Treatment of Graves' Disease

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Luigi Bartalena

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Abstract

Treatment of hyperthyroidism due to Graves' disease relies on the use of antithyroid drugs, radioiodine treatment, or thyroidectomy. None of these treatments are perfect, because they are not therapies targeting pathogenic mechanisms of the disease. Selection of either treatment is based on several criteria, but the choice should be shared with the informed patient. The major extrathyroidal manifestation of Graves' disease, i.e., Graves' orbitopathy, when moderate and active should be treated with high doses of intravenous glucocorticoids. This chapter provides an overview of treatment options for both hyperthyroidism and extra-

L. Bartalena (✉)
Department of Medicine and Surgery, University of Insubria, Endocrine Unit, ASST dei Sette Laghi, Ospedale di Circolo, Varese, Italy
e-mail: luigi.bartalena@uninsubria.it

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thyroidal manifestations, underscoring advantages and disadvantages of therapies, as well as preferred strategies in case of under particular circumstances, such as pregnancy and childhood.

Keywords
Graves' hyperthyroidism · Antithyroid drugs · Thionamides · Methimazole · Propylthiouracil · Radioiodine · Thyroidectomy · Pregnancy · Childhood · Subclinical hyperthyroidism · Graves' orbitopathy · Thyroid dermopathy

Introduction

Graves' disease is an autoimmune disorder and the most frequent cause of hyperthyroidism in iodine-sufficient areas (Bartalena 2013). Although recent years have witnessed relevant improvement in understanding the pathogenic mechanisms underpinning thyroid and extrathyroidal manifestations of this disease (see ▶ Chap. 14, "Graves' Disease" and ▶ 15, "Graves' Ophthalmopathy"), progress in the management has not been equally impressive. As a matter of fact, management of Graves' hyperthyroidism is still based on treatments used for the last 60–70 years (Bartalena 2013). All of these treatments are imperfect, because they do not target pathogenic mechanisms of disease, and either are associated with a high rate of recurrent hyperthyroidism (antithyroid drugs (ATDs)) or cause lifelong hypothyroidism (radioactive iodine (RAI) or thyroidectomy) (Fig. 1). Recently published guidelines (Ross et al. 2016) or reviews (Burch and Cooper 2015; Bartalena et al. 2016c; De Leo and Braverman 2016; Smith and Hegedus 2016) are a helpful guidance for the reader, but reflect the limited evidence currently available. The same considerations can be

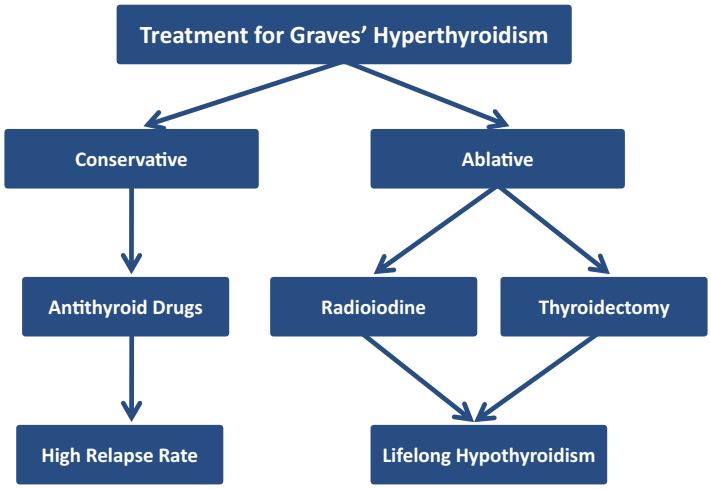

Fig. 1 Current treatments for hyperthyroidism due to Graves' disease and their limitations

applied to the major extrathyroidal expression of Graves' disease, Graves' orbitopathy (GO), although guidelines for its management have recently been published (Bartalena et al. 2016a), the very rare cutaneous manifestation, thyroid dermopathy (or pretibial myxedema), and the exceptional thyroid acropachy.

Treatment of Hyperthyroidism

None of the available treatments for Graves' hyperthyroidism fulfill all of the criteria for an ideal treatment for hyperthyroidism, which should eliminate the pathogenic factors, restore euthyroidism, avoid permanent hypothyroidism, and prevent development or progression of GO. Ideally, it should also be devoid of side effects, while having no negative impact on quality of life. Therefore, the choice of ATDs, RAI, or thyroidectomy as first-line treatment is often conditioned by physician's preference and experience, availability of facilities for RAI treatment, availability of a skilled surgeon, and costs (Bartalena 2013). Of particular importance is a shared decision-making process involving the informed patient and taking into account not only advantages and disadvantages, safety, and side effects of different treatments but also patient expectations and values (Brito et al. 2015). There are geographical differences in selecting treatments. While ATDs are the first choice in Europe, Asia, Oceania, and Latin America, RAI is preferred in North America (Burch et al. 2012; Bartalena et al. 2016b). However, recent reports suggest that ATDs are becoming increasingly popular as first-line treatment also in the USA (Emiliano et al. 2010; Brito et al. 2016). Worldwide, thyroidectomy is rarely used as first-line treatment (Bartalena 2013).

Antithyroid Drugs

Drugs and Regimens

Three thionamide-derived ATDs are currently used: *carbimazole* (CBZ), rapidly converted to its active (and more widely used) metabolite, *methimazole* (thiamazole, MMI), and *propylthiouracil* (PTU). These drugs mainly exert their effect by reducing thyroid hormone synthesis through inhibition of the enzyme thyroperoxidase (Cooper 2005). In addition, they may have some immunosuppressive actions, either direct or indirect, i.e., mediated by restoration of euthyroidism (Cooper 2005). PTU exerts also a peripheral effect consisting in the inhibition of dediodinase-mediated thyroxine (T4) to triiodothyronine (T3) conversion. In the initial phases of treatment, β-blockers (propranolol, atenolol, metoprolol) are useful to control heart rate prior to restoration of euthyroidism by ATDs, but should not be used in patients suffering from asthma (Cooper 2005). It is widely accepted that MMI should be preferred to PTU, except for particular situations, such as the first trimester of pregnancy (see section "Pregnancy"), thyroid storm (see section "Thyroid Storm"), or in patients experiencing minor side effects during MMI treatment and unwilling to undergo definitive treatment by RAI or surgery (Ross et al. 2016). MMI can be taken once daily, while PTU requires fractionated doses because of its shorter half-life.

