

2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism

George J. Kahaly^a Luigi Bartalena^b Lazlo Hegedüs^c Laurence Leenhardt^d
Kris Poppe^e Simon H. Pearce^f

^aDepartment of Medicine I, Johannes Gutenberg University (JGU) Medical Center, Mainz, Germany; ^bDepartment of Medicine and Surgery, University of Insubria, Varese, Italy; ^cDepartment of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark; ^dThyroid and Endocrine Tumors Unit, Pitié Salpêtrière Hospital, Sorbonne University, Paris, France; ^eEndocrine Unit, CHU Saint-Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium; ^fDepartment of Endocrinology, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK

Keywords

Graves' hyperthyroidism · Management · Antithyroid drugs · Radioiodine therapy · Thyroidectomy · Graves' orbitopathy

Abstract

Graves' disease (GD) is a systemic autoimmune disorder characterized by the infiltration of thyroid antigen-specific T cells into thyroid-stimulating hormone receptor (TSH-R)-expressing tissues. Stimulatory autoantibodies (Ab) in GD activate the TSH-R leading to thyroid hyperplasia and unregulated thyroid hormone production and secretion. Diagnosis of GD is straightforward in a patient with biochemically confirmed thyrotoxicosis, positive TSH-R-Ab, a hypervascular and hypoechoic thyroid gland (ultrasound), and associated orbitopathy. In GD, measurement of TSH-R-Ab is recommended for an accurate diagnosis/differential diagnosis, prior to stopping antithyroid drug (ATD) treatment and during pregnancy. Graves' hyperthyroidism is treated by decreasing thyroid hormone synthesis with the use of ATD, or by reducing the amount of thyroid tissue with radioactive io-

dine (RAI) treatment or total thyroidectomy. Patients with newly diagnosed Graves' hyperthyroidism are usually medically treated for 12–18 months with methimazole (MMI) as the preferred drug. In children with GD, a 24- to 36-month course of MMI is recommended. Patients with persistently high TSH-R-Ab at 12–18 months can continue MMI treatment, repeating the TSH-R-Ab measurement after an additional 12 months, or opt for therapy with RAI or thyroidectomy. Women treated with MMI should be switched to propylthiouracil when planning pregnancy and during the first trimester of pregnancy. If a patient relapses after completing a course of ATD, definitive treatment is recommended; however, continued long-term low-dose MMI can be considered. Thyroidectomy should be performed by an experienced high-volume thyroid surgeon. RAI is contraindicated in Graves' patients with active/severe orbitopathy, and steroid prophylaxis is warranted in Graves' patients with mild/active orbitopathy receiving RAI.

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Epidemiology and Pathogenesis

Hyperthyroidism occurs due to an inappropriately high synthesis and secretion of thyroid hormone (TH) by the thyroid [1]. TH increases tissue thermogenesis and the basal metabolic rate, and reduces serum cholesterol levels and systemic vascular resistance. The complications of untreated hyperthyroidism include weight loss, osteoporosis, fragility fractures, atrial fibrillation, embolic events, and cardiovascular dysfunction [2–4]. The prevalence of hyperthyroidism is 1.2–1.6, 0.5–0.6 overt and 0.7–1.0% subclinical [1, 5]. The most frequent causes are Graves' disease (GD) and toxic nodular goiter. GD is the most prevalent cause of hyperthyroidism in iodine-replete geographical areas, with 20–30 annual cases per 100,000 individuals [6]. GD occurs more often in women and has a population prevalence of 1–1.5%. Approximately 3% of women and 0.5% of men develop GD during their lifetime [7]. The peak incidence of GD occurs among patients aged 30–60 years, with an increased incidence among African Americans [8].

GD is an organ-specific autoimmune disease whose major manifestations are owing to circulating autoantibodies (Ab) that stimulate the thyroid-stimulating hormone receptor (TSH-R) leading to hyperthyroidism and goiter. TSH-R-stimulating Ab are predominantly of the IgG1 isotype and bind to a discontinuous epitope in the leucine-rich domain of the TSH-R extracellular domain, bounded roughly by amino acids 20–260 [9, 10]. TSH-R also interacts with IGF1 receptors (IGF1R) on the surface of thyrocytes and on orbital fibroblasts, with the TSH-R-Ab interaction with TSH-R activating both IGF1R downstream pathways and TSH-R signaling [11]. Circulating stimulatory TSH-R-Ab binding to the TSH-R enhance the production of intracellular cyclic AMP, leading to the release of TH and thyrocyte growth. About 30% of GD patients have family members who also have GD or Hashimoto's thyroiditis. Twin studies have shown that 80% of the susceptibility to GD is genetic [12]. There are well-established associations between alleles of the major histocompatibility complex with GD, with susceptibility being carried with HLA-DR3 and HLA-DR4 haplotypes [13]. Other susceptibility loci at which association has been replicated include those at cytotoxic T lymphocyte antigen-4, protein tyrosine phosphatase nonreceptor-22, basic leucine zipper transcription factor 2, and CD40 [14]. A noncoding variant within the TSH-R gene itself also confers susceptibility. Environmental factors, such as cigarette smoking, high dietary iodine intake, stress, and pregnancy,

also predispose to GD [15–17]. Oral contraceptive pill use appears protective, as is male sex, suggesting a strong influence of sex hormones [6, 15].

Methodology

The development of this guideline was commissioned by the Executive Committee (EC) and Publication Board of the European Thyroid Association (ETA), which selected a chairperson (G.J.K.) to lead the task force. Subsequently, in consultation with the ETA EC, G.J.K. assembled a team of European clinicians who authored this manuscript. Membership on the panel was based on clinical expertise, scholarly approach, representation of endocrinology and nuclear medicine, as well as ETA membership. The task force examined the relevant literature using a systematic PubMed search supplemented with additional published materials. An evidence-based medicine approach that incorporated the knowledge and experience of the panel was used to develop the text and a series of specific recommendations. The strength of the recommendations and the quality of evidence supporting each was rated according to the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE system) [18]. The ETA task force for this guideline used the following coding system: (a) strong recommendation indicated by 1, and (b) weak recommendation or suggestion indicated by 2. The evidence grading is depicted as follows: ○○○○ denotes very-low-quality evidence; ○○○○, low quality; ○○○○, moderate quality; ○○○○, high quality. The draft was discussed by the task force, and then posted on the ETA website for 4 weeks for critical evaluation by the ETA members.

Diagnosis

Serology

Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected hyperthyroidism and should be used as an initial screening test [19, 20]. However, when hyperthyroidism is strongly suspected, diagnostic accuracy improves when both a serum TSH and free T4 are assessed at the time of the initial evaluation. The relationship between free T4 and TSH (when the pituitary-thyroid axis is intact) is an inverse log-linear relationship; therefore, small changes in free T4 result in large changes in serum

