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Thyroid Eye Disease: Navigating the New Treatment Landscape

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Abbreviations: APD, afferent pupillary defect; CAS, Clinical Activity Score; CON, compressive optic neuropathy; EUGOGO, European Group on Graves' Orbitopathy; FDA, US Food and Drug Administration; GD, Graves disease; GI, gastrointestinal; IGF-1R, insulin-like growth factor 1 receptor; IgG, immunoglobulin G; IV, intravenous; MMF, mycophenolate; ORT, orbital radiation; QoL, quality of life; RCT, randomized controlled trial; TED, thyroid eye disease; TSH, thyrotropin; TSHR, thyrotropin receptor; TSI, thyroid-stimulating immunoglobulin.

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Thyroid eye disease (TED) is a complex inflammatory disease that can have a long clinical course with sight-threatening and debilitating ocular sequelae. Until recently, there were limited therapeutic options available. In the last decade we have gained a deeper understanding of the underlying pathophysiology, which has led to the development of novel effective targeted therapies. This article discusses the challenges encountered in the clinical evaluation and treatment of TED patients, with the goal to empower endocrinologists and ophthalmologists to work together to provide effective multidisciplinary care. We will review recommendations of past clinical guidelines around evaluation and management of TED patients, discuss the randomized controlled trials of new biologic therapies, and explore how to navigate the emerging therapeutic landscape.

Key Words: thyroid eye disease, Graves ophthalmopathy, thyroid orbitopathy, pathophysiology, treatment, teprotumumab, targeted therapy, Tepezza

Case Presentations

Case 1

A 67-year-old woman, a nonsmoker, presented with conjunctival injection, lid swelling, and proptosis for 8 weeks (Fig. 1A). She was treated initially for allergic conjunctivitis and then bacterial conjunctivitis with no improvement. Two months later she was diagnosed with thyroid eye disease (TED) and mild asymptomatic hyperthyroidism, with a high thyroid-stimulating immunoglobulin (TSI) level of 419% (normal < 130%). She was treated with oral and then intravenous (IV) steroids (methylprednisolone 500 mg IV weekly × 6 weeks followed by 250 mg IV weekly × 6 weeks). She received methimazole with restoration of euthyroidism. She was counseled to avoid tobacco exposure and to take selenium 100 mcg twice a day. On week 4 of IV steroids she presented with worsening vision and color vision and diplopia (Fig. 1B). Her visual acuity was 20/80 OD and 20/60 OS, she had a right relative afferent pupillary defect (APD), and on Ishihara plate assessment scored 1 out of 14 in the right eye and 14 out of 14 in the left. She

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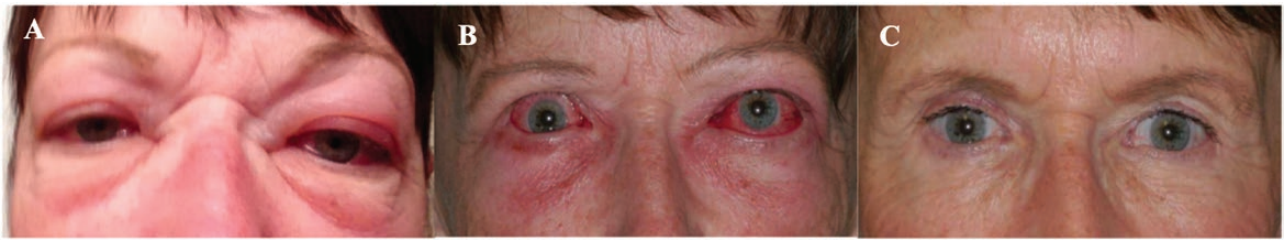

Figure 1. Case 1. A, Initial presentation of active moderate to severe thyroid eye disease with conjunctival injection, lid swelling and erythema, and proptosis. B, After high-dose oral steroids and 4 weeks of weekly intravenous (IV) 500-mg solumedrol, the patient presented with right compressive optic neuropathy and restrictive strabismus. Note the asymmetric pupil reflex with right hypotropia (inferior displacement of right eye), right upper lid retraction, worsening conjunctival injection, chemosis, eyelid erythema, and edema. C, Status post high-dose oral and IV steroids, orbital radiation, bilateral orbital decompression, strabismus surgery, and retraction repair.

was diagnosed with compressive optic neuropathy (CON) and underwent urgent evaluation by ophthalmology.

