2022 Update on Clinical Management of Graves Disease and Thyroid Eye Disease

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KEYWORDS

• Hyperthyroidism • Graves disease • Thyroid eye disease • Antithyroid drugs • Radioiodine therapy • Thyroidectomy

KEY POINTS

- Initial ATD dosing should be individualized based on thyroid hormone levels. PTU should be used only in the first trimester of pregnancy, thyroid storm, or when patients develop minor adverse reactions to MMI.

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- Baseline complete blood count with differential and liver function profile should be obtained prior to starting ATDs. Regular clinical and biochemical evaluation of thyroid function is required in patients taking ATDs.
- RAI is an effective and safe GD therapy which should be administered with sufficient activity to render the patient hypothyroid (greater than 150 μCi/g (5.55 MBq/g)), either in a fixed or calculated dose. RAI should not be used in patients with moderate or severe TED.
- General treatment of patients with TED includes (a) reversal of hyperthyroidism, (b) monitoring for and prompt treatment of hypothyroidism, and (c) cessation of smoking, if applicable.
- Treatment of TED should be initiated immediately to target the active, inflammatory phase of the disease to decrease disease severity. Surgical treatment may be required urgently in the case of compressive optic neuropathy, globe subluxation, or corneal decompensation.

INTRODUCTION

Background

Although the basic treatment options for hyperthyroidism due to Graves disease (GD) have seemed immutable for more than three-quarters of a century, its management remains complex. The endocrinologist must consider a multitude of factors including patient preference, age and comorbidity, pregnancy, or pregnancy potential, the influence of social factors such as tobacco smoking and the likelihood of adherence to medical therapy, and comanagement of extrathyroidal manifestations such as orbitopathy. This article leverages a multidisciplinary team to synthesize a current understanding of the pathophysiology, contemporary understanding of benefits and risks of treatment, and factors influencing trends in management of GD, arriving at a pragmatic approach to effective therapy. In addition, with the rollout of promising new therapeutic opportunities for thyroid eye disease (TED), a timely review of the complex management of this disorder is provided.

Diagnosis and Initial Management of Graves Disease

Initial triage

Evaluation of a new patient with thyrotoxicosis requires immediate answers to key questions (**Box 1**). Acute complications requiring immediate intervention include ischemia, atrial fibrillation,[1] congestive heart failure, thromboembolism,[2] stroke,[3] psychosis,[4] periodic paralysis,[5] and thyroid storm.[6] Each requires specific intervention in addition to normalization of thyroid hormone levels.

Diagnostic evaluation

A diagnosis of GD can be made clinically in a patient with diffuse goiter, elevations in serum thyroxine (T_4), and a suppressed thyroid-stimulating hormone (TSH) value. If uncertainty remains after initial evaluation, the 2016 American Thyroid Association (ATA) Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis suggest that any one or more of 3 methods may be used, including TSH-receptor (TSH-R) antibody (TRAb) testing, radioactive iodine uptake (RAIU), or demonstration of diffusely increased vascularity on Doppler flow ultrasonography.[7] Modern TRAb testing has high sensitivity and specificity for the diagnosis of GD, on the order of 97% and 99%, respectively.[8]

Table 1
Comparative adverse effects of methimazole and propylthiouracil

Adverse Side Effects	MMI	PTU	Mean Onset	Treatment
Pruritus or minor rash	6%	3%	18–22 d of treatment	Antihistamines, CS, ± stop ATD
Hepatotoxicity (cholestatic & hepatocellular)	0.4%	2.7%	28–90 d	Stop ATD
Liver failure	0.03%	0.05%	27–127 d	Stop ATD, supportive care
Agranulocytosis	0.1%–0.3%	0.1%–0.3%	30–90 d	Stop ATD, recommend GCSF, CS, supportive care
Vasculitis (p-ANCA positive)	≤0.1%	≤0.1%	Weeks to months	Stop ATD, CS
Drug-induced lupus	None	Case reports only	Weeks to months	Stop ATD, CS
Insulin autoimmune syndrome with symptomatic hypoglycaemia	6.3%	0%	30–60 d	Stop ATD, CS, diazoxide

Abbreviations: ATD, antithyroid drug; CS, corticosteroids; GCSF, granulocyte colony-stimulating factor; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies.

