung involvement [20]. At variance with agranulocytosis, it is observed mainly during long-term treatment. Thionamides should be withdrawn, and sometimes immunosuppressive drugs may be required.

Answer to Question 5: Thionamides have an overall low, but not negligible toxicity. Particular attention should be paid to agranulocytosis, liver toxicity, and vasculitis. In view of its better safety profile, MMI is the first choice thionamide.

Question 6: Is RAI treatment safe?

Radioiodine is an effective treatment for Graves' hyperthyroidism [47]. It is given with the deliberate purpose of causing hypothyroidism, which is indeed the final outcome in the large majority of patients [48]. RAI treatment is contraindicated during pregnancy and breast-feeding, and it is not recommended for large goiters or when there is suspicion of associated thyroid malignancy [2]. Adjuvant lithium therapy has been shown to increase the cure rate of hyperthyroidism [49, 50], but probably its most relevant effect is shortening of time to cure [49], which may, however, be important in the elderly with important comorbidities.

Radioiodine treatment can cause progression or de novo development of GO in about 15 % of patients [3]. This is more likely to occur in smokers [51], when mild GO preexists [52], in the presence of high concentrations of TRAb [53]. In these at-risk patients, low doses of prednisone (0.3–0.5 mg/kg body weight as starting dose) for 3 months [54], or even lower doses (0.1–0.2 mg/kg bodyweight) for 6 weeks [55] (steroid prophylaxis) appear to be effective in preventing deterioration of GO [56].

Some studies have reported an increased rate of cardiovascular [57, 58] or cerebrovascular [59] events after RAI treatment, as well as an increase in cancer incidence [59]. However, a recent metaanalysis of seven studies showed no increase in the overall risk of cancer, while the risk of renal and thyroid cancers was only slightly increased [60]. A large Finnish study showed no increase in the overall risk of cancer in patients treated with RAI compared with those treated with thyroidectomy, while hyperthyroidism per se appeared to be associated with an increased risk of gastric and respiratory tract cancers [61]. A recent large study from UK showed that, among patients aged 40 years or more, all-cause mortality was increased during incomplete control of hyperthyroidism with ATDs or after RAI not resulting in hypothyroidism, but not after RAI treatment resulting in hypothyroidism [62]. These data suggest that hyperthyroidism per se, rather the modality of treatment is important.

Multiple treatments with RAI for thyroid cancer may be associated with a decreased male gonadal function [63], but the doses used for hyperthyroidism are devoid of such an effect [64].

Answer to Question 6: RAI is a safe treatment, not associated with an increased all-cause or cardiovascular mortality or an increased overall risk of cancer. RAI treatment bears a small, but definite risk for progression of GO, which, in at-risk patients, can be prevented by steroid prophylaxis.

Question 7: When surgery is selected as definitive treatment, should the surgeon perform subtotal or total thyroidectomy ?

Thyroidectomy is far less frequently used than ATDs or RAI in the management of Graves' hyperthyroidism: In two recent surveys, surgery was selected as primary treatment by 1–2 % of respondents [12, 13]. However, if goiter size is large, there are suspicious nodules, or the patient refuses RAI treatment for recurrent hyperthyroidism, surgery is a valid and effective treatment. In a recent systematic review, thyroidectomy was found to be more than threefold successful than RAI [65]. This is at variance with another systematic review and network meta-analysis which failed to observe any difference in the relapse rate between RAI

and thyroidectomy [66]. Complications of thyroid surgery include hypoparathyroidism, recurrent laryngeal nerve palsy, bleeding, and wound infection [2]. A recent meta-analysis of randomized clinical trials comparing total and subtotal thyroidectomy showed that total (or near-total) thyroidectomy is associated with a lower risk of recurrent hyperthyroidism, with a slightly higher risk of transient hypoparathyroidism, but not with an increased risk of permanent hypoparathyroidism, recurrent laryngeal nerve palsy (either transient or permanent), or bleeding [67]. Selection of a skilled surgeon with a high operative volume is fundamental to reduce the risks of thyroid surgery. Preparation to surgery requires, under most circumstances, restoration of euthyroidism by ATDs [12, 13], while the use of iodine drops (saturated solution of potassium iodide or Lugol's solution) for 10–14 days prior to surgery seems to be used by only one-third of respondents to a recent European survey [13].