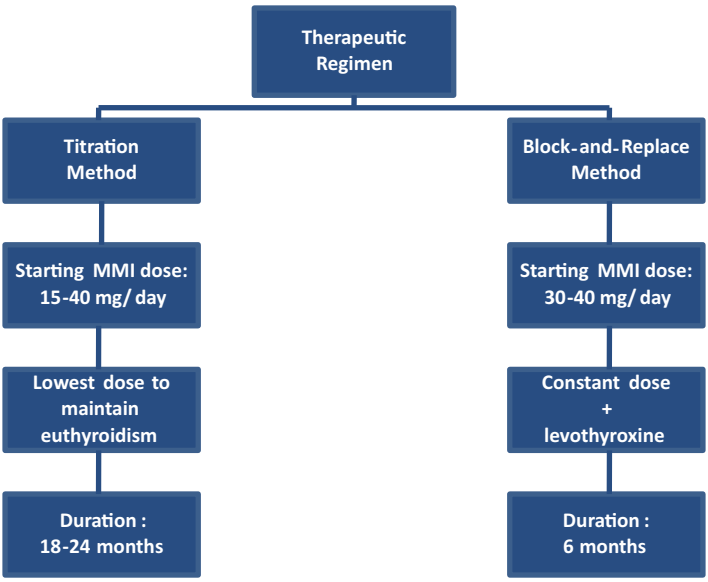

Fig. 2 Regimens of antithyroid drug treatment. *MMI* methimazole

There are two main regimens of ATD treatment: the "titration method" and the "block-and-replace method" (Fig. 2**)**. In both cases MMI is started with an initial daily dose of 10–40 mg (100–400 mg of PTU), depending on the severity of hyperthyroidism (Ross et al. 2016). After restoration of euthyroidism (usually in 4–6 weeks), in the titration method, the dose of MMI is gradually reduced to the lowest dose maintaining euthyroidism (usually 2.5–10 mg/day), and the treatment is continued for 12–18 months, because shorter courses have been reported to increase the likelihood of relapsing hyperthyroidism (Abraham et al. 2005). Longer periods of treatment may be considered in patients in whom serum TSH-receptor antibodies (TRAb), the ultimate cause of Graves' hyperthyroidism, are still detectable in serum, or in particular situations, such as in the elderly with important comorbidities. In the block-and-replace regimen, after restoration of euthyroidism, MMI is continued at the initial high doses, but levothyroxine is added to prevent hypothyroidism. This treatment is usually not continued for more than 6 months, because longer courses do not seem to increase the probability of achieving a permanent remission of hyperthyroidism (Abraham et al. 2005). The two regimens do not differ substantially in terms of risk of recurrences after drug withdrawal; the block-and-replace seems to bear a slightly higher risk of side effects (Abraham et al. 2005). In countries where high-dose (20–30 mg) tablets of MMI are unavailable, the high number of tablets per day in the block-and-replace regimen may jeopardize patient adherence to therapy. The block-and-replace regimen should not be used in pregnancy. In a recent European questionnaire-based survey, the titration method was preferred by 36% of respondents and the block-and-replace by 26%, while the remaining 38% would use the block-and-replace method *only* in selected cases (Bartalena et al. 2016b). The recent American guidelines underscore that the block-and-replace regimen is generally not recommended (Ross et al. 2016).

Table 1 Predictive factors of recurrence of hyperthyroidism after antithyroid drug treatment

Factor	Impact on the risk of recurrence
Age	Uncertain, probably higher risk of recurrence in the young
Gender	Uncertain
Thyroid size	Higher risk when goiter is large
Severity of hyperthyroidism	Uncertain
TSH-receptor antibody (TRAb)	High risk if TRAb is still positive at the end of treatment
Graves' orbitopathy (GO)	Uncertain, but high risk of relapse if GO is severe
Long-term treatment	Possible higher remission rate after long-term treatment
Smoking	Higher risk of relapse in smokers
Postpartum period	High risk of relapse in the postpartum period, also in women in remission

Outcome of Treatment

One of the major limitations of ATD treatment is the high rate of recurrences after treatment withdrawal (Piantanida et al. 2015). Relapses occur in 30–70% of ATD-treated patients (Bartalena 2013). Predictive factors of relapsing hyperthyroidism include large thyroid volume, young age, smoking, the postpartum period (Piantanida et al. 2015) (Table 1**)**. Probably TRAb is the most important predictor of ATD treatment outcome. High TRAb levels at diagnosis have been associated with an 84% risk of relapse over a 4-year period of follow-up (Tun et al. 2016). Even more important is the autoantibody status at the end of treatment, particularly using highly sensitive immunoassays. The large majority of TRAb-positive patients relapse (Tun et al. 2016), indicating that these patients should either continue ATD treatment longer or be switched to a definitive treatment with RAI or surgery (Piantanida et al. 2015). However, it should be underscored that also patients who are TRAb negative at the end of treatment relapse in about 30% of cases (Törring et al. 1996; Barbesino and Tomer 2013). Most relapses occur within 6–12 months after ATD discontinuation (Vitti et al. 1997), but regular monitoring of thyroid function is advised also after that period.