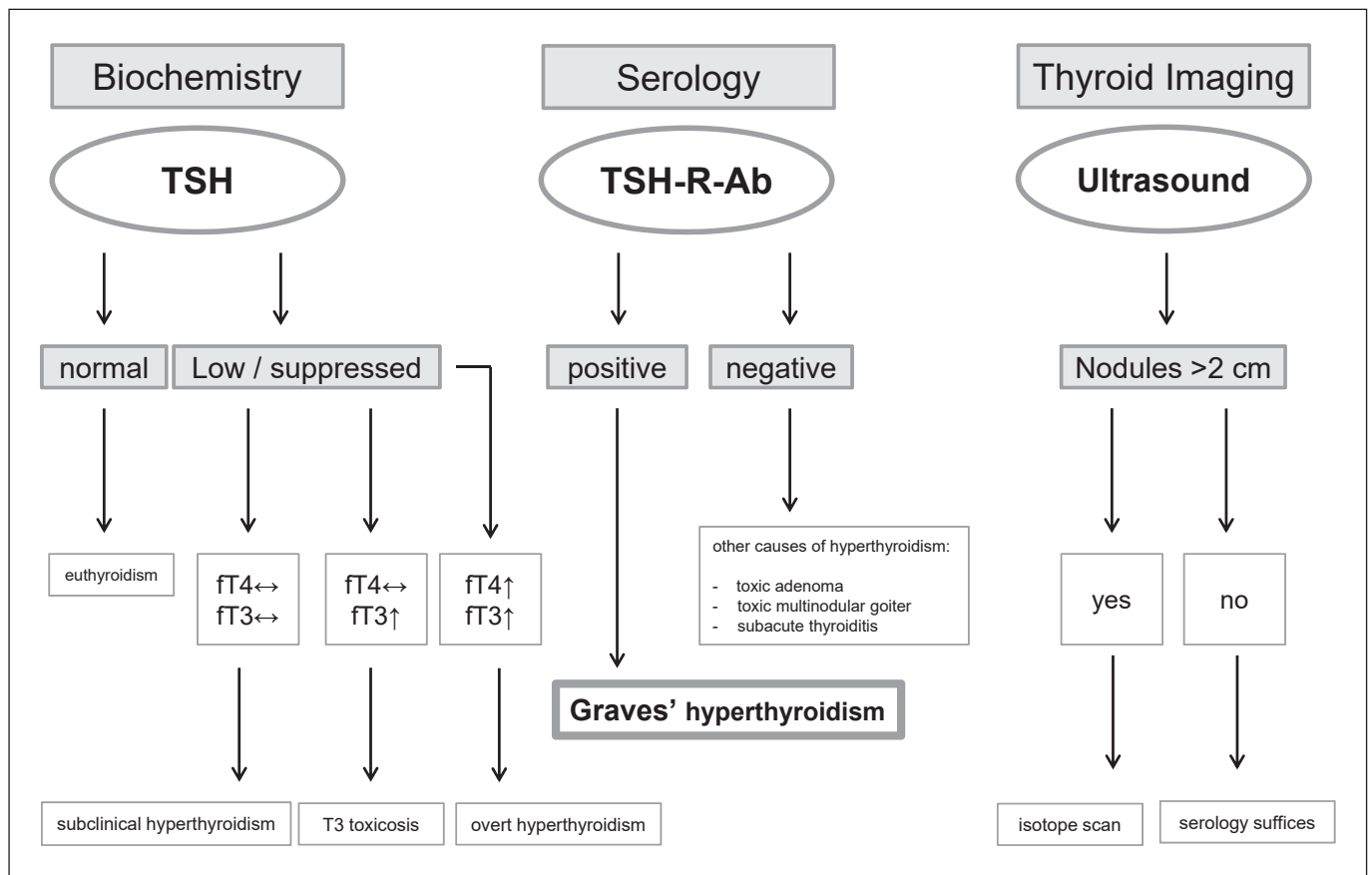


Fig. 1. Algorithm for investigating a patient with suspected Graves' hyperthyroidism.

TSH concentrations. Serum TSH levels are considerably more sensitive than direct TH measurements for assessing TH excess [20, 21]. In overt hyperthyroidism, both serum free T4 and T3 concentrations are elevated, and serum TSH is suppressed; however, in milder hyperthyroidism, serum total T4 and free T4 levels can be normal, only serum free T3 may be elevated, with an undetectable serum TSH (Fig. 1).

TSH-R-Ab are specific biomarkers for GD [2, 22]. Most immunoassays today use a competitive-binding assay and measure what are referred to as TSH-R binding inhibitory immunoglobulins (TBII). Binding assays only report the presence or absence of TSH-R-Ab and their concentrations, but do not indicate their functional activity [23, 24]. A meta-analysis of 21 studies showed that the overall pooled sensitivity and specificity of the serum TSH-R-Ab concentration measured with second- and third-generation binding assays were 97 and 98%, respectively [25]. In contrast, the highly sensitive cell-based bio-

assays [26–33] exclusively differentiate between the TSH-R-stimulating Ab (TSAb) and TSH-R-blocking Ab [34, 35]. Also, TSAb is a highly sensitive and predictive biomarker for the extrathyroidal manifestations of GD [36–42] as well as a useful predictive measure of fetal or neonatal hyperthyroidism [43, 44]. Finally, the incorporation and early utilization of TSAb into current diagnostic algorithms conferred a 46% shortened time to diagnosis of GD and a cost saving of 47% [45].

Recommendations

- 1 The measurement of TSH-R-Ab is a sensitive and specific tool for rapid and accurate diagnosis and differential diagnosis of Graves' hyperthyroidism. 1, ◯◯◯◯
- 2 When technically available, differentiation of TSH-R-Ab functionality is helpful and predictive in Graves' patients during pregnancy/postpartum, as well as for extrathyroidal manifestations. 2, ◯◯◯◯

Imaging

Considerable inter- and intraregional variation in diagnostic practice has been reported for GD [22]. In addition to thyroid function and TSH-R-Ab determination, most clinicians would request thyroid ultrasound (US) and less often isotope scanning [22]. In a study conducted among 263 endocrinologists in 992 hyperthyroid patients, thyroid US and scintigraphy were used in 93.8 and 40.3%, respectively [46]. Ordinarily, there is no indication for CT scan, MRI, or PET-CT of the thyroid gland. Thyroid US is a convenient, noninvasive, rapid, and accurate tool in the initial work-up of GD patients. It aids in the diagnosis, without exposing the patient to ionizing irradiation, and assists in determining the underlying etiology of thyrotoxicosis and detecting concomitant thyroid nodules [47–49]. Imaging results are highly dependent on equipment and the experience of the investigator. A high-frequency linear probe should be used. GD is often, but not invariably, characterized by diffuse thyroid enlargement and by hypoechogenicity, both assessed by US and conventional grey scale analysis [6].

A color-flow or power Doppler examination characterizes vascular patterns and quantifies thyroid vascularity [50]. The latter is significantly increased in untreated GD and typically shows a pulsatile pattern called “thyroid inferno” that is multiple small areas of increased intrathyroidal flow seen diffusely throughout the gland [51]. Accurate measurement of thyroid artery flow velocity and peak systolic velocity (PSV) requires adjustments of pulse repetition frequency of wall filters and control of the insonation angle at between 0 and 60°. In untreated GD, thyroidal artery flow velocity and PSV are significantly increased. The PSV can differentiate between thyrotoxicosis owing to GD from subacute thyroiditis or amiodarone-induced thyrotoxicosis type 2, where the blood flow is reduced [52]. Typical US patterns combined with positive TSH-R-Ab obviate the need for scintigraphy in the vast majority of cases. However, thyroid scintigraphy may be useful in the assessment of patients prior to radioactive iodine (RAI) treatment, especially when facing coexistent multinodular goiter [6].

Recommendations

- 3 US examination, comprising conventional grey scale analysis and color-flow or power Doppler examination is recommended as the imaging procedure to support the diagnosis of Graves’ hyperthyroidism. 1, ∅∅∅∅
- 4 Scintigraphy of the thyroid is suggested when thyroid nodularity coexists with hyperthyroidism, and prior to RAI therapy. 2, ∅∅∅∅

Table 1. Mechanism of action of antithyroid drugs

Intrathyroidal inhibition of:
Iodine oxidation/organification
Iodotyrosine coupling
Thyroglobulin biosynthesis
Follicular cell growth
Extrathyroidal inhibition of T4/T3 conversion (PTU)