Shared Decision Making in Graves Disease

Equipping a patient with an understanding of the benefits and risks associated with each of the treatment options for GD and taking into consideration their personal values are both critical. Patients are asked to choose between treatments that damage or remove the thyroid, on the one hand, and pharmacologic therapy with a low cure rate and a potential for serious adverse effects, on the other. Patients must be aware that medical therapy may be required chronically to sustain euthyroidism, and that serial laboratory testing and monitoring for adverse effects will be required. In addition, patients should be apprised of the risk of new or worsened orbitopathy after radioiodine therapy, and transient or permanent hypoparathyroidism or vocal cord dysfunction following thyroidectomy. Finally, patients should be familiar with the relative costs and cost-sharing associated with each of the 3 modalities. Detailed analyses of clinical factors and patient preferences favoring a specific treatment of hyperthyroidism in GD are available.[7,9] Clinical factors influencing choice of therapy are summarized in **Box 2**.

MEDICAL THERAPY WITH THIONAMIDES

Antithyroid Drug Dosing Principles

Antithyroid drugs (ATDs) are effective in controlling hyperthyroidism when given in proper doses with patient adherence. Methimazole (MMI) should be used in patients who choose ATD therapy for GD, except (1) during the first trimester of pregnancy when propylthiouracil (PTU) is preferred, (2) in the management of thyroid storm[6], and (3) in patients with minor adverse reactions to MMI who refuse radioactive iodine (RAI) therapy or surgery.[7]

Current practice guidelines suggest an initial MMI dosing of 5 to 10 mg daily if free T_4 is 1 to 1.5 times the upper limit of normal; 10 to 20 mg daily if free T_4 is 1.5 to 2 times the upper limit of normal; and 30 to 40 mg daily for free T_4 2 to 3 times the upper limit of

Box 1
Triage in patients presenting with overt thyrotoxicosis

- Is the patient experiencing acute complications requiring urgent intervention, such as ischemia, atrial fibrillation, or impending thyroid storm?
- What is the cause of the patient's thyrotoxicosis? Is GD apparent clinically?
- What are the patient's comorbidities?
- What initial testing is required?
- What therapy should be instituted at the first encounter?

normal.[7] The minimal effective dose of MMI is recommended to minimize adverse effects. MMI can be given once a day compared with PTU, which has a shorter duration of action and is usually administered as 50 to 150 mg 3 times daily. A comparison of adverse effects from MMI and PTU (Table 1).

Chronic Antithyroid Drug Therapy

ATDs have historically been prescribed with the objective of permitting a remission from GD within a prescribed period, after which patients were considered treatment failures and approached with radioiodine (RAI) therapy or thyroidectomy. However, chronic low-dose ATD therapy seems to be a reliable alternative to ablative therapy.[10,11] Patients in the United States increasingly select ATD therapy.[12,13] Adverse effects occur less frequently on low maintenance doses of MMI,[14,15] and most cases of agranulocytosis and severe hepatotoxicity occur within the first 3 months of therapy.[11,16] A study of patients failing to remit after an initial course of ATDs who were then randomized to either continued ATD therapy or radioiodine found 10-year costs

Box 2
Clinical factors that favor a particular treatment modality for hyperthyroidism in Graves disease*

ATDs
- Patients with high likelihood of remission (women, mild disease, small goiter, negative or low titers of thyrotropin receptor antibody)
- Elderly or those with comorbidities and increased surgical risk or short life expectancy
- Patients with moderate to severe active Graves ophthalmopathy

Radioiodine
- Contraindication to ATD use (severe adverse reactions, liver disease)
- Women planning pregnancy more than 6 to 12 months following RAI
- Patients with increased surgical risk (comorbidities, prior neck surgery, or radiation)
- Lack of access to high-volume thyroid surgeon

Surgery
- Patients with symptomatic compression or large goiters
- Patients with low RAIU
- When concurrent indications for surgery (thyroid cancer, hyperparathyroidism, suspicious thyroid nodules)
- Patients with moderate to severe active TED
- Women planning pregnancy in less than 6 months who wish to avoid ATDs

Abbreviations: ATD, antithyroid drug; RAI; radioactive iodine.