Answer to Question 7: If thyroid surgery is the selected form of definitive treatment, total thyroidectomy by a skilled surgeon is the procedure of choice.

Question 8: Should the patient be actively involved in the choice of treatment modality?

The different modalities of therapy for Graves' hyperthyroidism have advantages and disadvantages (Table 3). None of the available treatments is the best for all patients. Therefore, patients' preferences matter and may represent the ultimate reason for selecting either treatment [68]. Shared decision-making is fundamental for selection of the most suitable therapeutic option, because it puts the patient at the center of healthcare and balances benefits against harms of each treatment in the context of the individual patient by considering his/her comorbidities, personal expectations and values, and impact of the disease on quality of life [69]. This approach has been recommended by the American guidelines for hyperthyroidism [21]. Decision aids are tools developed to facilitate evidence-based sharing of information concerning therapeutic option between the clinician and the patient during the clinical encounter, thus increasing the level of involvement of the informed patient in the ultimate choice of treatment. Recently, an encounter tool for shared decision-making regarding treatment of Graves' disease was developed by the Mayo Clinic, with promising results in a pilot study compared to usual care [70]. These results should be confirmed by multicenter trials.

Answer to Question 8: Shared decision-making is fundamental, because the patient should be put at the center of healthcare. This is particularly true in the field of Graves' hyperthyroidism, because none of the available (and imperfect) treatments shows clear-cut superiority on the others.

Question 9: How should hyperthyroidism be treated if GO is present?

Graves' orbitopathy is in most cases associated with hyperthyroidism, although it may, more rarely, occur in euthyroid or even hypothyroid patients [3]. Therefore, a fundamental question is whether treatments for hyperthyroidism may influence, either positively or negatively, the natural history of GO. A widely shared view is that both ATDs and thyroidectomy are somehow neutral to the course of orbital disease [71]. ATDs probably have an indirect positive effect on GO due to correction of hyperthyroidism [72]. As noted above, RAI is associated with a low but definite risk of progression of GO, particularly in smokers [51, 52], which is usually preventable by low-dose oral prednisone in at-risk patients [55]. Thus, a first imperative measure is to correct hyperthyroidism promptly and to maintain euthyroidism stably [54, 73]. In patients with mild GO, any modality of treatment for hyperthyroidism, selected on the basis of

Table 3 Advantages and disadvantages of available treatments for Graves' hyperthyroidism

	Antithyroid drugs	Radioiodine	Thyroidectomy
Advantages	Conservative treatment No risk of permanent hypothyroidism No hospitalization No radiation risk No detrimental effect on GO Use in pregnancy and breast-feeding	Relapses are rare No hospitalization Relatively low cost No anesthetic or surgical risk	No radiation risk No relapse Prompt control of hyperthyroidism No detrimental effect on GO
Disadvantages	High relapse rate Frequent visits and testing Lack of compliance is not infrequent Side effects (rarely major)	Lifelong hypothyroidism Radiation risk (low) Slow control of hyperthyroidism Possible detrimental effect on GO (preventable)	Lifelong hypothyroidism Anesthetic and surgical risk Hospitalization Scar Possible hypoparathyroidism and recurrent laryngeal nerve palsy High cost

standard criteria, can be used, and steroid prophylaxis is recommended in at-risk patients if RAI is administered [74]. In patients with sight-threatening GO, priority should be given to orbital disease; thus, hyperthyroidism should be controlled by ATDs in the meantime that specific treatments are given for the orbital disease [74]. When GO is moderate-to-severe and active, GO should also be promptly treated by intravenous glucocorticoids [54]. Although there is no conclusive evidence that in this clinical setting the conservative approach (ATDs) is superior to the ablative approach (RAI or thyroidectomy, alone or in combination) [75–77], some experts prefer to cure GO first, maintaining meanwhile the patient under long-term ATD treatment [24, 27]. This issue remains controversial, because other expert thyroidologists treat GO and hyperthyroidism with a definitive therapy at the same time [11].

Answer to Question 9: With the exception of the emergent and sight-threatening GO, any modality of treatment for hyperthyroidism can be selected in patients with GO, particularly if mild. In moderate-to-severe and active GO, there is no evidence for a superiority of the conservative compared to the ablative approach, and selection of treatment for hyperthyroidism relies on personal experience and shared decision-making.

Question 10: How should hyperthyroidism be treated during pregnancy?