Case 2

A 55-year-old woman with no prior medical care presented to the emergency room with 3 days of right eye blurry vision, pain, and eyelid swelling. Her vision was 20/200 OD and 20/20 OS with loss of color vision (0/13 OD, 5/13 OS), a right relative APD, and significant bilateral restriction of eye movement. She had proptosis, eyelid retraction, lagophthalmos, periorbital edema and erythema, conjunctival injection, and chemosis (Fig. 2A). Laboratory data revealed mild hyperthyroidism and an elevated TSI of 277% (normal < 140%). She was diagnosed with active sight-threatening TED and treated for right CON with high-dose IV steroids (1 gm solumedrol daily × 3) with little response. She underwent emergent right orbital decompression, with improvement in visual acuity to 20/25 OD, followed by IV solumedrol 500 mg weekly. After the fifth week, she developed progressive diplopia, left eye pain, redness, and proptosis (Fig. 2B). Her vision worsened to 20/100 OS with reduced color vision of the left eye. She had steroid-resistant TED and developed significant confusion, tremors, and insomnia; therefore, steroids were discontinued.

Background

TED is an unpredictable autoimmune inflammatory disease that can be sight-threatening, debilitating, and disfiguring. Although most TED patients are hyperthyroid, in at least 10% of cases TED occurs in the setting of euthyroidism or hypothyroidism [1]. While the overall TED prevalence is about 40% in Graves patients [2], subclinical extraocular muscle enlargement can occur in nearly 70% of adult patients with Graves hyperthyroidism [3]. The majority of patients have mild, self-limited TED, 20% to 30% of patients experience moderate/severe disease, and 3% to 5% may develop sight-threatening disease, such as CON or exposure keratopathy [4]. In a recent study of newly diagnosed Graves patients, the prevalence of concurrent mild, moderate-severe, and sight-threatening disease was 20%, 5.8%, and 0.3%, respectively [5]. Leading risk factors for TED include cigarette smoking, thyroid dysfunction, radioactive iodine treatment, female sex, and increasing age [6, 7].

The heterogeneous presentation of TED, including the timing of onset, activity, and severity, can lead to delays in accurate diagnosis, with the average time to diagnosis from symptom onset being 9 months [8]. The disease is commonly initially misdiagnosed, up to 58% of the time in a recent UK survey [9]. Finally, the varied temporal relationship between onset of TED and Graves disease (GD) can add to the challenge in diagnosis because in 23% of patients, GD develops after the diagnosis of TED [10].

TED begins with an acute inflammatory/active phase that can last from 6 to 36 months [11], with symptoms including dry eyes, orbital or ocular surface pain, periorbital swelling, and eyelid retraction. Some patients develop disfiguring proptosis, diplopia, and vision loss. Over time, the inflammation subsides and the patient enters a chronic phase characterized by fibrosis, which can be accompanied by permanent disfigurement and functional vision loss. Theoretically, the optimal time to initiate therapy is during the active phase [12], as intervention then limits disease progression and visual morbidity and may decrease the need for reconstructive surgery.

Treatment of TED lends itself to a multidisciplinary approach, since it involves significant input of both endocrinology and oculoplastic orbital surgeons. Significant advances in treatment have occurred in recent years. Discussion of the various therapeutic considerations is the focus of this manuscript. We will first review the pathophysiology of TED and its clinical assessment, then we will discuss therapeutic options for TED.