**Data from* Refs.[7,10]

of management similar or slightly lower with chronic ATD therapy, and episodes of hypothyroidism occurred more frequently after RAI therapy than with chronic ATDs.[17] In another study, long-term ATDs in patients with GD treated up to 11 years and then followed for an average of 4.5 years after stopping ATDs found a remission rate of 63%.[18] A retrospective study of patients treated with either continued low-dose ATDs or radioiodine after an initial relapse following ATD therapy showed that ATD-treated patients had better preservation of euthyroidism, less weight gain, and less orbitopathy deterioration compared with those treated with radioiodine.[19] Conversely, chronic ATD therapy requires serial dose adjustment and monitoring for rare late-occurring adverse effects related to ATDs.[20]

Monitoring Patients Taking Antithyroid Drug Therapy

Pretreatment considerations

Before starting ATD therapy, a baseline complete blood cell count, including white blood cell count with differential, and a baseline liver function profile, including transaminases and bilirubin, should be obtained. Mild leukocytopenia is common in patients with GD before starting ATDs. Notably, 10% of African Americans have neutrophil counts less than 2000 normally. Mild transaminase elevation occurs frequently in thyrotoxicosis.[21] Patients should be counseled verbally and in writing regarding the potential side effects of ATD therapy.[7]

Monitoring therapy

Serum TSH, free T_4, and total or free T_3 levels should be obtained initially at 2- to 4-week intervals after starting ATDs, and the dosage should be adjusted accordingly. Serum TSH levels may remain low for months after initiating ATD therapy. Serum free T_4 levels may normalize despite persistent elevated total or free T_3 level; thus, serum total or free T_3 level should also be monitored.[7]

Once the patient is biochemically euthyroid, gradual lowering of the MMI dose is advised, with repeated laboratory testing in 4 to 6 weeks. Euthyroid levels should be achieved with minimal ATD therapy dosage, and repeat testing should be done at approximately 2 to 3 months or longer intervals for long-term therapy.

Patients should be advised regarding the potential adverse effects of ATDs. A differential white blood cell count should be obtained during febrile illness or pharyngitis in all patients taking ATDs. Liver function tests should be checked in patients taking ATDs who develop jaundice, pruritic rash, light-colored stool or dark urine, arthralgia, abdominal pain, anorexia, nausea, or fatigue. After discontinuation of ATDs, liver function tests should be monitored weekly until normalization occurs. Routine monitoring of complete blood cell count and liver function by endocrinologists is commonly performed,[13] although controversial.[7] ATDs should be discontinued if transaminase levels are more than 3 times the upper limit of normal or if the transaminitis worsens.[7]

RADIOIODINE THERAPY

Background and Mechanism

RAI has been a safe and effective treatment option for hyperthyroidism for more than 8 decades.[22] RAI is well-tolerated and has few associated adverse effects in treatment doses for GD.[7] RAI is a β-radiation emitter with a long physical half-life of just more than 8 days, which is rapidly concentrated by the thyroid after oral ingestion. The β-particle has a range in tissue of approximately 2 mm and induces DNA damage and eventual thyroid cell death, rendering most patients with GD hypothyroid over a period of 6 weeks to 6 months.

Preparation for Radioiodine Therapy

The ATA hyperthyroidism guidelines identify several contraindications to the use of RAI, including pregnancy, lactation, known or suspected coexistent thyroid cancer, inability to comply with radiation safety guidelines, and planned pregnancy within the subsequent 6 months.[7] Moderate to severe and sight-threatening TED is also considered a contraindication to RAI.[7,23,24] In this clinical setting, ATDs or thyroidectomy are favored, because these demonstrate no significant effect on the course of TED.[24,25]

Patients with active mild TED are candidates for oral glucocorticoid therapy (0.3–0.5 mg of prednisone per kg of body mass per day, started 1–3 days after RAI administration, tapered over 3 months).[7,23,26] Shorter courses at lower doses (0.2 mg per kg of body mass per day for 6 weeks) may be equally protective.[7,26] Prophylactic use of glucocorticoids in patients without preexisting orbitopathy remains controversial.[23]

The goal of RAI treatment in GD is to administer sufficient activity to render the patient hypothyroid.[7] This goal can be accomplished with the use of a fixed dose or calculating the activity based on goiter size and RAI uptake.[7,27] To achieve hypothyroidism, activity of greater than 150 μCi/g (5.55 MBq/g) should be administered.[7] The efficacy of RAI strongly depends on the activity administered, with success rates ranging from 61% with 5.4 mCi (200 MBq) to 86% with 15.7 mCi (580 MBq).[28] To avoid the necessity for retreatment, therapy with lower activities is generally not recommended.[7]

Radioactive Iodine Therapy Outcomes

ATDs have a treatment failure rate of approximately 50%, followed by 7% for RAI and less than 1% for thyroidectomy.[29,30] In a nationwide population-based study, patients undergoing thyroidectomy had the highest rate of complications, at 24%, mostly either transient or chronic hypoparathyroidism. Patients on ATD had a complication rate of 12%, followed by patients receiving RAI at 6%. New-onset TED occurred in 7% of patients on ATD and 6% of those receiving RAI.[29] Early and successful RAI treatment was associated with a 50% reduction in mortality compared with ATD treatment, but this advantage was lost when the RAI failed to resolve the hyperthyroidism.[31,32]