Management

Medical Treatment

Graves’ hyperthyroidism is treated by reducing TH synthesis, using ATD, or by reducing the amount of thyroid tissue with RAI treatment or total thyroidectomy [6, 47]. ATD represent the predominant therapy in Europe, Asia, and in the meantime in the USA [53, 54]. The main ATD are thionamides, such as propylthiouracil (PTU), carbimazole (CBZ), and the active metabolite of the latter, methimazole (MMI). CBZ is not an active substance; it has to be decarboxylated to MMI in the liver. Thionamides inhibit the coupling of iodothyronines and hence reduce the biosynthesis of TH [55]. All inhibit the function of thyroperoxidase, reducing oxidation and the organification of iodide (Table 1). ATD are indicated as a first-line treatment of GD, particularly in younger subjects, and for short-term treatment of GD before RAI therapy or thyroidectomy [2, 6, 22]. ATD reduce TSH-R-Ab levels and enhance rates of remission compared to no therapy. PTU at higher doses inhibits deiodination of T4 to T3 [56]. However, this effect is of minor benefit, except in severe thyrotoxicosis, and is offset by the much shorter half-life of this drug compared to MMI (Table 2). The initial dose of MMI is usually 10–30 mg once daily depending on the severity of hyperthyroidism (CBZ 15–40 mg/day). PTU is given at a dose of 100 mg every 8 h, and divided doses are given throughout the course. The starting dose of ATD can be gradually reduced (titration regimen) as thyrotoxicosis improves. Thyroid function tests are reviewed 3–4 weeks after starting treatment, and the dose is titrated based on free T4 and free T3 levels. A substantial proportion of patients reach euthyroidism within 3–4 weeks of treatment. TSH levels often remain suppressed for several months and therefore do not provide a sensitive index of early treatment response. The usual daily maintenance doses of ATD in the titration regimen are 2.5–10 mg of MMI and 50–100 mg of PTU. Alternatively, MMI daily doses of 30 mg may be given combined with levothyroxine (L-T4) supplementation (block and

Table 2. Pharmacology and pharmacokinetics of antithyroid drugs

	MMI	PTU
Absorption	rapid	rapid
Bioavailability	~100%	~100%
Peak serum level	60–120 min	60 min
Serum half-life	6–8 h	90 min
Thyroid concentration	5×10^5 mol/L	unknown
Thyroid turnover	slow	moderate
Duration of action	>24 h	8–12 h
Serum protein binding	nil	>75%
Crosses placenta	++	+
Levels in breast milk	++	+
Volume of distribution	40 L	20 L
Excretion	renal	renal
Metabolism during illness		
Renal	nil	nil
Liver	prolonged	nil
Potency	10×	1×
Normalization T3/T4	6 weeks	12 weeks
Adverse events	15%	20%
Agranulocytosis	0.6%	1–1.5%
Cross-reaction of adverse events	13.8%	15.2%
Compliance	high	fair
Costs	low	moderate

MMI, methimazole; PTU, propylthiouracil.

replace regimen) to avoid drug-induced hypothyroidism. Initial reports suggesting superior remission rates with the block-replace regimen have not been reproduced [2, 57]. The titration regimen is often preferred to minimize the dose of ATD.

The optimal duration of ATD therapy for the titration regimen is 12–18 months [57]. Continued L-T4 treatment following initial ATD therapy does not provide any benefit in terms of the recurrence of hyperthyroidism [5, 57]. Maximum remission rates (50–55%) are achieved within 12–18 months. Measurement of TSH-R-Ab levels prior to stopping ATD therapy is recommended, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating a greater chance of remission [5, 22]. Monitoring the titers of functional stimulatory and blocking TSH-R-Ab during treatment help in predicting the outcome [58, 59]. Patients with persistently high TSH-R-Ab at 12–18 months can continue MMI therapy, repeating the TSH-R-Ab measurement after an additional 12 months, or opt for RAI or thyroidectomy (Fig. 2). In line with this, arguments for an extended use of ATD in both adults and children with

GD have been published [60–62]. Relapse is most likely within the first 6–12 months after ATD withdrawal, but may occur years later. Patients with severe hyperthyroidism, large goiters, or persistent high titers of TSH-R-Ab are most likely to relapse when treatment stops, but the outcome is difficult to predict. All patients should be followed closely for relapse during the first year after treatment and at least annually thereafter.

Recommendations

- Patients with newly diagnosed Graves' hyperthyroidism should be treated with ATD. RAI therapy or thyroidectomy may be considered in patients who prefer this approach. 1, ∅∅∅∅
- MMI (CBZ) should be used in every non-pregnant patient who chooses ATD therapy for Graves' hyperthyroidism. 1, ∅∅∅∅
- MMI is administered for 12–18 months then discontinued if the TSH and TSH-R-Ab levels are normal. 1, ∅∅∅∅
- Measurement of TSH-R-Ab levels prior to stopping ATD therapy is recommended, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating a greater chance of remission. 1, ∅∅∅∅
- Patients with persistently high TSH-R-Ab at 12–18 months can continue MMI therapy, repeating the TSH-R-Ab measurement after an additional 12 months, or opt for RAI or thyroidectomy. 1, ∅∅∅∅

Adverse Events

Common side effects of ATD (Table 3) are rash, urticaria, and arthralgia (1–5%). Minor cutaneous reactions are managed with concurrent antihistamine therapy without stopping the ATD. These may resolve spontaneously or after substituting an alternative ATD [56]. In the case of a serious allergic reaction, prescribing the alternative drug is not recommended. Rare but major side effects [63] include hepatitis, a lupus-like syndrome, and agranulocytosis (neutrophil count <500/mL), which occurs in 0.1–1.0% of cases [64, 65]. Agranulocytosis tend to occur abruptly within 3 months after the initiation of ATD therapy [65]. The cumulative incidence of ATD-induced agranulocytosis and pancytopenia at 100 and 150 days after the initiation of ATD was 0.28 and 0.29%, respectively [66]. Genetic determinants of ATD-induced agranulocytosis [67] have shown that the alleles HLA-B*38:02 and HLA-DRB1*08:03 are independent susceptibility loci for agranulocytosis. Carrying both HLA-B*38:02 and HLA-DRB1*08:03 increases the odds ratio to 48.41 (95%

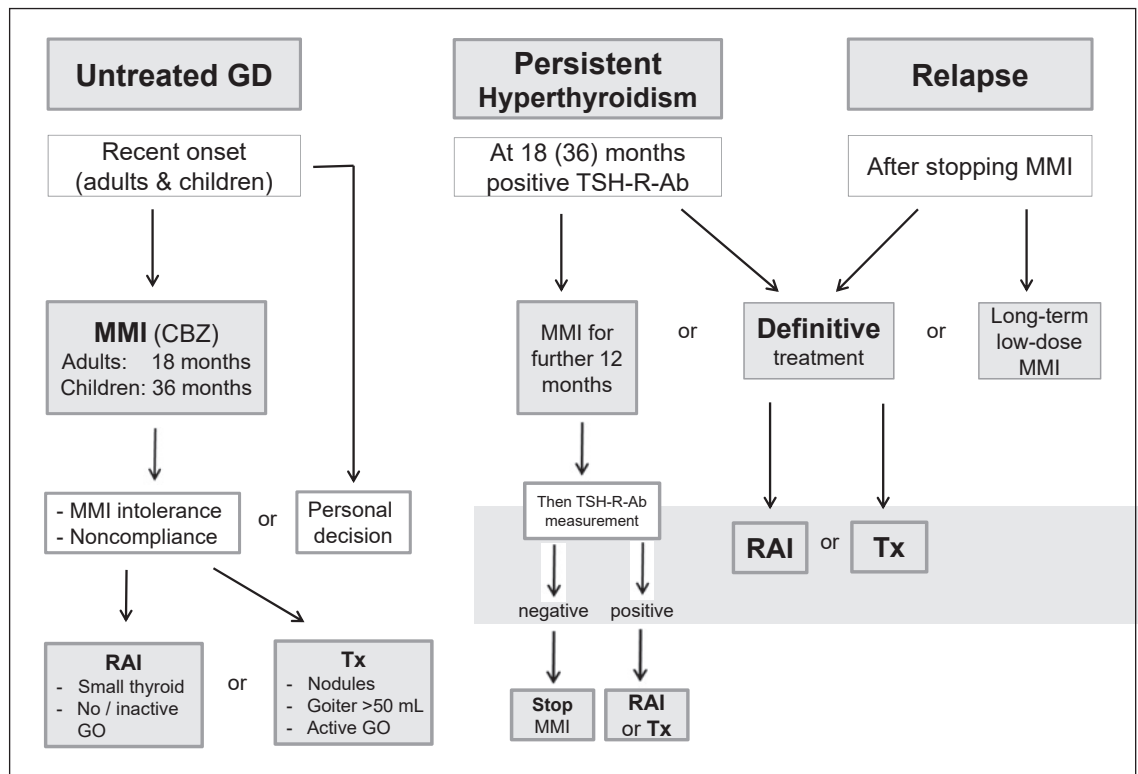


Fig. 2. Algorithm for the management of a patient with Graves' hyperthyroidism. GD, Graves' disease; MMI, methimazole; CBZ, carbimazole; GO, Graves' orbitopathy; RAI, radioactive iodine; Tx, total thyroidectomy.