Pathophysiology

Active TED is characterized by inflammation and infiltration of the thyroid and orbital tissues by immune cells. The loss

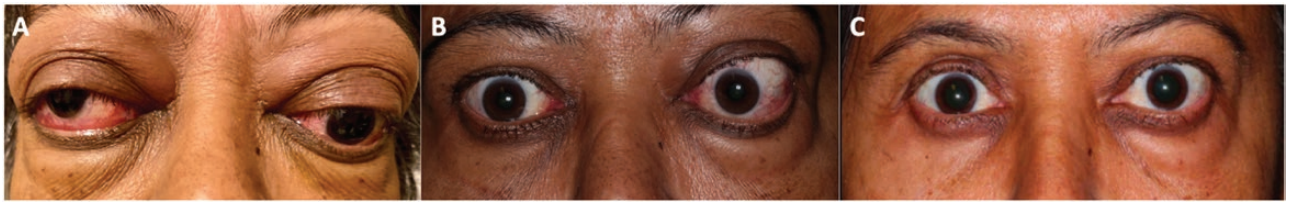

Figure 2. Case 2. A, Initial presentation to the emergency room with loss of vision and bilateral eyelid swelling, chemosis, injection, proptosis, and restrictive strabismus. B, After high-dose intravenous (IV) steroids and right orbital decompression for compressive optic neuropathy (CON) and 5 weeks of weekly IV 500-mg solumedrol, the patient's photo shows persistent left proptosis, eyelid swelling, and injection, while her disease has progressed to left CON. C, After 8 infusions of IV teprotumumab, her active inflammatory signs have resolved, though she still has left relative proptosis compared to the right decompressed eye.

of tolerance by T cells to the thyrotropin receptor (TSHR) allows for the development of autoimmunity directed against it. Subsequent activation and differentiation of B cells into plasma cells leads to the production of anti-TSHR antibodies [13]. Another crucial autoantigen involved in TED pathogenesis is the insulin-like growth factor 1 receptor (IGF-1R). This is overexpressed in thyrocytes and fibroblasts in patients with GD and TED [14, 15]. IGF-1R and TSHR colocalize to the perinuclear and cytoplasmic compartments in fibroblasts and thyrocytes [16]. Cross-reactivity against this complex is thought to underlie the autoimmune ophthalmic response [17], leading to the TED cycle.

Immune recognition of the TSHR and IGF-1R complex on orbital fibroblasts leads to orbital tissue reactivity and remodeling via induction of cytokines and hyaluronan synthesis [18]. Cytokines stimulate secretion of glycosaminoglycans, including hyaluronan, which increases intraorbital tissue volume via adipose and muscle expansion and tissue inflammation [12]. Activated orbital fibroblasts proliferate and differentiate into adipocytes and myofibroblasts, also increasing orbital tissue volume. Consequently, the eyeball may protrude beyond the bony orbit, the extraocular muscles may enlarge restricting eye movement, the optic nerve can be compressed or stretched affecting vision, and the inflammatory cascade can result in eye pain, redness, and swelling.

Clinical Assessment

Clinical assessment of TED is aimed to answer 2 questions: 1) Is the disease active or inactive? and 2) Is the disease mild, moderate/severe, or sight-threatening?

Activity of the Disease

To assess activity, the most commonly used system is the Clinical Activity Score (CAS) [19]. At the initial visit CAS is reported on a scale of 1 to 7 and assigns points for the following: spontaneous orbital pain, gaze-evoked orbital pain, eyelid swelling due to active TED, eyelid erythema, conjunctival redness due to active TED, chemosis, or caruncle/plica inflammation. An initial score of 3 or greater is considered active disease. On follow-up visit, CAS is scored out of 10 to include increase of more than 2 mm in proptosis, decrease in ocular excursion in any one direction of more than 8°, and decrease of acuity equivalent to 1 Snellen line. A follow-up score of 4 or greater is considered active disease [19].

Severity of the Disease

Severity is a function of the degree of diplopia, proptosis, and soft-tissue changes, as well as the impact on quality of life (QoL). It is categorized by the European Group on Graves' Orbitopathy (EUGOGO) guidelines [20]. Diplopia is classified as absent or transient, inconstant (at the extremes of gaze), or constant. Proptosis is measured through a Hertel exophthalmometer, which can be obtained and used by endocrinologists. QoL can be assessed via a validated EUGOGO questionnaire (https://www.eugogo.eu/eugogo-service/downloads/quality-of-life-questionnaire). Mild TED is TED that has a minor impact on QoL with one or more of the following: lid retraction less than 2 mm, mild soft-tissue involvement, proptosis less than 3 mm, and transient or absent diplopia. Moderate to severe TED is disease that is not sight-threatening but has a sufficient impact on the QoL to justify the risks of immunosuppressive or other systemic therapy (if active) or rehabilitative surgery (if inactive). This involves one or more of the following: moderate or severe soft-tissue involvement, proptosis greater than 3 mm, and inconstant or constant diplopia [20]. Finally, sight-threatening disease has either CON or corneal breakdown limiting vision [21].