Specifically addressing TED outcomes, RAI therapy for GD is associated with new or worsened TED with an incidence of 10% to 39%,[7,25,33–35] and in approximately 5%, these changes persisted after 1 year, requiring additional treatment.[25,36] The mechanism of this association is incompletely understood, but it is postulated that RAI-induced leakage of thyroid antigen and increased production of TRAb, thyroid peroxidase, and thyroglobulin contributes to the development or worsening of TED.[34] The risk of worsening TED can be mitigated and almost eliminated in cases of mild disease with a short course of oral glucocorticoids and avoiding posttreatment hypothyroidism.[7,36]

Radioactive Iodine Usage Trends in the United States

RAI was favored by 60% in the United States in a 2011 survey of endocrinologists,[13] reduced from 69% in 1990. A 2020 analysis of private insurance claims in 4661 patients for GD showed that only 33% of this selected group received initial therapy with RAI, whereas another 8.9% received RAI after ATD failure.[29]

Radioactive Iodine and Cancer Controversy

The association of RAI use in hyperthyroidism with an increased cancer incidence remains controversial. RAI in patients with hyperthyroidism has been associated with

increased,[37–39] similar,[40] and even decreased[41,42] rates of overall cancer mortality. Those studies that demonstrated increased rates have been criticized for failing to adjust for confounders such as smoking, obesity, alcohol intake, and thyroid status.[31,39,43] In a recent analysis of a multicenter cohort of patients with hyperthyroidism treated with ATDs, RAI, or surgery, there were no differences in solid cancer mortality among groups when controlling for confounders, but within the RAI subgroup there was a modest dose-dependent association between RAI and mortality.[44] Hyperthyroidism itself is associated with an increased cancer risk, making a lack of a hyperthyroid control group a challenge in interpreting cohort studies.[31,42,43] The risks of both cardiovascular and cancer mortality in patients with hyperthyroidism can primarily be attributed to thyroid hormone excess, leading some to conclude that even a marginal increased cancer mortality in RAI would be offset by improved hyperthyroidism control with RAI over ATD.[31]

THYROIDECTOMY

Overview

Surgery is recommended by fewer than 1% of thyroid experts for the initial management of GD.[13] Indications include large goiters with compressive symptoms, concurrent suspicious thyroid nodules or hyperparathyroidism requiring surgery, and patient preference.[7] Health disparities are evident in the selection of thyroidectomy to treat GD, with black Americans twice as likely in one study to undergo surgery than whites with GD,[45] and this surgery is more frequently performed by lower-volume surgeons than that seen in whites.[46]

Preparation for Thyroidectomy

Patients selecting thyroidectomy to treat GD should first be rendered euthyroid using ATDs[7]; this typically requires 1 to 3 months of ATDs before thyroidectomy. Rapid preoperative preparation is occasionally needed for patients requiring urgent surgery[47] or in patients with contraindications to ATDs. Safe and effective oral therapy with a combination of β-blockers (propranolol 40 mg every 8 hours), high-dose glucocorticoids (betamethasone 0.5 mg every 6 hours), and sodium iopanoate (500 mg every 6 hours) has been reported in a small number of patients requiring urgent surgery.[48] This regimen was given for 5 days with surgery performed on the sixth day. Dexamethasone and hydrocortisone decrease T_4-to-T_3 conversion and have an important role in this setting. A recent case series reported the combination of iodine, dexamethasone, and propranolol to rapidly restore euthyroidism before thyroidectomy in 10 patients with GD.[49] Emergent preparation for thyroid surgery at our center in patients unable to use ATDs[47] has involved the regimen in **Box 3**, typically given in the inpatient setting for 5 to 10 days before thyroidectomy, with rapid correction of thyrotoxicosis.