Side Effects

ATDs are generally well tolerated, but they may be associated with side effects (Table 2). These are usually mild and, at least in the case of MMI, most commonly observed during the initial phase of treatment, when relatively higher doses of the drug are given (Cooper 2005). Frequent side effects, such a skin reaction or itching, do not require treatment withdrawal, are usually transient, and can be controlled with antihistamines (Bartalena et al. 2016c). The most serious adverse events are hepatotoxicity, agranulocytosis, and vasculitis. *Hepatotoxicity* is rare using methimazole (0.03%), usually, although not always, with cholestatic characteristics (Wang et al. 2014), while it is more frequent, usually with features of hepatocellular necrosis, in PTU-treated patients (Wang et al. 2014; Yang et al. 2015). Hepatocellular necrosis may occur abruptly and be rapidly progressive and potentially lethal, requiring liver transplantation (Ruiz et al. 2003; Wang et al. 2014; Yang et al. 2015; Bartalena et al. 2016c; Ross et al. 2016). PTU hepatotoxicity is more common in children, and therefore, some authors discourage its

Table 2 Side effects of antithyroid drugs

	Side effect	Frequency
Blood	Mild leukopenia	Relatively frequent
	Agranulocytosis	Rare (0.2–1.2%)
	Aplastic anemia	Very rare
	Thrombocytopenia	Very rare
Skin	Skin rash	Relatively frequent (>5%)[a]
	Urticaria	Relatively frequent (>5%)[a]
	Itching	Relatively frequent (>5%)[a]
	Aplasia cutis	Very rare (MMI)
Liver	Hepatocellular necrosis	Very rare (PTU) (0.07%)
	Cholestasis	Very rare (MMI/CBZ) (0.03%)
Collagen	Polyarthritis	Uncommon
	SLE-like syndrome	Very rare (PTU>MMI)
	Vasculitis	Very rare (PTU>MMI) (<1%)
Miscellaneous	Loss of taste	Rare (MMI)
	Hypothrombinemia	Rare (PTU)
	Hypoglycemia	Very rare (MMI)

MMI methimazole, *CBZ* carbimazole, *PTU* propylthiouracil
[a]These side effects are usually transient, do not require antithyroid drug withdrawal, and can be controlled with anti-histamines

use, particularly in the pediatric population (Rivkees and Szarfman 2010). It should be mentioned that hyperthyroidism per se may account for an increase in serum transaminase or other liver enzyme levels that usually normalize upon restoration of euthyroidism. If, however, a sudden increase of more than threefold in serum transaminase concentrations is found during PTU (or, more rarely, MMI) treatment, ATDs should be immediately withdrawn. The usefulness of routine monitoring of liver function tests, in the absence of suspicious symptoms or signs (such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain, dark urine, acholic feces), has not been demonstrated (Kim et al. 2001; Ross et al. 2016). *Agranulocytosis*, i.e., a granulocyte count $<0.5 \times 10^9$/l, is an infrequent (0.2–1.2%) (Watanabe et al. 2012; Yang et al. 2016) but potentially lethal adverse event. Its onset is usually abrupt, making the value of routine white blood cell (WBC) count monitoring questionable (Bartalena et al. 2016c). The patient should be informed that an urgent WBC count should be obtained in the presence of high fever, sore throat, or other signs/symptoms of infection (Cooper 2005). If agranulocytosis develops, ATDs should be immediately discontinued. It is uncertain whether therapy with granulocyte colony-stimulating factor may shorten the time of recovery from agranulocytosis (Fukata et al. 1999; Yang et al. 2016). *Vasculitis* associated with positive antineutrophil cytoplasmic antibody (ANCA) tests is observed in <1% of ATD-treated patients, more frequently with PTU than with MMI (Bartalena et al. 2016c). It is heralded by fever, polyarthralgias, and renal and lung involvement and is more frequently observed during long-term therapy (Bartalena et al. 2016c).

MMI should be preferred to PTU for its more favorable safety profile. If minor side effects using either MMI or PTU occur, the other thionamide can be used, but

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

Treatment	Advantages	Disadvantages
Antithyroid drugs	Conservative treatment	High relapse rate
	No hospitalization required	Frequent visits and testing
	Low risk of hypothyroidism	Lack of compliance
	No radiation	Adverse events (rarely major)
	No negative effect on GO	
	Use during pregnancy and breastfeeding	
Radioiodine	Definitive treatment	Lifelong hypothyroidism
	Relatively low cost	Radiation risk
	No hospitalization required	Slow control of hyperthyroidism
	No anesthetic/surgical risk	Possible progression or de novo occurrence of GO
Thyroidectomy	Definitive treatment	Lifelong hypothyroidism
	No radiation risk	Anesthetic/surgical risk
	Prompt control of hyperthyroidism	Hospitalization
	No negative effect on GO	Cost Permanent scar

cross-reactivity between the two drugs is common. Therefore, in case of serious side effects, exposure to the alternative thionamide is contraindicated. For ATD treatment in pregnancy, see section Pregnancy.

Advantages and Disadvantages

As illustrated in Table 3, ATD treatments have advantages and disadvantages. The major advantage is that it is a conservative treatment, thus avoiding destruction (by RAI) or removal (by thyroidectomy) of the thyroid (Bartalena et al. 2016c). Therefore, there is no risk of permanent hypothyroidism, unless the latter reflects the natural evolution of the underlying autoimmune thyroid disorder. Overall, thionamides have an acceptable safety profile, particularly if low doses of the drug are sufficient, as in the majority of cases, to maintain stable euthyroidism. As pointed out above, careful surveillance is, however, required for potential treatment-related adverse events. No hospitalization is required, neither radiation risks nor detrimental effects on GO are associated with ATDs. These drugs can be used, with some precautions, during pregnancy and breastfeeding (Ross et al. 2016) (see section Pregnancy). The major drawback of ATD treatment is the high rate of recurrences that requires either a second course of pharmacological treatment or an ablative treatment, thereby simply postponing the final treatment of hyperthyroidism (Bartalena et al. 2016c). The lack of compliance with treatment is not infrequent, but this is a general problem that can occur also with levothyroxine treatment for hypothyroidism following RAI treatment of thyroidectomy. Frequent visit and testing is required during the treatment course.