Role of the Endocrinologist

Endocrinologists play an important role in the prompt diagnosis of TED because they see patients with dysthyroidism regularly. In addition to modifying risk factors for TED by

maintaining euthyroidism, counseling about strict tobacco avoidance, and using radioactive iodine judiciously, endocrinologists need to determine who needs ophthalmologic evaluation and how urgently. All GD patients should be evaluated for the presence of ocular symptoms. If symptoms are present, one should obtain a CAS and assess the degree of diplopia, proptosis, soft-tissue changes, and QoL [19, 20]. If the patient has TED findings, a nonurgent evaluation by ophthalmology for a baseline comprehensive eye assessment is indicated. A screening protocol and recommendations for referral are also outlined in the 2008 EUGOGO consensus statement [21]. Sight-threatening disease can also be evaluated by the endocrinologist (Fig. 3). The risk of corneal compromise can be assessed by evaluating for lagophthalmos (failure to fully close the lids when asking the patient to gently close the eyes). Optic nerve health can be assessed by evaluation for a relative APD using a penlight, assessment of visual acuity using a Snellen chart, and assessment of color perception using Ishihara plates (available for free online). Orbital imaging can be obtained to assess for optic nerve compression if the clinical exam suggests optic nerve compromise. Should there be any concern for sight-threatening disease, urgent evaluation by ophthalmology is indicated.

Role of the Ophthalmologist

Ophthalmologists specializing in TED, typically oculoplastic orbital surgeons, should be involved in TED diagnosis and management. A collaborative relationship between the endocrinologist and ophthalmologist is ideal to provide the most comprehensive care. Patients with TED should be referred for ophthalmic evaluation. A complete eye exam can differentiate common ocular conditions such as dry eye or allergies from TED. Additionally, a baseline eye exam is helpful to compare progressive symptoms of TED against. Finally, CON can occur silently and requires optic nerve evaluation and visual field testing. The ophthalmologist will help determine whether the disease is active, manage ocular symptoms and coexisting ocular conditions, and work with the endocrinologist to manage TED.

Therapeutic Approach

Treatment of TED has evolved over the years, from nonspecific immunosuppression to targeted biologic therapies. EUGOGO has published clinical guidelines for the evaluation and management of TED [20]. The 2016 guidelines were published prior to the release of teprotumumab and the use of other biologic agents. Recent randomized controlled trials (RCTs) offer alternatives to traditional treatment. We will review treatment options for the various categories of activity and severity, with a focus on therapies that have shown benefit in RCTs.

Mild Active Thyroid Eye Disease

Supportive treatment is the mainstay in mild disease. This involves the maintenance of euthyroidism, strict tobacco avoidance, eye lubrication with drops or ointments, and