THYROID EYE DISEASE

Referral Guidance

TED is a debilitating autoimmune disease with an incidence of 1.9 cases per 10,000 population per year.[50] Although most frequently associated with hyperthyroidism secondary to GD, about 10% of patients with TED are euthyroid or hypothyroid. The mechanism of action is not completely understood but is characterized by the activation of orbital fibroblasts by TRAb binding, leading to the expression of extracellular matrix molecules and deposition of glycosaminoglycans, resulting in swelling, congestion, and connective tissue modeling. The overall result is extraocular muscle enlargement and orbital fat expansion. As discussed later, recent work has suggested

a role for cross-linking of the insulinlike growth factor 1 (IGF-1) receptor with the TSH-R in orbital tissue.[51]

Control of thyroid function is crucial in all patients with TED; however, the course and severity does not always correlate with thyroid hormone levels. When assessing patients for TED activity, the 7-point Clinical Activity Score (CAS) is frequently used, in which one point is assigned for pain behind the eyes, pain with eye movement, eyelid swelling, eyelid edema, conjunctival redness, chemosis (scleral edema), or caruncle swelling, and a score of 3 or greater is considered active disease.[52]The EUGOGO (European Group of Graves' Orbitopathy) system is commonly used to describe TED severity as mild, moderate to severe, or sight threatening, whereas the VISA (Vision, Inflammation, Strabismus, and Appearance) system may be used to assess both TED activity and severity.[53] If a patient exhibits any significant signs of TED or is experiencing eye discomfort, referral to an ophthalmologist is indicated.

Thyroid Eye Disease Risk Factors

In contrast to GD for which women are at higher risk, the role of sex in TED is controversial. Recent studies do not find an obvious sex-related risk for TED, whereas earlier studies suggested a slightly increased risk for men. This variability might relate to changes in smoking trends over the years. The prevalence of TED is higher with aging (40–60 years), and peaks in the fifth and sixth decades of life.[54–57]

Identified risk factors for TED include smoking, sex, advanced age, genetics including HLA DRB3*0101/*0202 heterozygosity,[58] wider lateral wall orbital angle, high TRAb levels, high pretreatment levels of T_3 and T_4, uncontrolled hypothyroidism/hyperthyroidism, and RAI therapy. Smoking is the most important risk factor for TED with the risk proportional to the number of cigarettes smoked per day. Former smokers have lower risk than current smokers. Patients should be referred to smoking cessation programs. Recent data suggest that statin usage is correlated with a lower risk of orbitopathy in patients with GD.[59]

Eye Assessment

Formal ophthalmology assessment

TED is diagnosed when 2 of 3 findings occur together, including immune-related thyroid dysfunction, one or more ocular signs, or radiologic evidence of tendon-sparing fusiform enlargement of one or more extraocular muscles. The most common signs of TED are eyelid retraction (Dalrymple sign), lid lag of the upper eyelid on downgaze (von Graefe sign), and lid edema. TED is the most common cause of proptosis, both unilateral and bilateral, in adults. Other clinical features include lagophthalmos, exposure keratopathy, chemosis and conjunctival injection, restrictive extraocular motility, and compressive optic neuropathy. Patients with TED typically have symptoms of ocular surface discomfort, such as tearing, dry eyes, swelling of the lids, or redness

Box 3
Rapid preparation for thyroidectomy in patients unable to use antithyroid drugs

- Propranolol, 60 mg orally, twice daily
- Dexamethasone, 2 mg intravenously, 4 times daily
- Cholestyramine, 4 g orally, 4 times daily
- SSKI*, 2 drops orally, 3 times daily

*SSKI, supersaturated potassium iodide.

of the lids or conjunctiva. Compressive optic neuropathy, often heralded by dyschromatopsia, decreased vision, and/or visual field defects, is considered an ophthalmic emergency requiring immediate treatment.

At every ophthalmology visit, best-corrected visual acuity, color vision, extraocular motility, and intraocular pressure are measured, and a pupillary examination is performed to assess for relative afferent pupillary defect. An external examination is performed assessing standard lid measurements, exophthalmometry, and resistance to retropulsion. A slit lamp and dilated funduscopic examination are performed. Static perimetric visual field examination is required at baseline to assess for visual field deficits with interval repeat testing as indicated by disease activity and severity.

Imaging

The diagnosis of TED is usually made clinically.[60,61] In unusual or unilateral cases, orbital imaging can play an important role in establishing the diagnosis, providing a differential diagnosis for management, and assisting in clinical and surgical follow-up. MRI, computed tomography (CT), ultrasonography, color Doppler imaging, and octreotide scintigraphy can each play a role in TED diagnosis and management.[60,61] CT continues to play a key role in the diagnosis of TED due to its superior characterization of the bones and soft tissues and remains the preferred imaging modality for orbital decompression planning in patients requiring surgical management.[23,61] MRI is considered the preferred imaging modality for detecting disease activity, given its superior ability to characterize soft tissues, and is also considered by some to be the preferred choice for diagnosis of TED.[23] MRI does not subject the lens of the eye to ionizing radiation, an important benefit over CT.[60,61] As in GD treatment options, significant regional practice variation exists in the use of imaging in moderate TED, with providers in the European Union obtaining CT and MRI imaging more often than those in the United States.[62]