Radioiodine Treatment

Modalities of Radioiodine Administration

RAI therapy is performed using ^{131}I. This radioisotope (β and γ radiation emitter) is rapidly concentrated into the thyroid, where it causes progressive thyrocyte necrosis, fibrosis, and glandular atrophy (Ross 2011; Bonnema and Hegedus 2012). RAI treatment is still the preferred treatment in North America (Burch et al. 2012). ^{131}I can be administered in fixed amounts or as calculated doses based on thyroidal RAI uptake and half-life determination and thyroid size (Bonnema and Hegedus 2012). However, evidence of the superiority of such calculations and consensus on the use of either approach are missing. In a survey among UK endocrinologists, it appeared that fixed doses are employed by 70% of respondents (Vaidya et al. 2008). Whether RAI should be administered after restoration of euthyroidism with ATDs is also a matter of argument. The recent American guidelines state that pretreatment with MMI might be considered only in patients who are at risk of complications due to exacerbation of hyperthyroidism after ^{131}I treatment (e.g., patients with relevant cardiovascular comorbidities, or in the elderly) (Ross et al. 2016). In European countries, RAI treatment is carried out after ATD pretreatment in the large majority of cases (Bartalena et al. 2016b). MMI, in any case, is preferred to PTU, because the latter might have radioprotective effects and reduce the efficacy of RAI treatment (Bartalena 2013). ATDs are usually withdrawn 5–7 days before RAI administration; they are resumed 7–10 days after treatment only in patients whose hyperthyroidism, because of associated comorbidities, must be promptly controlled, before RAI stably controls thyroid hyperfunction (Bartalena 2013). Lithium carbonate, administered concomitantly with RAI and continued for a few weeks, may facilitate prompt control of hyperthyroidism in these at-risk patients, although it does not increase the long-term cure rate achieved with RAI therapy (Bogazzi et al. 2010).

Outcome of Treatment

RAI treatment is given with the deliberate purpose of inducing hypothyroidism, which, indeed, represents the final outcome in the large majority of patients (Vaidya et al. 2008; Bonnema and Hegedus 2012). Doses of RAI should be generous enough to achieve this goal. The use of low activities, aiming at restoring euthyroidism without inducing hypothyroidism, is associated with an increased risk of retreatment (Bonnema and Hegedus 2012). As a matter of fact, a small proportion (5–10%) of patients require a second dose of RAI, which should not be given earlier than 6 months after the first treatment (Burch and Cooper 2015).

Contraindications and Safety Measures

RAI is absolutely contraindicated during pregnancy and breastfeeding. A pregnancy test should be obtained 2 days before treatment in women with childbearing potential (Ross et al. 2016). Pregnancy should be postponed for 4–6 months in women, also allowing for stable restoration of euthyroidism, and for 3–4 months in men to permit sperm production turnover (Ross et al. 2016). Practice guidelines from the American Thyroid Association recommend avoiding RAI treatment if the woman has

Table 4 Safety of radioiodine

Side effect	Action
Exacerbation of hyperthyroidism	Debated. Pretreat with antithyroid drugs
Actinic thyroiditis	Rare and usually transient. Treat with steroids
Sialadenitis	Lemon juice
Teratogenicity	Not relevant. Pregnancy postponed for 6 months after RAI treatment
Cardiovascular and cerebrovascular risk	Recent data are reassuring. Related to hyperthyroidism per se rather than to RAI treatment
Cancer	Slight increase in the risk of thyroid and renal cancer. Likely role of hyperthyroidism per se
Graves' orbitopathy	Possible de novo occurrence or progression in at-risk patients (mainly smokers). Preventable by low-dose oral prednisone given concomitantly with RAI

interrupted breastfeeding since less than 6 weeks, to reduce radiation exposure of the breast tissue (Sisson et al. 2011). RAI is also contraindicated if thyroidal iodine uptake is low, e.g., because of iodine contamination, or there are nodules suspicious for being malignant. Very large goiters may require more than one treatment and should probably be preferably treated surgically.

Radiation safety measures, such as sleeping alone for 3–6 days or keeping a distance of 1 m from adults and 2 m from pregnant women and children, have been recommended (Sisson et al. 2011), but vary among countries and are dependent on the administered activities (Bonnema and Hegedus 2012).

Side Effects

In the early period after RAI therapy, transient *exacerbation of hyperthyroidism* may occur because of the cytolytic effect of RAI (Table 4). Whether ATD pretreatment, which reduces intrathyroidal thyroid hormone stores, may avoid this phenomenon is debated (Bonnema et al. 2003; Bonnema and Hegedus 2012). In a recent European survey, 61% of expert thyroidologists always treat patients with ATDs prior to RAI treatment, and only 4% never do so, while the remaining 35% pretreat with ATDs in the presence of relevant comorbidities (Bartalena et al. 2016b). Sometimes RAI therapy may be followed by *actinic thyroiditis*, heralded by thyroid pain and swelling. This is usually mild and transient, not requiring treatment (Bonnema and Hegedus 2012). *Sialadenitis* may also occur, involving submandibular glands and parotids, but these phenomena are permanent in a minority of patients (Bonnema and Hegedus 2012). Lemon juice may help reduce this side effect. *Teratogenicity* does not seem to be an issue in thyroid cancer patients treated with RAI doses higher than those used for hyperthyroidism (Sawka et al. 2008). Doses of RAI used for hyperthyroidism are not not associated with a decreased male gonadal function (Ceccarelli et al. 2006). Graves' hyperthyroidism per se is associated with increased morbidity and mortality (Brandt et al. 2011, 2013a, b). While some studies reported an increased risk of *cardiovascular* (Franklyn et al. 1998; Metso et al. 2007) and *cerebrovascular* events, as well as occurrence of *cancer* (La Cour et al. 2015) following

RAI treatment, a recent meta-analysis failed to reveal any overall increased risk of cancer, except for a slight increase in the risk of thyroid and renal cancer (Hieu et al. 2012). A recent Finnish study observed, however, an increased risk of gastric and respiratory tract cancer due to hyperthyroidism per se, with no difference between patients treated with RAI or thyroidectomy (Ryodi et al. 2015). In addition, a recent study from the UK showed that all-cause mortality (including cardiovascular mortality) was increased during ATD treatment when control of hyperthyroidism was poor or when RAI treatment did not cause hypothyroidism, but not in RAI-treated patients developing hypothyroidism (Boelaert et al. 2013).