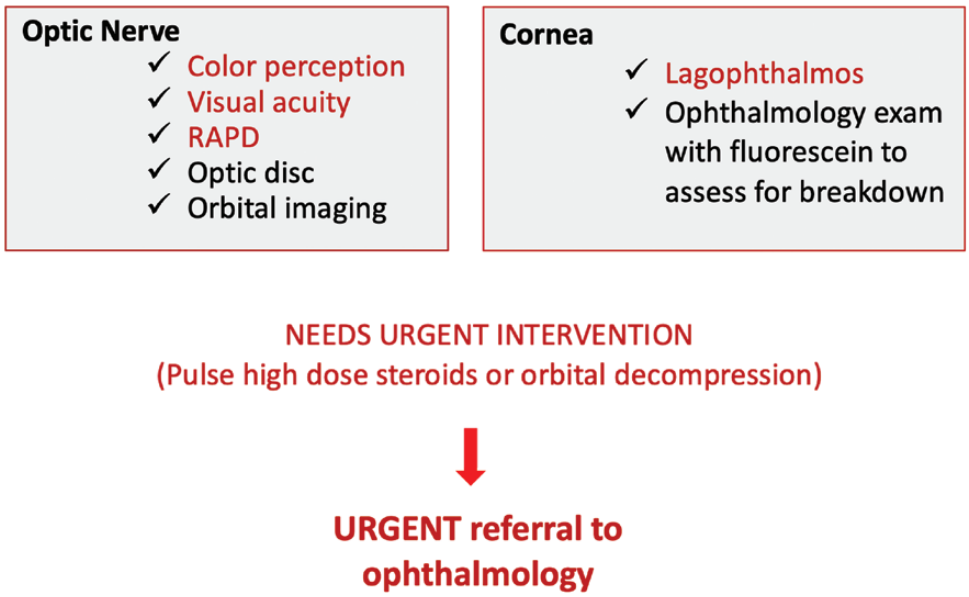

Figure 3. Endocrinologist's assessment for sight-threatening disease. The optic nerve and cornea can be evaluated for evidence of sight-threatening disease. Items in red can be assessed by the endocrinologist in the clinic. Any suspicion for sight-threatening disease should prompt urgent referral to the ophthalmologist for urgent intervention.

selenium. Selenium, an antioxidant, when given as 100 mcg twice a day for 6 months, significantly decreased inflammation and improved QoL in patients with mild active TED [22]. Patients with signs of mild TED, per the EUGOGO guidelines, should be referred to centers with both endocrinological and ophthalmological expertise, except for the mildest cases that improve with restoring euthyroidism and topical lubricants [20].

Moderate-Severe Active Thyroid Eye Disease

Current medical therapies target this active stage in efforts to decrease inflammation, minimize worsening of functional ocular sequelae, and in some cases improve ocular signs, including proptosis and double vision. The mainstay of treatment for years has been steroids and orbital radiation (ORT) [20]. In recent years, a number of biologics have been assessed in RCTs: rituximab, tocilizumab, and teprotumumab (Table 1).

Steroids

Corticosteroids have been used to treat TED since the 1950s. In 2001 and 2005, RCTs showed the superiority of IV over oral steroids [23, 24]. Kahaly et al randomly assigned patients to oral vs IV steroids (methylprednisolone 500 mg IV weekly × 6 doses followed by 250 mg IV × 6 doses) and showed a response rate of 51% vs 77% at 12 weeks' follow-up, defined by improvement in 3 parameters of a composite ophthalmic end point [24]. There was significant improvement in disease severity, activity, and QoL, minimal improvement in proptosis (median decrease of 2 vs 1 mm), and no significant improvement in diplopia with IV compared with oral steroids [21]. Bartalena et al tried 3 different doses of IV steroids and showed that the 4.5-g dose was associated with the least toxicity, but the 7.47-g dose resulted in greater improvement in a composite ophthalmic outcome, CAS, and diplopia in 12 weeks, but not proptosis or QoL [25]. Proptosis improved by only 2 mm or more in 20% to 32% of patients and diplopia improved in 21% to 46%, with the 3 different doses at 12 weeks [25]. A recent meta-analysis confirmed the efficacy of IV steroids over oral steroids (risk ratio 1.51; 95% CI, 1.25-1.83 [26]) and a significantly better side effect profile [26], with findings confirmed in a second meta-analysis [27]. Meta-analysis of the RCT subset showed that IV steroids resulted in an average decrease of CAS of 2.5, inactivation of TED in 59%, and improvement of diplopia in about a third of patients [28]. Notably, steroids were shown to have either no effect [27] or a minor effect on proptosis (1.14 mm in RCTs) [28].