General Treatment Measures

General treatment of patients with TED includes (1) reversal of hyperthyroidism, (2) monitoring for and prompt treatment of hypothyroidism, and (3) cessation of smoking, if applicable. Clinicians should advise their patients with GD to stop smoking and refer them to a structured smoking cessation program. Because both first- and secondhand smoking increase TED risk, patients with exposure to secondhand smoke should be advised of its negative effects and avoidance of second-hand smoke.[63,64]

Local measures to improve symptoms may include eye shades, artificial tears, elevation of head during sleep, and avoidance of eye cosmetics. For mild, active TED, topical artificial tears in drop, gel, and ointment (1% methylcellulose drops and/or petrolatum jelly) are key to maintaining a healthy ocular surface. If there are signs of focal eye inflammation, topical glucocorticoid ophthalmic drops may reduce inflammation, but evidence supporting this practice is scarce. Topical cyclosporine has been shown to be beneficial in reducing ocular surface inflammation. Selenium supplementation has been shown to improve the course of mild TED in areas of relative selenium deficiency.[65] Eye patching or prisms can be useful to treat diplopia while waiting for eye muscle stability before strabismus surgery.

TED is a self-limiting disease, with patients progressing from the active to quiescent phase within 1 to 3 years with a 5% to 10% risk of future recurrence. Once TED is diagnosed, treatment should commence immediately to target the active, inflammatory phase of the disease and decrease disease severity that can be more recalcitrant to treatment in the chronic or fibrotic phase of the disease.

Medical Therapy for Thyroid Eye Disease

Glucocorticoids

Intravenous (IV) glucocorticoids (IVGC) are considered first-line therapy in patients with moderate to severe TED. The preferred regimen involves delivery of a 4.5 g dose of methylprednisolone over 12 weeks, typically given as 0.5 mg IV weekly for 6 weeks and then 0.25 g weekly for another 6 weeks.[66] For patients with diplopia due to extraocular muscle involvement, higher cumulative doses up to 7.5 g have been used with greater benefit,[67] but it is important that the total dose remain under 8 g, to avoid potentially severe toxicity.[68,69] Oral glucocorticoids are less effective and more poorly tolerated than IVGC.[66] Topical glucocorticoid drops and intraocular depot injections have not been shown to be efficacious when compared with systemic therapy, and intraocular injections are associated with potentially severe adverse effects, including blindness. Patients receiving glucocorticoids for TED require continuous surveillance for a host of adverse effects including hyperglycemia, hypertension, glaucoma, hip osteonecrosis, and psychosis.

Teprotumumab

Teprotumumab, an IGF-1 receptor inhibitor, was approved to treat TED by the US Food and Drug Administration in 2020, based on the results of two 24-week trials comparing teprotumumab with placebo in patients with active, moderate to severe orbitopathy.[70,71] In the first trial, improvement of CAS by 2 points or more *and* reduction in proptosis by greater than or equal to 2 mm, together, occurred in 69% of patients with teprotumumab versus 20% with placebo.[71] In the second trial, the primary outcome of proptosis improvement by greater than or equal to 2 mm occurred in 83% of patients treated with teprotumumab versus 10% with placebo,[70] whereas a secondary outcome of combined improvement in CAS and proptosis occurred in 78% with teprotumumab versus 7% with placebo.[70] Assessment of the durability of effect will require further long-term follow-up studies. Cost may play a key role in clinical decision making.

Teprotumumab is administered IV every 3 weeks (10 mg/kg first dose, then 20 mg/kg) for a total of 8 infusions. Common side effects include nausea, diarrhea, muscle spasms, hearing impairment, dysgeusia, headaches, dry skin, infusion reactions, alopecia, paresthesia, weight loss, and hyperglycemia. Other possible serious effects reported include optic neuropathy, encephalopathy, urinary retention, inflammatory bowel disease activation, and neurocognitive decline.[72] Teprotumumab is contraindicated in pregnancy and not approved for children younger than 18 years.