RAI treatment can cause **progression or de novo development of** GO, particularly in smokers (Träisk et al. 2009) in patients with preexisting GO (Bartalena et al. 1998), or with high-serum TRAb levels (Eckstein et al. 2006). This occurs in approximately 15% of cases, is often transient, and can be prevented by a concomitant short-term course of low-dose oral prednisone (steroid prophylaxis) (Shiber et al. 2014). Steroid prophylaxis is recommended in at-risk patients, but can be avoided in patients with long-term inactive GO, or in those without risk of progression (Bartalena et al. 2016a). Post-RAI hypothyroidism should be avoided or promptly controlled by levothyroxine replacement, because it is an important risk factor for RAI-associated progression of GO (Tallstedt et al. 1994; Perros et al. 2005).

Advantages and Disadvantages

RAI has advantages and disadvantages (Table 3). The former include the relatively low cost, no need for hospitalization, and the lack of anesthetic and surgical risk. It is, however, an ablative treatment, and the patient is bound to lifelong thyroid hormone replacement therapy to correct hypothyroidism. Control of hyperthyroidism is not immediate, there is a small radiation risk, and GO may progress or de novo occur, particularly in smokers (Bonnema and Hegedus 2012).

Thyroidectomy

Thyroidectomy is the least commonly used among the three available therapies for newly diagnosed Graves' hyperthyroidism, since it is selected in no more than 1–2% of cases (Burch et al. 2012; Bartalena et al. 2016b). It is, however, indicated in the presence of suspicious nodules, when hyperthyroidism relapses after ATD treatment and goiter is large or the patient refuses RAI treatment, or if facilities for RAI treatment are not available (Bartalena 2013). A recent meta-analysis showed greater effectiveness of surgical treatment compared to RAI treatment in terms of risk of relapsing hyperthyroidism (Genovese et al. 2013). This is, however, controversial, because another systematic review failed to show any significant difference between the two definitive treatments (Sundaresh et al. 2013).

Extent of Thyroidectomy

If thyroidectomy is the selected treatment, near-total or total thyroidectomy should be the procedure of choice, because subtotal thyroidectomy is associated with a

higher chance of relapse of hyperthyroidism, while the rate of complications is not significantly different (Genovese et al. 2013; Guo et al. 2013).

Preparation to Surgery

Patients should be rendered euthyroid by ATDs prior to surgery, to avoid the risk of exacerbation of hyperthyroidism caused by anesthetic and surgical stress, as well as by thyroid manipulation (Ross et al. 2016). Although recent guidelines recommend that iodine drops (KI, saturated solution of KI, Lugol's solution) be given preoperatively for 10 days (Ross et al. 2016), in clinical practice, at least in Europe, they are used by no more than one third of respondents to a recent survey (Bartalena et al. 2016b). Indeed, they are useful to reduce thyroid vascularity and intraoperative blood loss (Erbil et al. 2008). In the event that thyroidectomy is an emergency procedure, and to achieve a rapid control of hyperthyroidism, in addition to ATDs and iodinated drops, glucocorticoids, β-blockers, and, possibly, cholestyramine can be used (Ross et al. 2016).

Complications

Thyroid surgery may be complicated by hypoparathyroidism (transient or permanent) and cause hypocalcemia and recurrent laryngeal nerve palsy (transient or permanent), causing hoarseness, bleeding, or wound infection (Bartalena et al. 2016c) (Table 5). Calcium and vitamin D status should be assessed preoperatively and repleted, if required, or even given prophylactically (Ross et al. 2016). If the patient is inadequately prepared by ATDs, thyroid surgery may be followed by a marked worsening of thyrotoxicosis. The rate of complications following thyroidectomy is inversely correlated with the surgeon's experience (Sosa et al. 2008). Accordingly, to minimize the risks of thyroid surgery, it is fundamental to select a skilled surgeon with a high annual volume of thyroidectomies (Bartalena et al. 2016c).

Advantages and Disadvantages

Advantages of thyroidectomy include the absence of radiation risk, the prompt control of hyperthyroidism, the lack of detrimental effects on GO, the absence of radiation risk (Table 3). On the other hand, it implies an anesthetic and surgical risk and requires hospitalization, a permanent scar will be left, and costs are higher than

Table 5 Complications of thyroidectomy

Complication	Action
Exacerbation of hyperthyroidism	Render the patient euthyroid with antithyroid drugs prior to surgery
Hypoparathyroidism	May be transient or permanent. Give vitamin D and calcium preoperatively in at-risk patients
Laryngeal nerve palsy	May be transient or permanent. Intraoperative neuromonitoring of laryngeal nerve helps to detect early damage
Blood loss and hemorrhage	Preoperative treatment with saturated solution of KI or Lugol's solution reduces thyroid vascularity
Wound infection	Accurate care of the wound, drainage, antibiotics

using the other modalities of treatment (Table 3) (Bartalena 2016c). However, in one US study, surgery was more cost-effective than lifelong ATDs or RAI treatment (In et al. 2009). As for RAI treatment, total thyroidectomy is inevitably bound to permanent hypothyroidism and lifelong levothyroxine replacement therapy.

Role of Patients in Selecting Therapy

Because all of the available therapeutic options for Graves' hyperthyroidism have limitations, patient choice may eventually constitute the reason for the choice of treatment. In this regard, shared decision-making is an essential process, because it puts the patient at the center of healthcare taking into account his/her wishes, values, expectations, impact on quality of life, and comorbidities (Ting et al. 2014). The level of involvement of the informed patient can be increased by encounter tools for shared decision-making, such as that recently developed by the Mayo Clinic Specialists (Brito et al. 2015).