There are limited data regarding the long-term efficacy of IV steroids. In the Kahaly study, no relapse rates are given, though at the 6-month follow-up there were fewer patients who had undergone orbital decompression (14% vs 32%) and strabismus surgery (20% vs 35%) in the IV steroid group compared with the oral steroid group [24]. In a post hoc analysis of the Bartalena study [25], it was found that, among patients with improvement in the composite index at 6 weeks, 65% remained improved compared to baseline at 12 weeks (at the end of the steroid course) and 53% at 24 weeks [29]. About one-third of patients were classified as unchanged and 12% were in the "deteriorated" category, compared to baseline, at 24 weeks [29]. Of the patients who showed no change at 6 weeks, 35% had improvement whereas 13% deteriorated at 24 weeks [29].

Side effects of IV steroids [25, 27, 28, 30] can include liver failure and death, especially if cumulative doses exceed 6 to 8 g, with a mortality rate of 0.6% [28]. However, serious adverse events have typically occurred in studies using daily and/or alternate single doses of more than 500 mg IV methylprednisolone [28], such as those used for treatment of CON. Liver enzyme elevation is dose-dependent, with little risk of hepatotoxicity with current TED dosing regimens and liver enzyme monitoring [31]. A recent study showed that with the most commonly used IV steroid regimen (cumulative dose of 4.5 g), almost 39% of patients experienced at least one adverse event, with 91% of adverse events graded as mild [32]. Contraindications to IV steroids include recent hepatitis, liver dysfunction (5× elevation of liver enzymes), cardiovascular morbidity, severe hypertension, inadequately managed diabetes, and severe steroid-responsive glaucoma [28].

Orbital radiation

ORT was described as treatment for TED in the 1970s, given as 20 Gy per orbit over 10 days [33]. ORT may induce lymphocyte apoptosis and the terminal differentiation of orbital fibroblasts, which work together to break the inflammatory cycle [34]. Correct patient selection is critical. Patients with early, active, progressing, moderate-severe disease have the highest response rates [35]. Overall, efficacy data are mixed and long-term RCT data are lacking. Initial RCTs in the 2000s established the benefit of ORT with a response rate of 50% to 60% [36, 37], as defined by improvement in a composite ophthalmic outcome at 24 weeks and 12 months, respectively, while one RCT showed no effect [38]. The main outcome improved was eye motility (odds ratio [OR] 4.88 in a recent meta-analysis [39]), with no significant effect on proptosis, CAS, or lid aperture [36, 37]. A review of 5 observational studies and 9 RCTs concluded with level 1 evidence that proptosis, eyelid retraction, and soft-tissue changes do not improve with ORT [40]. Despite improving extraocular motility, ORT did not

Table 1. Biologic therapies in active, moderate/severe thyroid eye disease

Therapy	Country, year	No.	Primary outcome	Treatment status	CAS < 3 after treatment, %	Improvement in proptosis[b]	Improvement in diplopia[b]	Adverse effects
RTX vs IV steroids (1000 mg IV every 2 wk × or 500 mg IV × 1)	Italy, 2015	32	% decrease CAS by ≥ 2 or with CAS < 3, 100% vs 69%, $P = .043$	Some with prior steroids	100% vs 69% at wk 24, $P = .043$	No	Yes with RTX in right eye at wk 24, $P = .04$	87% vs 63%, [a]cytokine release syndrome, decrease of vision, infusion reaction
RTX vs placebo (1000 mg IV every 2 wk × 2)	USA, 2015	25	% decrease CAS by ≥ 2 or reduction in CAS, no difference compared with placebo	Some with prior steroids	31% vs 17% at wk 24, $P = .41$	No	No	62% vs 33%, [a]infection, optic neuropathy, vasculitis
Tocilizumab vs placebo (8 mg/kg IV every 4 wk × 4)	Spain, 2018	32	% decrease CAS by ≥ 2, 93% vs 59%, $P = .04$	All steroid-resistant	87% vs 35% at wk 16, $P = .005$[c]	−1.5 mm vs 0 at wk 16, $P = .01$[c]	No	60% vs 24%, [a]infection, headache, hypercholesterolemia, cytopenias
Teprotumumab vs placebo (10 mg/kg IV followed by 20 mg/kg IV every 3 wk × 8 doses total)	USA, 2017	88	% decrease CAS by ≥ 2 and proptosis decrease by ≥ 2 mm, 69% vs 20%, $P < .001$	Prior exposure to < 1 g methylprednisolone	69% vs 21%[d] at wk 24, $P < .001$	−2.46 mm vs −0.15 mm, $P < .001$	68% vs 26% at wk 24, $P < .001$	74% vs 73%, [a]nausea, muscle spasms, diarrhea, hyperglycemia. alopecia, headache, weight loss, hearing impairment
Teprotumumab vs placebo (10 mg/kg IV followed by 20 mg/kg IV every 3 wk × 8 doses total)	USA, 2020	83	Proptosis decrease by ≥ 2 mm, 83% vs 10%, $P < .001$	Prior exposure to < 1 g methylprednisolone	59% vs 21%[d] at wk 24, $P < .001$	−3.32 mm vs −0.53 mm at wk 24, $P < .05$	68% vs 29% at wk 24, $P = .001$	85% vs 69%, [a]muscle spasms, alopecia, nausea, fatigue, diarrhea, headache