Table 3. Adverse events of antithyroid drugs

Common (1.0–5.0%)
Skin rash
Urticaria
Arthralgia, polyarthritis
Fever
Transient mild leukopenia
Rare (0.2–1.0%)
Gastrointestinal
Abnormalities of taste and smell
Agranulocytosis
Very rare (<0.1%)
Aplastic anemia (PTU, CBZ)
Thrombocytopenia (PTU, CBZ)
Vasculitis, lupus-like, ANCA+ (PTU)
Hepatitis (PTU)
Hypoglycemia (anti-insulin Abs; PTU)
Cholestatic jaundice (CBZ/MMI)

PTU, propylthiouracil; MMI, methimazole; CBZ, carbimazole; ANCA, antineutrophil cytoplasmic antibody.

CI 21.66–108.22). In Caucasians, a different HLA-B allele (B*27:05; OR 7.3, 95% CI 3.81–13.96) and rare NOX3 variants have been tentatively associated [68, 69].

MMI (CBZ) and PTU exert dissimilar incidence rates of hepatotoxicity. PTU-associated hepatotoxicity occurs foremost in children in contrast to that associated with MMI, which is usually milder with a cholestatic pattern [70]. In a study comprising 71,379 ATD initiators [71], MMI was associated in a dose-dependent manner with an increased risk for hepatitis and cholestasis. ATD are stopped and not restarted if a patient develops major side effects. Patients should be given written instructions regarding the symptoms of possible agranulocytosis (e.g., sore throat, fever, mouth ulcers) and the need to stop treatment pending a complete blood count. The use of routine hematological and liver function tests is not useful, as the onset of agranulocytosis is abrupt [56].

Recommendations

10 Patients should be informed of potential side effects of ATD and the necessity of informing the physician promptly if they should develop jaundice, light-col-

ored stools, dark urine, fever, pharyngitis, or cystitis. 1, ØØØØ

11 In patients taking ATD, a differential white blood cell count should be obtained during febrile illness and/or pharyngitis, and liver function should be assessed in those who experience jaundice, light-colored stools, or dark urine. 1, ØØØØ

Beta-Adrenergic Blockade

Propranolol (20–40 mg every 6 h) or longer acting beta-blockers (i.e., atenolol/bisoprolol), are useful to control adrenergic symptoms such as palpitations and tremor, especially in the early stages before ATD take effect. High doses of propranolol (40 mg 4 times daily) inhibit peripheral conversion of T4 to T3. Cardioselective beta-blockers with higher cardioprotective effects and superior prevention of atrial fibrillation represent an alternative choice, especially for patients with asthma. Anticoagulation with warfarin or direct oral anticoagulants should be considered in all patients with atrial fibrillation. If digoxin is used, increased doses are often needed in the thyrotoxic state [2, 5, 6, 72].

Recommendation

12 Beta-adrenergic blockade is recommended in all suitable patients with Graves' hyperthyroidism. 1, ØØØØ

Relapse after a Course of ATD Treatment

A meta-analysis [73] has confirmed the high relapse rate following ATD therapy (52.7%) in comparison with RAI (15%, OR 6.25) or surgery (10%, OR 9.09), along with a significant side-effect profile for these drugs (13%). Another meta-analysis evaluating 54 trials and 7,595 participants showed several risk factors predicting persistence (49%) in GD [74]. Orbitopathy, smoking, thyroid volume, free T4, total T3, and TSH-R-Ab were significantly associated with relapse. In a prospective study introducing the quantitative predictive "GREAT" score for GD [75], 37% of patients with a first episode of Graves' hyperthyroidism relapsed within 2 years after ATD withdrawal. Lower age, higher serum TSH-R-Ab and free T4, larger goiters at diagnosis, PTPN22 C/T polymorphism, and HLA subtypes DQB1*02, DQA1*05, and DRB1*03 were independent predictors for recurrence.

On the other hand, the benefits of long-term ATD treatment after recurrence were shown in patients with GD relapse after the discontinuation of ATD therapy for 12–24 months [76]. Either RAI treatment and L-T4 replacement or MMI (2.5–7 mg/daily) were used. No notable side effects were observed. Thyroid dysfunction was

predominant in the RAI group ($p < 0.001$), and euthyroidism was more common in the MMI group ($p < 0.001$). Graves' orbitopathy (GO) deterioration was higher post-RAI ($p < 0.0005$) over all periods of follow-up (OR 21.1, 95% CI 1.5–298, $p < 0.0003$). Patients gained more weight post-RAI ($p < 0.005$). Thus, low MMI doses were efficient, safe, and offered better outcomes for GO than RAI treatment. In another trial [77], long-term MMI treatment of GD was safe, while the complications and expenses of ATD did not exceed that of RAI.

Recommendation

13 If a patient with GD becomes hyperthyroid after completing a first course of ATD, definitive treatment with RAI or thyroidectomy is recommended. Continued long-term low-dose MMI can be considered in patients not in remission who prefer this approach. 1, ØØØØ

Subclinical Graves' Hyperthyroidism

Endogenous mild or subclinical hyperthyroidism (SH) is associated with increased risk of coronary heart disease mortality, incident atrial fibrillation, heart failure, fractures, and excess mortality in patients with serum TSH levels < 0.1 mIU/L [78–82]. In addition, in the presence of TSH-R-Ab indicating "subclinical" GD, the rate of progression to overt hyperthyroidism is up to 30% in the subsequent 3 years [83]. Therefore, despite the absence of randomized trials, treatment is indicated in patients older than 65 years with a TSH that is persistently < 0.1 mIU/L to potentially avoid these serious adverse events and the risk of progression to overt hyperthyroidism. Treatment might be considered in patients older than 65 years with TSH levels of 0.1–0.39 mIU/L because of their increased risk of atrial fibrillation, and might also be reasonable in younger (< 65 years) symptomatic patients with TSH < 0.1 mIU/L because of the risk of progression, especially in the presence of risk factors or comorbidity.

Recommendations

14 Treatment of SH is recommended in Graves' patients > 65 years with serum TSH levels that are persistently < 0.1 mIU/L. 1, ØØØØ

15 ATD should be the first choice of treatment of Graves' SH. 1, ØØØØ

Thyroid Storm

With a mortality rate estimated at 10%, the life-threatening thyroid storm demands a rapid diagnosis and emergency treatment [84, 85]. The condition manifests

as decompensation of multiple organs with impaired consciousness, high fever, heart failure, diarrhea, and jaundice. Diagnostic criteria for thyroid storm in patients with severe Graves' thyrotoxicosis include hyperpyrexia, tachycardia, arrhythmia, congestive heart failure, agitation, delirium, psychosis, stupor, coma, nausea, vomiting, diarrhea, hepatic failure, and the presence of an identified precipitant [86]. The "Burch-Wartofsky Point Scale" system grades the severity of individual manifestations, with a point total of ≥ 45 consistent with thyroid storm, 25–44 points classified as impending thyroid storm, and < 25 points indicating that thyroid storm as unlikely. Nationwide surveys in Japan have revealed the high morbidity and mortality rates of this condition and have subsequently offered a multimodality treatment, including intravenous MMI or PTU (40 or 400 mg every 8 h), glucocorticoids (methylprednisolone 50 mg i.v.), beta-blockers (propranolol 40 mg every 6 h), and monitoring in an intensive care unit [87]. The most common cause of death from thyroid storm was multiple organ failure, followed by heart and respiratory failure, arrhythmia, disseminated intravascular coagulation, gastrointestinal perforation, hypoxic brain syndrome, and sepsis [88].