Selenium

Selenium may improve symptoms in patients with mild TED, especially in regions of selenium insufficiency. One study compared selenium (100 μg twice a day), pentoxifylline (600 mg twice a day), or placebo in 159 patients with mild TED from a region in which selenium levels are marginally decreased.[65] These patients had at least one sign of mild orbitopathy (chemosis, mild to moderate eyelid swelling, exophthalmos $\leq$22 mm) and disease duration of less than 18 months. After 6 months of treatment, selenium (but not pentoxifylline) was associated with an improved quality of life (both visual functioning and appearance scores), and less eye involvement and slowed the progression of TED. Evaluation at 12 months confirmed the results at 6 months. Neither placebo nor pentoxifylline improved quality-of-life measures.

It is uncertain whether selenium benefits individuals with mild TED who reside in selenium-sufficient regions such as the United States.

At present, the european thyroid association (ETA)/ EUGOGO recommends 6 months of selenium supplementation in patients with mild TED of short duration

because it may improve eye manifestations and quality of life and prevent TED progression to severe forms.[73,74]

Mycophenolate mofetil

Mycophenolate mofetil is an immunosuppressive with relatively mild side effects, commonly used after organ transplantation. As a potent selective, noncompetitive, and reversible inhibitor of inosine-5′-monophosphate dehydrogenase, it inhibits T- and B-lymphocyte proliferation and reduces immunoglobulin production; it also suppresses dendritic cell maturation, reducing its ability for antigen presentation to T lymphocytes.[75,76] In a trial comparing mycophenolate mofetil 500 mg twice a day for 24 weeks with glucocorticoids 0.5 g IV daily for 3 days, followed by 60 mg oral daily for 8 weeks and then tapered in 174 Chinese patients with active moderate to severe TED, the overall result was better with mycophenolate at 24 weeks (91.3% vs 67.9%) with concurrent improvement in 3 or more features including CAS, diplopia, proptosis, visual acuity, soft tissue swelling, or diplopia.[77] Another randomized study of 164 patients with active moderate to severe TED treated with methylprednisolone alone versus methylprednisolone with mycophenolate showed no significant difference in the rate of response at 12 weeks or rate of relapse at 24 and 36 weeks; however, posthoc analysis showed that addition of mycophenolate to methylprednisolone improved response to therapy at 24 weeks in patients with active and moderate to severe TED.[78] A recent study found a favorable risk-benefit ratio for low-dose mycophenolate therapy in active moderate to severe TED.[79] The 2021 EUGOGO Clinical Practice Guidelines recommend combined use of IVGC and mycophenolate as first-line therapy for active moderate to severe TED.[74]

Tocilizumab

Tocilizumab is a humanized monoclonal antibody against the interleukin (IL)-6 receptor. Dosing is 8 mg/kg at 4 monthly infusions. This agent targets IL-6. A randomized trial of 32 patients with moderate to severe corticosteroid-resistant TED randomly assigned patients to tocilizumab (8 mg/kg) or placebo, administered IV at weeks 0, 4, 8, and 12. Tocilizumab therapy was associated with greater improvement in CAS at 16 weeks (93.3% vs 58.8%) and improved composite ophthalmic score at 16 weeks (73.3% vs 29.4%); however, no significant differences persisted between groups at 40 weeks.[80] Case reports and a small series of 9 patients (aged 40–84 years) with chronic, active, moderate to severe TED treated with subcutaneous tocilizumab after failing other interventions showed clinical improvement in CAS, with decreases in thyroid-stimulating immunoglobulins (TSI) also observed.[81,82] Optimal duration of treatment with tocilizumab remains undetermined.

Rituximab

Rituximab is a chimeric human and mouse monoclonal antibody against CD20 antigen on B cells. Rituximab decreases TRAb levels and depletes B cells in the thyroid and retro-orbital tissues.[83] For treatment of TED, 2 infusions of rituximab (1000 mg each and 2 weeks apart) have been used without immunosuppressive effects.

Two prospective studies using rituximab for TED produced conflicting results,[84,85] possibly related to shorter disease duration in the trial showing beneficial effects.[84] Both trials reported a high rate of adverse effects from rituximab (ie, optic neuropathy and infusion reactions). Meta-analyses suggest that IV rituximab has an acute and long-lasting beneficial effect on reducing both CAS and TRAb; however, the effect on proptosis is limited.[86–88] At present, the therapeutic role of rituximab remains uncertain.

Surgical Approach to Thyroid Eye Disease: What an Endocrinologist Needs to Know

Surgery for TED is typically performed either emergently, such as for optic neuropathy, globe subluxation, or corneal thinning/perforation due to exposure keratopathy, or for rehabilitation after the disease has run its active course.