Abbreviations: CAS, Clinical Activity Score; IV, intravenous; RTX, rituximab.
[a]In patients receiving biologic agent (partial list).
[b]Compared with baseline.
[c]*P* was not significant at 40 weeks.
[d]CAS equal to 0 or 1.

affect the need for additional treatment or rehabilitative surgery in the next 1.5 years in an RCT of patients with moderate/severe TED [36], whereas it decreased the need for further surgery in an RCT of patients with mild TED (from 84% to 66%) [37].

Three RCTs have studied the combination of ORT with steroids. High-dose oral steroids for 5 to 6 months plus ORT were more effective than either therapy alone, as assessed by a drop in the ophthalmopathy index in 2 small RCTs (N = 24, 26) [35, 41]. Intravenous steroids plus ORT improved more frequently a composite ophthalmic endpoint at 1 year compared with oral steroids plus ORT (87.8 vs 63.4%) [23], resulted in a greater decrease in CAS (2.8 vs 2) and fewer surgical procedures in follow-up (7% vs 22%), and had fewer side effects than the oral steroid/ORT group (56.1% vs 85.4%) [23]. Both treatments had similar effects on proptosis (mean decrease of 1.3-1.6 mm) and diplopia (improvement in about 50%).

ORT's risks include retinopathy [42] and transient exacerbation of inflammatory symptoms. There is no increased risk of cataracts when using a high-voltage linear accelerator in fractionated doses [43], while the risk of retinopathy is none [44] or very low (1%) [43] with appropriate irradiation techniques and doses. Even though there is a theoretical concern for malignancy, no radiation-induced malignancy was seen in the 2 largest long-term follow-up studies, with up to 29 and 36 years of follow-up [44, 45]. Absolute contraindications are severe hypertension and diabetic retinopathy, and ORT should be avoided in patients younger than 35 [21, 46].

Intravenous steroids plus mycophenolate

Mycophenolate (MMF), a prodrug of mycophenolic acid, inhibits proliferation of T and B lymphocytes, suppresses antibody production, and modulates chemotaxis of activated lymphocytes [47]. A recent RCT (N = 164) showed that the combination of IV steroids for 12 weeks with MMF 360 mg orally twice a day for 24 weeks had an equivalent outcome to IV steroid monotherapy at 12 weeks but superior outcomes (defined as improvement in composite ophthalmic index in the most affected eye) by 24 weeks, increasing to 71% from 53% [47], with a sustained response at 36 weeks. Notably, neither group had a significant benefit in proptosis, both groups had similar improvement in QoL and similar effects on diplopia score, while addition of MMF did not change the rates of relapse nor did it affect development of CON [47]. Side effects occurred in similar percentages of patients in the 2 groups (20% vs 25%), with gastrointestinal (GI) disorders seen more commonly in the combination group, with no patient discontinuing because of toxicity [47].