Special Situations

Pregnancy (see also ▶ Chap. 23, "Thyroid Physiology and Thyroid Diseases in Pregnancy")

Because RAI treatment is contraindicated, and thyroidectomy should be performed (during the second trimester) only in exceptional cases, such as intolerance to or major adverse events due to ATDs, thionamides represent the treatment of choice for Graves' hyperthyroidism in pregnant women (DeGroot et al. 2012; Stagnaro-Green et al. 2011). According to recent guidelines, PTU should be used during the first trimester and replaced by MMI during the second and third trimester (Ross et al. 2016). This approach is motivated by the observation that exposure to MMI in early pregnancy is associated with an increased risk of fetal malformations (CBZ/MMI embryopathy) (Bowman et al. 2012), but, on the other hand, PTU can cause severe hepatotoxicity in the mother (Cooper and Rivkees 2009) (Table 6). Recent studies from Denmark reported that both MMI and PTU can indeed cause fetal malformations, although those caused by PTU are probably milder (Linding Andersen et al. 2013, 2014). A recent retrospective Italian study found that the rate of malformations in the offspring of women exposed to MMI was not higher than in the general population (Gianetti et al. 2015). A large American insurance database study reported a 13% increase in fetal malformations in hyperthyroid women, but no association with ATD treatment (Korelitz et al. 2013). In addition, a study from Japan did not find any increase in hyperthyroidism-associated malformations (Yoshihara et al. 2012). Despite these controversial results, it seems advisable to follow current guidelines, using PTU in the first trimester and switching to MMI in the second and third trimesters (Bartalena et al. 2016c). Furthermore, the lowest dose of ATDs should be employed during pregnancy, keeping serum FT4 in the upper third of normal range (Bartalena et al. 2016c).

Table 6 Birth defects that have been associated with exposure to carbimazole/methimazole and propylthiouracil in early pregnancy

Carbimazole/methimazole	Propylthiouracil
Choanal atresia	Face and neck (preauricular sinus/cyst)
Omphalocele	Fistula of branchial cleft
Esophageal atresia	Congenital hydronephrosis
Omphalomesenteric duct anomalies	Single cyst of the kidney
Aplasia cutis	Posterior urethral valve
Malformations of the nipples	Megaureter
Anomalies of the eyes	
Malformations of the circulatory system (heart septal defect, ventricular septal defect, pulmonary valve stenosis, pulmonary artery stenosis)	
Malformations of the urinary system	

Derived from Linding Andersen et al. (2013, 2014)

Childhood

Graves' disease is the most frequent etiology of hyperthyroidism in childhood (Rivkees 2016). ATDs represent the first-line therapy in children, and MMI is the preferred thionamide, based on a better safety profile, just as in adults (Rivkees and Szarfman 2010; Rivkees 2016). Unfortunately, the rate of relapses after ATD withdrawal is higher than in adults (Havgaard Kjaer et al. 2015). Although it is unsettled whether long-term ATD treatment for many years may increase the chance of a permanent remission, this approach is reasonable for children who are too young for RAI treatment or surgery, but in the end most of the children will need an ablative treatment (Rivkees 2016). Although data are reassuring on long-term safety of RAI, according to recent American guidelines, RAI treatment should be avoided if children are <5 years of age (Ross et al. 2016). Thyroidectomy is a valid option in children, although it seems to be associated with a higher risk of complications (Rivkees 2016). Therefore, thyroidectomy should be opted for in children who are too young to be treated with RAI, and it should be performed by a skilled surgeon, as in adults (Ross et al. 2016).

Presence of Graves' Orbitopathy (see also ▶ Chap. 15, "Graves' Ophthalmopathy")

Management of hyperthyroidism in patients with associated GO is challenging (Table 7). Patients with mild GO can be treated with either of therapeutic options (ATDs, RAI treatment, or thyroidectomy). If RAI is selected and the patient has mild signs or symptoms of activity, steroid prophylaxis is recommended in most of the patients (see Radioiodine Treatment) (Bartalena et al. 2015). When GO is very severe and sight-threatening, priority should be given to the cure of GO (medically or surgically), and hyperthyroidism should be controlled with ATDs (Bartalena et al. 2015). If GO is moderate-to-severe, but stably inactive, hyperthyroidism can be treated by any of the available treatments without any particular precaution

Table 7 Treatment of Graves' hyperthyroidism in the presence of Graves' orbitopathy

Severity of GO	Activity of GO	Treatment for hyperthyroidism
Mild	Active	Any treatment for hyperthyroidism, depending on standard criteria and patient choice. If RAI is selected, steroid prophylaxis (see text) is advised
Mild	Inactive	Any treatment for hyperthyroidism, as above. Steroid prophylaxis after RAI is not necessary in the absence of risk factors for RAI-associated progression of GO (smoking, high TRAb levels)
Moderate to severe	Active	Priority should be given to prompt management of GO with intravenous glucocorticoids. It is unsettled whether hyperthyroidism should be in the meanwhile treated conservatively or whether the thyroid should be concomitantly ablated
Moderate to severe	Inactive	Any treatment for hyperthyroidism, as above. No steroid prophylaxis is required
Sight threatening (dysthyroid optic neuropathy and/or corneal breakdown)	Active	Emergent treatment for GO (high doses of intravenous glucocorticoids and/or orbital decompression). Keep the patient euthyroid with antithyroid drugs, and postpone definitive treatment until GO is cured

concerning GO. If moderate-to-severe GO is in its active phase, it should be treated promptly, because efficacy of treatment is inversely related to duration of GO (Bartalena et al. 2016c). Under these circumstances, it is still unsettled whether ATDs, given for prolonged periods of time, are preferable to thyroid ablation performed concomitantly with the management of GO (Bartalena et al. 2015).