Dysthyroid optic neuropathy (DON) occurring in the setting of TED is due to inflammation and congestion of the orbital apex, which compresses the blood supply of the optic nerve within the bony orbit. DON presents with insidious, progressive, typically bilateral (but asymmetric) vision loss; dyschromatopsia; and visual field deficits. DON is surgically treated with orbital decompression to relieve the pressure on the optic nerve and blood supply; this is often performed in combination with systemic IV corticosteroids. Orbital decompression is performed by removing bone, and sometimes orbital fat, to expand the boundaries of the orbit,[89] allowing for the enlarged retro-ocular tissue mass to decompress from its normal confined space. The most commonly decompressed walls of the orbit are the lateral, medial, and floor. Orbital roof decompressions are performed rarely, and always with the involvement of neurosurgeons. This surgery is performed under general anesthesia and, if done emergently, requires inpatient admission for close interval evaluation.

Globe subluxation occurs when the pressure inside the orbit due to tissue expansion leads to anterior displacement of the eye, usually when then equator of the globe protrudes beyond the retracted lids. This is a rare and dramatic orbital complication. Immediate treatment is vital, with digital or surgical repositioning of the globe.[90] If this fails, lateral tarsorrhaphy or orbital decompression is warranted to protect the exposed ocular surface.

If corneal integrity is threatened due to prolonged exposure from proptosis, eyelid retraction, lagophthalmos, or a poor Bell reflex, urgent surgery is also indicated. Corneal desiccation can lead to decreased vision, diminished barrier to infection, corneal thinning, and corneal perforation. If the cornea has perforated, it must be emergently repaired or patched to maintain the integrity of the globe. If the cornea is threatened, a surgical temporary tarsorrhaphy may be performed to close the lids partially or fully and decrease corneal exposure.

Nonemergent surgery for TED can be considered when the disease is in the quiescent phase and no reactivation is suspected. The surgery occurs in 3 phases—orbital decompression, strabismus surgery, and eyelid surgery—with the potential for more than one surgery per phase. Because orbital decompression can alter globe positioning, decrease eyelid retraction, and affect extraocular motility, it should precede any strabismus or eyelid surgeries.[91]

TED affects extraocular muscles through inflammation and fibrosis of the muscle belly, leading to diplopia through restriction of extraocular motility. Most patients with diplopia due to strabismus will not require surgery and can be managed with prism spectacles. Strabismus surgery is reserved for patients with intractable diplopia in primary gaze or with reading, abnormal head positioning due to compensation for diplopia, or cosmetically unacceptable globe position. Owing to the relationship of the vertical eye muscles with the eyelid, strabismus surgery should be performed before eyelid procedures.

Eyelid changes due to TED are common and include upper and lower eyelid retraction and eyelid fat compartment expansion. Eyelid retraction surgery is aimed at lowering the upper eyelid and raising the lower eyelid to correct the “thyroid stare” appearance. Eyelid contouring is targeted to restore the natural height and contour of the eyelid, including decreasing the fat compartment expansion and minimizing

the temporal flare, which occur as part of the disease state. Eyelid surgery is typically the last step in the rehabilitation of the patient's appearance. The total time between onset of TED to the final eyelid surgery can span several years.

CLINICS CARE POINTS

- Assess new patients with hyperthyroidism for acute severe complications including cardiac ischemia, arrhythmia, congestive heart failure, and thyroid storm
- Shared decision making that includes the patient and family members should be maximized when selecting primary treatment of GD
- Liver-associated enzymes and a complete blood cell count should be obtained before starting ATDs
- Dosing with methimazole should be individualized and based on the severity of thyrotoxicosis
- Patients treated with ATDs should be repeatedly apprised of warning signs for agranulocytosis, hepatotoxicity, and vasculitis
- Radioiodine therapy should be avoided in patients with active moderate to severe TED
- Patients unable to take ATDs who are not candidates for radioiodine therapy may generally be prepared for surgery with combination therapy using corticosteroids, potassium iodide, beta-adrenergic blocking agents, and cholestyramine to normalize thyroid hormone levels preoperatively
- TED should be comanaged by endocrinologists and ophthalmologists with experience managing this disorder
- IVGCs should be considered primary initial therapy for active TED
- Teprotumumab should be considered in patients with moderate to severe TED with proptosis, but it should be acknowledged that the long-term durability of benefit and cost-effectiveness remain to be determined
- Surgical rehabilitation should be considered for stable TED and includes orbital decompression to reduce proptosis and congestion, strabismus surgery to improve ocular motility, and eyelid procedures to treat fibrosis-related eyelid retraction

DISCLOSURE

The authors have nothing to disclose.

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