Recommendation

16 A multimodality treatment approach to GD patients with thyroid storm should be used, including ATD therapy, glucocorticoid administration, beta-adrenergic blockade, cooling blankets, volume resuscitation, nutritional support, respiratory care, and monitoring in an intensive care unit. 1, $\emptyset\emptyset\circ\circ$

RAI Treatment

RAI has been used since 1941; however, there have been few well-designed prospective trials, leaving many questions about indications, optimal dose, efficacy, and side-effects [89]. The cellular effect of the ionizing radiation leads to genetic damage, mutations, or cell death. The DNA damage from radiation is mediated via a combination of direct effects, through breakage of molecular bonds, or indirectly through the formation of free radicals. This leads to a decrease in thyroid function and/or reduction in thyroid size. There are neither good measures of individual radiosensitivity nor ideal methods of predicting the clinical response to RAI therapy.

Indications and Applied RAI Dose

Patients with side-effects to or recurrence after a course of ATD, cardiac arrhythmias, and thyrotoxic periodic pa-

ralysis are candidates for RAI. Only one study has compared the ATD, surgery, and RAI head-to-head [90]. In that randomized study, the risk of relapse was highest after ATD, but there were no significant differences in sick leave or satisfaction with the therapy. There are contradictory reports pertaining to the cost effectiveness of GD treatment [91–94]. Some centers use RAI in pediatric patients, in which case ablative doses should be used with the aim of rapid hypothyroidism. Other side-effects are not different from those in adults [95]. RAI is contraindicated in pregnancy and during breast feeding, and conception should be postponed until at least 6 months after the therapy. There is no evidence of detrimental effects on long-term fertility, miscarriage, stillbirths, or congenital defects in the offspring [96]. The same 6-month period applies for males. ALARA (as low as reasonably achievable) is an important principle with radiation treatment, but an elusive goal when balancing rapid relief of hyperthyroidism and postponing hypothyroidism. Therefore, many have given up meticulous dose calculation and offer fixed activities of, for example, 185, 370, or 555 MBq, based on validated clinical parameters, such as thyroid size [89].

Effect on Thyroid Function and Size

Thyroid function is normalized within 3–12 months after RAI therapy in 50–90% of patients [89]. The patient should be informed that repeated doses of RAI may be needed. The incidence rate of hypothyroidism is 5–50% after the first year, and is positively associated with the thyroid RAI dose. This is followed by a yearly hypothyroidism rate of 3–5%, which is largely independent of the RAI dose [97]. Even with low-dose RAI, which increases persistent/recurrent disease, hypothyroidism is inevitable [98]. Thyroid size is normalized within a year of RAI [97]. RAI is not contraindicated in large goiters, even if partially retrosternal or intrathoracic. ATD should be temporarily paused for a week before and after RAI therapy [99].

Adverse Effects of RAI Therapy

There may be thyroid pain, swelling, and sialoadenitis. GD is associated with increased morbidity and mortality [100, 101]. Its treatment decreases mortality [102], while RAI per se does not increase mortality [89]. There is neither evidence of increased thyroid cancer nor total cancer mortality following RAI therapy [103]. Posttherapy thyroid storm is extremely rare, and in non-ATD-pretreated patients TH levels are normally not elevated post-RAI, but decline after a few days [104]. Transient hyperthy-

Table 4. Advantages and disadvantages of total thyroidectomy for Graves' hyperthyroidism

Advantages	Disadvantages
No recurrent hyperthyroidism	Risk of postoperative hypoparathyroidism
No radiation risk	Risk of recurrent nerve palsy
Rapid control of hyperthyroidism	Permanent hypothyroidism
No reported detrimental effect on the course of Graves' orbitopathy	Risks related to anesthesia or surgery
	Hospitalization
	Costs
	Permanent scar

roidism can be prevented by pre-RAI ATD treatment, but only if ATD are resumed post-RAI [105]. Posttherapy flare-up relates to high TSH-R-Ab levels. It is difficult to differentiate between treatment failure and transient hyperthyroidism. However, if thyrotoxicosis has not improved after 3 months, treatment failure is likely. Transient hypothyroidism is seen in 3–20% of cases and does not invariably lead to permanent hypothyroidism, but treatment with TH is generally recommended to avoid the development of or a flare-up of GO. De novo or flare-up of GO is seen in 15–33% of cases after RAI therapy [106]. Prophylactic glucocorticoids prevent this without influencing the ultimate outcome of thyroid function [107].

Recommendations

- 17 There are no absolute indications for RAI therapy, but it is often recommended for patients with side-effects to or recurrence after a course of ATD. 1, ∅∅○○
- 18 Verbal as well as written information on all aspects of efficacy and potential side-effects of RAI therapy should be provided. 1, ∅∅○○
- 19 If ATD are used before RAI therapy they should be paused around 1 week before and after therapy in order not to decrease the efficacy of RAI therapy. 1, ∅∅∅∅
- 20 No dose calculation can secure long-term euthyroidism and it is fully acceptable to offer a fixed dose of RAI. 1, ∅∅∅∅
- 21 Pregnancy and breast feeding constitute absolute contraindications to RAI therapy. 1, ∅∅∅∅
- 22 Conception should be postponed until at least 6 months after RAI in both males and females. 1, ∅∅∅∅
- 23 If used in children, ablative doses aiming at rapid hypothyroidism should be administered. 1, ∅∅○○

Surgery

Thyroidectomy is the least commonly selected treatment for newly diagnosed Graves' hyperthyroidism. In recent American and European questionnaire-based surveys, surgery represented the first-line treatment in 0.9% [108] and 2.1% [22] of cases, respectively. However, thyroidectomy is an effective treatment when goiter is large, there is coincident primary hyperparathyroidism or suspicion of malignant nodules, the patient wishes to avoid exposure to ATD or RAI [109], or facilities for RAI treatment are not available [2]. Advantages of thyroidectomy include the absence of radiation risk, the rapid control of hyperthyroidism, and the usual absence of detrimental effects on GO (Table 4). However, thyroidectomy is a high-cost procedure requiring hospitalization, it bears an anesthetic and surgical risk, a permanent scar is left, and there may be complications. Similar to RAI, long-term L-T4 replacement therapy is required to maintain euthyroidism.

If surgery is selected, total thyroidectomy is the procedure of choice, because it bears the same risk of complications as bilateral subtotal thyroidectomy, while the rate of recurrent hyperthyroidism is lower [110, 111]. Whether thyroidectomy is more effective than RAI as a definitive treatment preventing relapses of hyperthyroidism is a matter of debate due to conflicting results of two systematic reviews – favoring thyroidectomy [110], or showing no significant differences between the two treatments [73].

To minimize the risk of complications (hypoparathyroidism, laryngeal nerve palsy, wound infection, hemorrhage), surgery should be performed by a skilled high-volume surgeon [112]. To minimize the risk of intra- or postoperative exacerbation of thyrotoxicosis, hyperthyroidism should be adequately controlled by ATD treatment prior to surgery [109]. The use of a saturated solution of potassium iodide (SSKI) is helpful in the immedi-

ate preoperative period (10 days) to decrease thyroid vascularity and intraoperative blood loss [113]. However, this preparation is used by less than 40% of thyroidologists [22]. When thyroidectomy must be performed before an adequate control of hyperthyroidism is achieved, in addition to ATD, beta-blockers, glucocorticoids, and eventually SSKI may be helpful. Vitamin D deficiency should be corrected prior to surgery to reduce the risk of postoperative hypocalcemia [114].