Antithyroid drugs are the treatment of choice for Graves' hyperthyroidism during pregnancy, because RAI is contraindicated and thyroidectomy (to be performed in the second trimester) should be limited to exceptional cases of intolerance to or severe side effects of ATDs [78]. Pregnant women should be given PTU during the first trimester, and then switched to MMI during the second and third trimesters [79, 80]. The reason for this is based on reports showing that exposure to MMI during the first trimester is associated with a higher rate of fetal malformation (so-called CBZ/MMI embryopathy) [81, 82], but, on the other hand, PTU may be associated with severe liver toxicity in the mother [83]. A recent Danish nationwide study showed that both MMI and PTU may be associated with malformations, even if the spectrum of birth defects is different and probably milder with PTU [84, 85]. A recent study from Italy observed that rate of major malformations in newborns of mothers treated with either ATD was not higher than in the general population [86]. An insurance database of more than 900,000 pregnant women in USA showed a 13 % increased risk of birth defects in women who were hyperthyroid compared to those without a diagnosis of hyperthyroidism, with no association with ATD use [87]. However, a Japanese study failed to find an association between maternal hyperthyroidism and birth defects [88]. Although some negative studies may have limitations (e.g., small sample size, lack of study outcomes at optimal ages) [89], this issue still is somehow controversial. For the time being, it appears reasonable to follow current guidelines using the lowest dose of ATD (PTU in the first trimester, MMI in the second and third trimesters), which maintains serum FT4 at the upper limit of the normal range [79, 80].

Answer to Question 10: ATDs are the treatment of choice during pregnancy. PTU should be used during the first trimester, and MMI during the remaining trimesters. The lowest dose of ATD should be employed, maintaining serum FT4 levels at the upper normal limit.

Question 11: Which is the best approach to Graves' hyperthyroidism in childhood?

Graves' disease is the most common cause of hyperthyroidism in children [6]. As for adults, ATD treatment is the first-line treatment in children. Because of liver toxicity of PTU also in children [90], MMI is the ATD of choice, usually given using the titration regimen [6]. Permanent remission of hyperthyroidism is even lower than in adults, averaging 30 % or less [6, 91]. It is uncertain whether continuing ATD treatment for many years may increase the rate of remission, but this approach may be reasonable in children who are too young for surgery or RAI treatment [6]. Thus, most children with hyperthyroidism due to Graves' disease will eventually need a definitive treatment. Although evidence is limited, long-term data in patients given RAI during childhood seem reassuring [6, 92]. Thus, RAI should be considered as a possible option in children with small goiter. Based on theoretical considerations on the possible risks of malignancy following RAI treatment in children, this should be delayed as much as possible and avoided in children younger than 10 year [22]. On the other side, thyroidectomy in children seems to be afflicted by a higher burden of complications with respect to adults [93]. When surgery is chosen, it should be performed by a skilled, high-volume surgeon [6].

Answer to Question 11: ATDs are the treatment of choice for Graves' hyperthyroidism in childhood, and MMI should be used. Treatment may need to be continued longer that in adults. Remission rate is low, and definitive treatment is often required. RAI may be used in children with small goiter, delaying treatment as much as possible. When surgery is chosen, it should be performed by a skilled, high-volume surgeon.

Question 12: Which is the treatment approach to immune reconstitution Graves' disease?

Graves' disease may develop following immune reconstitution from a lymphopenic condition [94]. This has been reported in patients treated with alemtuzumab for multiple sclerosis [95, 96], during highly active antiretroviral therapy (HAART) for HIV infection [97, 98], or following bone marrow or hematopoietic stem cell transplantation [99, 100]. Although evidence is scant, it would appear that Graves' disease occurring under these circumstances may more frequently be associated with remission of hyperthyroidism (or even progression to hypothyroidism) after ATD treatment [101, 102]. Accordingly, ATDs should be considered the first-line treatment in these patients.

Answer to Question 12: ATDs are the treatment of choice for Graves' hyperthyroidism occurring during immune reconstitution.

Concluding remarks

Unmet needs remain in the field of management of Graves' hyperthyroidism. The fundamental problem is that, despite better understanding of the pathogenesis of Graves' disease, therapies targeting pathogenic pathways are presently lacking. Current treatments are largely imperfect, but evidence may help optimizing their use in different clinical settings.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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