Subclinical Hyperthyroidism (see also ▶ Chap. 14, "Graves' Disease")

Although hyperthyroidism due to Graves' disease is usually overt, subclinical hyperthyroidism is not infrequent at diagnosis, involving up to 20–30% of early diagnosed patients (Bartalena et al. 2016d; Zhyzhneuskaya et al. 2016). These patients may either remain subclinical hyperthyroid, revert to euthyroidism, or progress to overt hyperthyroidism (rule of thirds) (Zhyzhneuskaya et al. 2016). The choice between active treatment of subclinical hyperthyroid patients versus strict surveillance depends on the degree of TSH suppression, the age of the patient, and the presence of comorbidities that make this condition a risky situation (Biondi et al. 2015).

Management of Graves' Hyperthyroidism During Immune Reconstitution

Graves' disease my occur during immune reconstitution from a lymphopenic disorder, such as highly active antiretroviral therapy (HAART) for HIV infection, alemtuzumab for multiple sclerosis, and bone marrow or stem cell transplantation

(Weetman 2014). Evidence is limited on the management of Graves' hyperthyroidism in these conditions, but ATDs are indicated as first-line treatment, also because they are probably associated with a higher rate of remission of hyperthyroidism compared to the general Graves' patients (Weetman 2014).

Thyroid Storm

Thyroid storm is an endocrine emergency, characterized by an exacerbation of thyrotoxic symptoms with possible systemic decompensation (heart failure, liver failure, psychosis, coma), usually triggered by precipitant events (e.g., infections or other acute illnesses, thyroid or nonthyroidal surgery in undiagnosed or inadequately treated hyperthyroid patient), and with a substantial mortality rate (Angell et al. 2015). Management of this life-threatening condition should be aggressive and include high doses of ATDs (PTU rather than MMI in view of its peripheral effect on T4 to T3 conversion), β- blockers, inorganic iodine, glucocorticoids, cooling with acetaminophen and cooling blankets, blood volume respiratory and nutritional support, and treatment of the underlying disorder precipitating thyroid storm (Ross et al. 2016).

Treatment of Graves' Orbitopathy

Severe and sight-threatening forms of GO are rare nowadays, and even mild GO is found in only 25% of newly diagnosed Graves' patients, is often remitting upon restoration of euthyroidism (Tanda et al. 2013), and rarely progresses to more severe forms (Piantanida et al. 2013). Moderate-to-severe forms account for approximately 5% of cases (Bartalena and Fatourechi 2014).

Mild GO

In most cases of mild GO, a watchful strategy is sufficient, supported by local measures (artificial tears, ointments) and removal of risk factors (particularly smoking). In a randomized placebo-controlled clinical trial, selenium supplementation improved mild GO and prevented its progression to moderate-to-severe forms (Marcocci et al. 2011). In rare patients, whose quality of life is deeply impaired despite GO being objectively mild, intravenous glucocorticoid treatment, as for moderate-to-severe GO, may be considered, although, under these circumstances, risks likely outweigh benefits (Bartalena et al. 2016a).

Moderate-To-Severe GO

Management of these forms depend on the degree of activity of the disease. In active GO, treatment is medical, whereas in inactive forms treatment is surgical.

Active

First-Line Treatment

High-dose intravenous glucocorticoids are the first-line treatment for moderate-to-severe and active GO (Zang et al. 2011) (Fig. 3), because they are more effective and better tolerated than oral glucocorticoids (Marcocci et al. 2001; Kahaly et al. 2005). Intravenous glucocorticoids are usually given in 12 slow (2–3 h), weekly infusions. Modalities of pulse administration and cumulative doses of the drug are extremely variable throughout Europe (Lazarus et al. 2010), but the most common regimen consists in the administration of a total of 4.5 g of methylprednisolone (6 infusions of 500 mg, followed by 6 infusions of 250 mg) (Kahaly et al. 2005). In a large randomized clinical trial by EUGOGO, three different cumulative doses of methylprednisolone (2.25 g, 4.98 g, 7.47 g) were assessed (Bartalena et al. 2012): although the highest dose was slightly more effective, it was also associated with more frequent side effects (Bartalena et al. 2012). In view of the potential serious adverse events of this treatment (Marcocci et al. 2012), EUGOGO recommended a medium dose (4.5 g) for most cases, reserving the higher dose (7.5 g) to most severe forms within the spectrum of moderate-to-severe GO (Bartalena et al. 2016a). The cumulative dose of glucocorticoids should not be higher than 8 g to reduce the risk of hepatotoxicity (Le Moli et al. 2007; Sisti et al. 2015a), and the single dose should not exceed 0.75 g (Riedl et al. 2015). Contraindications to high-dose intravenous glucocorticoids are represented by severe cardiovascular problems, psychiatric disorders, uncontrolled hypertension or diabetes, liver dysfunction, and recent viral hepatitis (Zang et al. 2011). Soft tissue changes and extraocular muscle dysfunction usually respond very well to treatment, while exophthalmos is less responsive (Bartalena and Fatourechi 2014). To improve final outcome, treatment should be started within 1 year from the onset of GO (Bartalena et al. 2016a). Unfortunately GO flares up in about one third of patients after glucocorticoid withdrawal (Bartalena et al. 2012). In these cases, patients should be either submitted to a second course of intravenous glucocorticoids or to a second-line treatment (Bartalena 2011) (Fig. 3).

Second-Line Treatments

Orbital radiotherapy is particularly effective on disturbances of ocular motility (Tanda and Bartalena 2012). It is commonly given in 10 daily fractions over a 2-week period, using a cumulative dose of 20 Gy per eye (Tanda and Bartalena 2012), but different protocols with lower doses or more prolonged regimens have been proposed (Kahaly et al. 2000). The association of orbital radiotherapy and *oral* glucocorticoids is more effective than either treatment alone (Tanda and Bartalena 2012). Randomized clinical trials showing that the combination of orbital radiotherapy and *intravenous* glucocorticoids is more effective than either treatment alone are missing, but a recent retrospective study showed the effectiveness of combination therapy (Sisti et al. 2015b) Orbital radiotherapy is safe, but should not be used in patients with diabetic or hypertensive retinopathy (Bartalena et al. 2016a).