Recommendations

- 24 If surgery is selected, total thyroidectomy is the procedure of choice, and should be performed by a skilled surgeon with high annual volumes of thyroidectomies. 1, ∅∅∅∅
- 25 Euthyroidism should be restored by ATD prior to surgery to avoid peri- or postoperative exacerbation of thyrotoxicosis. 1, ∅∅∅∅
- 26 Vitamin D deficiency should be corrected to reduce the postoperative risk of hypocalcemia. 1, ∅∅∅∅
- 27 A solution containing potassium iodide can be given for 10 days prior to surgery. 2, ∅∅∅∅

Treatment of Graves' Hyperthyroidism in Patients with Orbitopathy

Thyroid dysfunction, both hyper- and hypothyroidism, can influence the course of GO. Accordingly, the ETA/EUGOGO guideline [115] and an Italian consensus statement [116] recommended that prompt restoration and stable maintenance of euthyroidism are priorities in patients with GO. How to manage hyperthyroidism when GO is present is, however, a challenging dilemma [117]. ATD per se do not influence the natural course of GO, but might be beneficial for GO indirectly, as a consequence of the restoration of euthyroidism [118, 119]. Hypothyroidism can also cause the progression of GO [120]. RAI causes the progression or de novo occurrence of GO [119, 121, 122], particularly in smokers [123], those with pre-existing [119] and recent-onset GO [124], late correction of post-RAI hypothyroidism [125, 126], and high TSH-R-Ab levels [127]. In patients at risk of RAI-associated GO occurrence or progression, oral low-dose steroid prophylaxis [115, 128] is effective, as shown by two RCTs [119, 121] and two meta-analyses [129, 130]. Steroid prophylaxis can be avoided in patients with absent or inactive GO if other risk factors for RAI-associated progression of GO are absent [115, 130]. Thyroidectomy does not seem to impact the natural history of GO [122, 131] (Table 5).

Table 5. Treatment of hyperthyroidism due to GD in the presence of GO

Degree of severity and activity of GO	ATD	RAI	Tx
Mild and inactive	Yes	Yes ¹	Yes
Mild and active	Yes ²	Yes ³	Yes
Moderate-to-severe and inactive	Yes	Yes ¹	Yes
Moderate-to-severe and active	Yes	No	No
Sight threatening	Yes	No	No

ATD, antithyroid drugs; RAI, radioactive iodine; Tx, total thyroidectomy; GD, Graves' disease; GO, Graves' orbitopathy.

¹ Steroid prophylaxis in selected cases.

² Selenium supplementation for 6 months.

³ Steroid prophylaxis warranted (see text).

Mild and Inactive

Treatment for hyperthyroidism is unlikely to cause ocular changes and, therefore, is chosen irrespective of GO [116, 117]. If RAI treatment is selected, steroid prophylaxis is not indicated unless other risk factors for GO progression exist [115]. Rehabilitative surgery may be required for cosmetic or functional reasons.

Mild and Active GO

Treatment of hyperthyroidism is mostly independent of GO and relies on established criteria [2]. There is no RCT evidence that the long-term outcome of GO of this degree is better using ATD than definitive treatment. Steroid prophylaxis is indicated if RAI treatment is employed [130]. If ATD treatment is chosen, a 6-month selenium supplementation improves mild and active GO and prevents its progression to more severe forms [132].

Moderate-to-Severe and Inactive GO

The choice of thyroid treatment is mostly independent of GO. If RAI is selected, steroid prophylaxis can be avoided if other risk factors for GO reactivation are absent [117].

Moderate-to-Severe and Active GO

Rapid correction of hyperthyroidism with ATD and stable maintenance of euthyroidism are, per se, beneficial for GO and therefore strongly recommended [60, 61, 115]. Thyroid ablation has been alternatively advocated [133]. Prompt therapy for GO is warranted.

Sight-Threatening GO

Sight-threatening GO is an endocrine emergency because of the risk of sight loss due to dysthyroid optic neu-

ropathy and/or corneal breakdown. Hyperthyroidism must be treated with ATD and immediate treatment with high-dose intravenous steroids is imperative with subsequent orbital decompression if response to steroids is inadequate within 2–4 weeks [115].

Recommendations

- 28 In patients with GO, hyperthyroidism should be promptly controlled by ATD, and euthyroidism stably maintained. 1, ∅∅∅∅
- 29 Patients treated with RAI should receive steroid prophylaxis if mild and active GO preexists or there are risk factors for RAI-associated GO occurrence or progression. 1, ∅∅∅∅
- 30 In patients with moderate-to-severe and active GO, treatment of GO should be the priority. Euthyroidism should be promptly restored with ATD and stably maintained. 1, ∅∅∅∅
- 31 Patients with sight-threatening GO should be treated with ATD. 1, ∅∅∅∅
- 32 Treatment for hyperthyroidism in patients with inactive GO can be selected independently of GO. 1, ∅∅∅∅

Pregnancy and Postpartum

Women Planning Pregnancy

The choice of therapy depends on the patient's preference, disease history, the presence of high TSH-R-Ab levels, and the timescale for conception [134–138]. Pregnancy should be postponed if hyperthyroidism is inadequately controlled until euthyroidism is reached and confirmed on two occasions over 2 months on a stable therapeutic regimen. Patients should be informed about: (1) the increased risk of ATD-associated birth defects; (2) the possibility of stopping ATD during gestational weeks 6–10; (3) the preference for PTU, when ATD are necessary before/during the first trimester of pregnancy; (4) the advice to switch from PTU to MMI after 16 weeks of pregnancy; and (5) not to use block-replacement therapy. Pregnancy should be delayed for 6 months post-RAI, and contraception is advised during that period. Thyroidectomy is indicated in the case of contraindications/rejection of ATD/RAI. After surgery, euthyroidism should be confirmed prior to conception.

Recommendations

- 33 Women with GD of reproductive age should be offered preconception counseling and be stably euthyroid before attempting pregnancy. 1, ∅∅∅∅

- 34 Women with GD should be instructed to immediately confirm pregnancy and contact their physician. 1, ∅∅∅∅

- 35 Women treated with MMI should be switched to PTU when planning pregnancy and/or during the first trimester of pregnancy. 1, ∅∅∅∅

Pregnant Women and GD

The initial ATD daily dose depends on the severity of hyperthyroidism: MMI 5–15 mg, CBZ 10–30 mg, PTU 50–200 mg [139, 140]. MMI (CBZ) embryopathy, including dysmorphic facies, aplasia cutis, choanal or esophageal atresia, abdominal wall defects, umbilicocele, and ventricular septal defects, affects 2–4% of children who have been exposed to MMI, especially during gestational weeks 6–10 [137, 141]. The prevalence of birth defects is the same with PTU, but the spectrum of defects is less severe, primarily consisting of face and neck cysts and urinary tract abnormalities in males [142]. Propranolol 10–40 mg, 3–4 times daily may be used; however, long-term treatment should be avoided since beta-blockers may cause intrauterine growth restriction, fetal bradycardia, and neonatal hypoglycemia [143]. Thyroidectomy may be indicated in the case of allergy/contraindications to ATD and should be performed in the second trimester of pregnancy [136, 144].

Only 5% of TSH-R-Ab-negative patients relapse within 8 weeks after ATD withdrawal [145]. Therefore, when pregnancy is determined and remission is probable, ATD can be withdrawn and thyroid function monitored every 2 weeks during the first trimester of pregnancy. If the pregnant woman remains euthyroid, thyroid function is monitored every 4 weeks during the second/third trimester. A treatment period of less than 6 months, a high daily ATD dose, high levels of TSH-R-Ab, low/suppressed serum TSH levels while on medication, and the presence of GO increased the recurrence risk after ATD withdrawal [146, 147]. Maternal FT₄ (or TT₄) values should be maintained at the upper limit of the pregnancy-specific thyroid function tests [148]. During the third trimester, discontinuation of ATD is often feasible due to the disappearance of maternal TSH-R-Ab [135, 136]. In contrast, monitoring for the onset of neonatal dysthyroidism is indicated in the presence of high TSH-R-Ab serum levels (>3 times the cut-off) in the mother in late pregnancy [149–151]. In line with this and as a strong recommendation, all patients with a history of autoimmune thyroid disease should have their TSH-R-Ab serum levels measured at the first presentation of pregnancy using either a sensitive binding or a functional cell-based bioassay, and,

if they are elevated, again at 18–22 weeks of gestation [5, 21–23, 43, 44, 149, 150]. Finally, fetal/neonatal hyperthyroidism requires an acute management, including MMI, beta-blockade, and cardiovascular support therapy [43].

Recommendations

- 36 All patients with a history of autoimmune thyroid disease should have their TSH-R-Ab serum levels measured at the first presentation of pregnancy using either a sensitive binding or a functional cell-based bioassay and, if they are elevated, again at 18–22 weeks of gestation. 1, ØØØØ
- 37 If the maternal TSH-R-Ab concentration remains high (>3 times the cut-off), monitoring of the fetus for thyroid dysfunction throughout pregnancy is recommended. 1, ØØØØ
- 38 During pregnancy the lowest possible dose of ATD should be given and the block-and-replace ATD regimen is discouraged. 1, ØØØØ
- 39 Maternal FT4 (TT4) and TSH should be measured every 2 weeks after the initiation of therapy, and every 4 weeks after achieving the target value. 1, ØØØØ
- 40 A change from PTU to MMI should be considered if ATD are required after 16 weeks gestation. 1, ØØØØ
- 41 In women on a low dose of MMI (<5–10 mg/day) or PTU (<50–100 mg/day), ATD may be stopped during gestation prior to weeks 6–10. 2, ØØØØ

Postpartum Phase

The risk of GD recurrence was highest 7–9 months postpartum (RR 3.8) in studies conducted in Denmark and Japan [135, 152]. Only small amounts of ATD enter into breast milk, and low doses of PTU (<250 mg) and MMI (<20 mg) are considered safe for the mother and child. ATD should be taken after having breastfed the child and in divided doses [153, 154].

Recommendations

- 42 Lactating women with GD should be offered the same treatments as non-lactating women. 1, ØØØØ
- 43 MMI is recommended during lactation, given the concerns about PTU-mediated hepatotoxicity. 1, ØØØØ

The Elderly, Children and Adolescents, and Immune Reconstitution

Elderly

Although the incidence of GD decreases with advancing age, cases may still occur in patients in their 8th and

9th decades of life. A typical presentation with weight loss, tremor, agitation, and heat intolerance can occur; however, older individuals sometimes present with subtle symptoms such as fatigue, mood disturbance, or breathlessness (termed “apathetic thyrotoxicosis”). Dramatic presentations with atrial fibrillation, congestive cardiac failure, or ischemic acute coronary syndrome are also more frequent in older people. Treatment for those with severe thyrotoxicosis should be along similar lines to that in younger people, with an initial course of ATD to render the patient euthyroid, along with beta-blockers if appropriate. If there is atrial fibrillation or other tachyarrhythmia or cardiac compromise, it is good practice to proceed to early definitive therapy, normally with RAI, to prevent any further heart complication from recurrent hyperthyroidism. In older or frail patients with milder hyperthyroidism and without cardiac compromise, long-term low-dose MMI (CBZ) 2.5–5 mg daily is an effective and well-tolerated treatment, especially when there is no access to RAI and/or contraindication to thyroidectomy. Older patients are more likely to suffer severe consequences from ATD-induced agranulocytosis [155], and it is important to be meticulous in warning people about this issue, and providing written information to family or caregivers in the case of cognitive impairment. In addition, older patients have a higher chance of developing GO [156], so should be carefully assessed for this: where relevant, smoking cessation advice should be given and treatment-related hypothyroidism should be assiduously avoided.

Recommendations

- 44 Older patients who have had atrial fibrillation, cardiac failure, or cardiac ischemic symptoms precipitated by hyperthyroidism should undergo definitive therapy, usually RAI. 1, ØØØØ
- 45 Long-term MMI (CBZ) should be considered as a satisfactory treatment for older individuals with mild GD. 2, ØØØØ

Childhood and Adolescence

Children and teenagers frequently present late with GD and in retrospect features such as impaired educational performance, change in behavior, anxiety, or sleep disturbance may have been present for years before the cause is recognized. Importantly, the diagnosis is easily overlooked in teenage girls with weight loss who are assumed to have an eating disorder. The outcome of ATD treatment of younger people with GD is disappointing, as compared to the results in adults. Remission rates fol-

lowing 2 or more years of ATD therapy do not exceed 25% [157, 158], and this necessitates longer-term ATD administration in most children. Furthermore, there is a higher prevalence of adverse reactions to ATD in children and this means that PTU is no longer recommended for use in childhood, owing to hepatic failure in up to 1 in 2,000 children exposed [159]. If children develop adverse reactions while taking ATD, early surgery with total thyroidectomy is generally recommended. Over recent years, more confidence has been gained about the safety of RAI, particularly in postpubertal younger people [160]. Thus, long-term low-dose MMI (CBZ) followed, if necessary, by surgery or RAI when the child reaches a suitable age (16 years or older) is frequently the sequence of therapy in this age group. Any episode of hyperthyroidism or hypothyroidism (as a consequence of treatment), will likely have an effect on educational progress, and this factor should be taken into account in all decision making.

Recommendations

- 46 PTU should be avoided in children and adolescents. 1, ∅∅∅∅
- 47 Long-term MMI (CBZ) should be the mainstay of treatment in children with GD. 1, ∅∅∅∅
- 48 Thyroidectomy is the primary definitive therapy in childhood, but in postpubertal children RAI can be considered. 2, ∅∅∅∅

Immune Reconstitution

The first demonstration of immune reconstitution GD was in multiple sclerosis patients who had received lymphocyte-depleting alemtuzumab (Campath-H1) antibody treatment [161]. This treatment causes initial lymphopenia, but 12–24 months later 20–30% of patients developed TSH-R-Ab-positive GD, as lymphocyte populations recover. A similar pattern of GD has been observed in patients with HIV who have received effective highly active antiretroviral therapy, with hyperthyroidism developing as CD4 lymphocyte counts increase [162]. Immune reconstitution GD has also been observed in bone marrow transplant patients. In most cases, the hyperthyroidism is manageable and, depending on the underlying condition, it is not an indication to discontinue the immunomodulatory therapy that precipitated it. Although initial reports suggested that definitive therapy was warranted in these patients, additional experience now suggests that they can be managed similarly to patients with “spontaneous” GD [163]. However, as the immunological “insult” may be

transient in these cases, a reasonable approach is to treat with ATD until circulating TSH-R-Ab become undetectable.

Recommendations

- 49 Graves’ hyperthyroidism precipitated by an immunomodulatory therapy is not a mandatory indication to stop that precipitating treatment, nor is it a mandatory indication for definitive therapy for hyperthyroidism. 1, ∅∅∅∅
- 50 Sequential monitoring of serum TSH-R-Ab levels can be used to guide the duration of ATD therapy in patients with immune reconstitution GD. 2, ∅∅∅∅

Perspectives and Conclusions

Ongoing preclinical and clinical trials are assessing the effectiveness of novel drugs and/or substances that could modify the natural history of GD by modulating its pathogenesis. These therapeutic agents include TSH-R monoclonal Abs [164], immunomodulatory TSH-R peptides, and small-molecule TSH-R ligands [165] that can block the thyroid-stimulating effect of TSH-R-Ab, thus acting as TSH-R-Ab antagonists. However, the data are still too preliminary to predict whether these compounds will become available for the daily management of GD patients. Likewise, the use of biologicals, such as rituximab, although based on a sound rationale, is not supported by sufficient evidence [166]. Currently the optimal management depends on patient preference and specific patient clinical features such as age, history of arrhythmia or ischemic heart disease, size of goiter, and severity of thyrotoxicosis. Since each of the treatment modalities has unique limitations and adverse consequences, physicians need to be familiar with the advantages and disadvantages of each therapy in order to best counsel their patients.