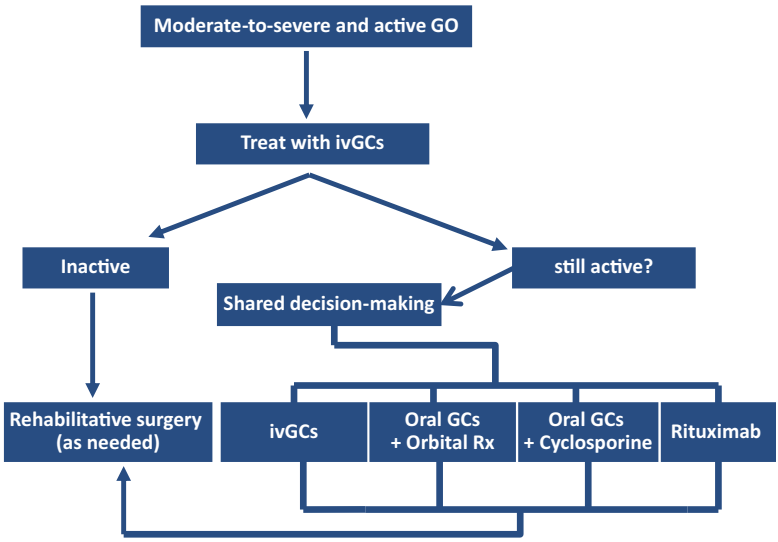

Fig. 3 Treatment of moderate-to-severe and active Graves' orbitopathy (*GO*). *ivGCs* intravenous glucocorticoids, *Rx* radiotherapy, *Rehabilitative surgery* orbital decompression, squint surgery, eyelid surgery (Derived from Bartalena et al. 2016a)

The combination of **cyclosporine** and oral glucocorticoids can be considered a valid alternative. This is based on the results of two randomized clinical trials (Kahaly et al. 1986; Prummel et al. 1989) reporting that the combined treatment was more effective than either drug alone. The starting dose of cyclosporine was 5 mg/kg body weight in one study (Kahaly et al. 1986) and 7.5 mg/kg body weight in the other one (Prummel et al. 1989). Cyclosporine treatment may cause side effects, including dose-dependent liver and renal toxicity, infections, and gingival hyperplasia (Bartalena et al. 2016a).

The use of **rituximab**, CD20+ B cell-depleting monoclonal antibody has been reported, after a few uncontrolled studies (Hegedus et al. 2011; Salvi et al. 2013), in two small randomized clinical trials, comparing rituximab with placebo (Stan et al. 2015) or with intravenous glucocorticoids (Salvi et al. 2015). Results were conflicting, because in the first study, the effects of rituximab did not differ from those of placebo (Stan et al. 2015), whereas in the other one rituximab inactivated GO as well as intravenous glucocorticoids, without any relapse after treatment discontinuation, at variance with glucocorticoids (Salvi et al. 2015). The reasons for this discrepancy between the two studies remain elusive, but in the first study, the duration of disease was longer and patients were older, possibly making these patients less responsive to treatment (Stan and Salvi 2016). In the absence of larger, multicenter randomized clinical trials, for the time being rituximab cannot be recommended as first-line treatment for GO. Rituximab treatment is not devoid of side effects. In particular, in the above studies, progression of dysthyroid optic neuropathy (DON) cumulatively occurred in 4 of 25 patients (16%) during rituximab

treatment (Wiersinga 2016). Accordingly, rituximab should not be administered to patients with impending or overt DON (Bartalena et al. 2016a).

Because all of the available treatments for moderate-to-severe and active GO are often unsatisfactory, pros and cons of each treatment should be discussed with the patient in a shared decision-making dialogue (Stiggelbout et al. 2012).

Inactive

Medical treatment is ineffective in patients whose GO is inactive. In such patients, residual manifestations (exophthalmos, strabismus, eyelid malposition) can be corrected surgically by orbital decompression, squint surgery, and eyelid surgery, respectively. GO should be inactive for at least 6 months prior to rehabilitative surgery. Should all of the three procedures be needed, they should be performed in the above order.

Very Severe (Sight-Threatening) Graves' Orbitopathy

Dysthyroid optic neuropathy (DON) and corneal breakdown are sight-threatening and constitute an emergency situation. Very high doses of intravenous methylprednisolone (500–1000 mg for 3 consecutive days or on alternate days during the first week, to be repeated during the second week) are the first-line treatment, but, if the response is inadequate, patients should urgently be submitted to orbital decompression (Bartalena et al. 2016a).

Treatment of Thyroid Dermopathy and Acropachy

Thyroid dermopathy (also known as pretibial myxedema) is a very rare manifestation, affecting approximately 4% of Graves' patients with GO (Bartalena and Fatourechi 2014). Thyroid acropachy is even rarer, occurring in 0.3% of Graves' patients (Bartalena and Fatourechi 2014). In most cases, thyroid dermopathy is mild and may remit spontaneously or following treatment with local glucocorticoids (fluocinolone acetonide, clobetasol propionate, or triamcinolone cream base 0.05–0.1%) covered by Saran plastic wrap occlusive dressing (12 h/day for 4–6 weeks) (Bartalena and Fatourechi 2014). Compression stockings (20–40 mmHg pressure), complete decompressive physiotherapy, and manual lymphatic drainage or massage may help also in severe (elephantiasic) forms. Surgery is contraindicated, because it may worsen skin lesions (Bartalena and Fatourechi 2014). The benefit of intralesional injections of a solution of lidocaine, dexamethasone, and saline needs to be confirmed in larger studies (Bartalena and Fatourechi 2014). As to the effectiveness of systemic immunosuppressive treatments, as well as of plasmapheresis or intravenous immunoglobulins, evidence of benefit is anecdotal (Bartalena and Fatourechi 2014).

For acropachy there is no treatment, except for pain-relieving drugs in the case of periostitis (Bartalena and Fatourechi 2014).

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