The target audience for this guideline are physicians providing care for patients with GD. In this document rational medical practice is outlined. This guideline does not replace clinical judgment, individual decision making, or the wishes of the patient or family. Rather, each recommendation should be evaluated in light of these elements in order that optimal patient care is delivered. When the level of care required is best provided in centers where there is specific expertise, referral to such centers should be considered. The 50 recommendations that form these guidelines are presented together in Table 6.

Table 6. 50 recommendations that form these guidelines

Number	Recommendation	Strength and level of evidence
1	The measurement of TSH-R-Ab is a sensitive and specific tool for rapid and accurate diagnosis and differential diagnosis of Graves' hyperthyroidism	1, 0000
2	When technically available, differentiation of TSH-R-Ab functionality is helpful and predictive in Graves' patients during pregnancy/post-partum, as well as for extra-thyroidal manifestations	2, 0000
3	US examination, comprising conventional grey scale analysis and color-flow or power Doppler examination is recommended as the imaging procedure to support the diagnosis of Graves' hyperthyroidism	1, 0000
4	Scintigraphy of the thyroid is suggested when thyroid nodularity coexists with hyperthyroidism, and prior to radioactive iodine therapy	2, 0000
5	Patients with newly diagnosed Graves' hyperthyroidism should be treated with ATD. RAI therapy or thyroidectomy may be considered in patients who prefer this approach	1, 0000
6	MMI (CBZ) should be used in every non-pregnant patient who chooses ATD therapy for Graves' hyperthyroidism	1, 0000
7	MMI is administered for 12–18 months then discontinued if the TSH and TSH-R-Ab levels are normal	1, 0000
8	Measurement of TSH-R-Ab levels prior to stopping ATD therapy is recommended, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating a greater chance of remission	1, 0000
9	Patients with persistently high TSH-R-Ab at 12–18 months can continue MMI therapy, repeating the TSH-R-Ab measurement an after additional 12 months, or opt for RAI or thyroidectomy	1, 0000
10	Patients should be informed of potential side effects of ATD and the necessity of informing the physician promptly if they should develop jaundice, light-colored stools, dark urine, fever, pharyngitis, or cystitis	1, 0000
11	In patients taking ATD, a differential white blood cell count should be obtained during febrile illness and/or pharyngitis, and liver function should be assessed in those who experience jaundice, light-colored stools, or dark urine	1, 0000
12	Beta-adrenergic blockade is recommended in all suitable patients with Graves' hyperthyroidism	1, 0000
13	If a patient with GD becomes hyperthyroid after completing a first course of ATD, definitive treatment with RAI or thyroidectomy is recommended. Continued long-term low-dose MMI can be considered in patients not in remission who prefer this approach	1, 0000
14	Treatment of SH is recommended in Graves' patients >65 years with serum TSH levels that are persistently <0.1 mIU/L	1, 0000
15	ATD should be the first choice of treatment of Graves' SH	1, 0000
16	A multimodality treatment approach to GD patients with thyroid storm should be used, including ATD therapy, glucocorticoid administration, beta-adrenergic blockade, cooling blankets, volume resuscitation, nutritional support, respiratory care, and monitoring in an intensive care unit	1, 0000
17	There are no absolute indications for RAI therapy, but it is often recommended for patients with side-effects to, or recurrence after a course of ATD	1, 0000
18	Verbal as well as written information on all aspects of efficacy and potential side-effects of RAI therapy should be provided	1, 0000
19	If ATD are used before RAI therapy they should be paused around 1 week before and after therapy in order not to decrease the efficacy of RAI	1, 0000
20	No dose calculation can secure long-term euthyroidism and it is fully acceptable to offer a fixed dose of RAI	1, 0000
21	Pregnancy and breast feeding constitute absolute contraindications to RAI therapy	1, 0000
22	Conception should be postponed until at least 6 months after RAI in both males and females	1, 0000
23	If used in children, ablative doses aiming at rapid hypothyroidism should be administered	1, 0000
24	If surgery is selected, total thyroidectomy is the procedure of choice, and should be performed by a skilled surgeon with high annual volumes of thyroidectomies	1, 0000
25	Euthyroidism should be restored by ATD prior to surgery to avoid peri- or postoperative exacerbation of thyrotoxicosis	1, 0000
26	Vitamin D deficiency should be corrected to reduce the postoperative risk of hypocalcemia	1, 0000

Table 6 (continued)

Number	Recommendation	Strength and level of evidence
27	A solution containing potassium iodide can be given for 10 days prior to surgery	2, 0000
28	In patients with GO, hyperthyroidism should be promptly controlled by ATD, and euthyroidism stably maintained	1, 0000
29	Patients treated with RAI should receive steroid prophylaxis if mild and active GO preexists or there are risk factors for RAI-associated GO occurrence or progression	1, 0000
30	In patients with moderate-to-severe and active GO, treatment of GO should be the priority. Euthyroidism should be promptly restored with ATD and stably maintained	1, 0000
31	Patients with sight-threatening GO should be treated with ATD	1, 0000
32	Treatment for hyperthyroidism in patients with inactive GO can be selected independently of GO	1, 0000
33	Women with GD of reproductive age should be offered preconception counseling and be stably euthyroid before attempting pregnancy	1, 0000
34	Women with GD should be instructed to immediately confirm pregnancy and contact their physician	1, 0000
35	Women treated with MMI should be switched to PTU when planning pregnancy and/or during the first trimester of pregnancy	1, 0000
36	All patients with a history of autoimmune thyroid disease should have their TSH-R-Ab serum levels measured at the first presentation of pregnancy using either a sensitive binding or a functional cell-based bioassay and, if they are elevated, again at 18–22 weeks of gestation	1, 0000
37	If the maternal TSH-R-Ab concentration remains high (>3 times the cut-off), monitoring of the fetus for thyroid dysfunction throughout pregnancy is recommended	1, 0000
38	During pregnancy the lowest possible dose of ATD should be given and the block-and-replace ATD regimen is discouraged	1, 0000
39	Maternal FT4 (TT4) and TSH should be measured every 2 weeks after initiation of therapy, and every 4 weeks after achieving the target value	1, 0000
40	A change from PTU to MMI should be considered if ATD are required after 16 weeks gestation	1, 0000
41	In women on a low dose of MMI (<5–10 mg/day) or PTU (<50–100 mg/day), ATD may be stopped during gestation prior to weeks 6–10	2, 0000
42	Lactating women with GD should be offered the same treatments as non-lactating women	1, 0000
43	MMI is recommended during lactation, given the concerns about PTU-mediated hepatotoxicity	1, 0000
44	Older patients who have had atrial fibrillation, cardiac failure, or cardiac ischemic symptoms precipitated by hyperthyroidism should undergo definitive therapy, usually RAI	1, 0000
45	Long-term MMI (CBZ) should be considered as a satisfactory treatment for older individuals with mild GD	2, 0000
46	PTU should be avoided in children and adolescents	1, 0000
47	Long-term MMI (CBZ) should be the mainstay of treatment in children with GD	1, 0000
48	Thyroidectomy is the primary definitive therapy in childhood, but in post-pubertal children RAI can be considered	2, 0000
49	Graves' hyperthyroidism precipitated by an immunomodulatory therapy is not a mandatory indication to stop that precipitating treatment, nor is it a mandatory indication for definitive therapy for hyperthyroidism	1, 0000
50	Sequential monitoring of serum TSH-R-Ab levels can be used to guide the duration of ATD therapy in patients with immune reconstitution GD	2, 0000

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