Rituximab

Rituximab is a monoclonal antibody against CD20 used in 2 RCTs in 2015 with conflicting results [48, 49]. An Italian RCT showed superiority of rituximab (1000 mg IV weekly × 2) vs IV methylprednisolone in improving CAS at 24 weeks in 32 patients with active moderate/severe TED [48]. A US RCT showed no difference between rituximab vs placebo, in 25 patients with active moderate/severe TED, in CAS at 24 or 52 weeks [49]. Neither study showed a significant effect on diplopia, proptosis, or QoL [48, 49]. The Italian study involved younger patients, more smokers, and a much smaller percentage of recipients of prior radioiodine therapy compared with the US study. Importantly, in the Italian study the average duration of TED was 4 to 5 months, vs 10 to 12 months in the US study, suggesting that early intervention with rituximab may be needed to halt the inflammatory response.

Long-term effects of rituximab in the 2 RCTs were assessed at a year. In the Italian study, 31.2% of patients receiving IV steroids had reactivation of TED compared to none in the rituximab group, and fewer surgical procedures were carried out after rituximab vs after IV steroids (5/15 vs 12/16) [48]. In the US study, treatment failure, defined as a CAS decrease of fewer than 2 points or need for additional therapy, occurred in 50% of rituximab-treated patients, similar to placebo [49]. Side effects with rituximab affected 21 of 28 total patients, with infusion reaction occurring in 13 of 28 and less common reactions being myalgias, skin reactions, optic neuropathy, GI side effects, and transient loss of vision [48, 49].

Tocilizumab

Tocilizumab is a monoclonal antibody against the interleukin 6 receptor. Its effect was investigated in active, steroid-resistant, moderate/severe TED in a single small RCT from Spain that randomly assigned 32 patients to 4 monthly cycles of IV tocilizumab at a dose of 8 mg/kg vs placebo [50]. Tocilizumab resulted in an improvement in CAS by at least 2 points in 93% of treated patients at week 16 vs 59% in the placebo group. The effect on proptosis was minimal (1.5 mm). Importantly, these effects were not significant at the 40-week follow-up. There was no significant effect on diplopia or QoL. Longer-term follow-up has not been published. Side effects were common, with more than one adverse event occurring in 60% of treated patients vs 24% of placebo, with the most common ones being infections, headache, cytopenias, and cholesterol abnormalities [50]. Important limitations of the study include its small size, short duration of treatment, and long recruitment period, with very variable disease duration among participants and the question of whether some patients had already entered the stable phase by the time of treatment.

The results need to be confirmed in a larger RCT, of longer duration, ideally comparing tocilizumab against IV steroids or teprotumumab.

Teprotumumab

Teprotumumab is a monoclonal antibody against the IGF-1R. It blocks autoantibodies from attacking orbital fibroblasts, inhibits the cytokine cascade, prevents muscle and fat tissue remodeling, and stops hyaluronan buildup in the orbit. After phase 2 and phase 3 studies [51, 52] demonstrated its efficacy, it became the first and only US Food and Drug Administration (FDA)-approved drug for TED in 2020. In the phase 3 RCT of 83 treatment-naive patients with active moderate/severe TED, IV teprotumumab (10 mg/kg followed by 20 mg/kg) every 3 weeks × 8 doses resulted in an improvement in proptosis of 2 mm or more in 83% of patients compared with 10% in the placebo group [52]. The mean change in proptosis from baseline was 3.32 mm, similar to that achieved via a single-wall orbital decompression. Overall response (a reduction of ≥ 2 in CAS plus a reduction in proptosis of ≥ 2 mm) occurred in 78% of patients vs 7% with placebo. Diplopia improved by 1 or more grades in 68% vs in 29% with placebo. There was significant improvement in Graves ophthalmopathy-specific QoL at 24 weeks [52]. Preliminary long-term data from the phase 2 and 3 clinical trials, 72 weeks after starting treatment, demonstrated maintenance of proptosis response in 53% and 56% of proptosis responders and maintenance of 1 or more grades of improvement in diplopia in 69% and 58% of diplopia responders, respectively [53, 54].

Side effects were experienced by 85% of patients on teprotumumab vs 69% on placebo, mostly grade 1 or 2. The most common were muscle spasms (30%), alopecia (20%,) hyperglycemia (10%), diarrhea (10%), and hearing impairment (10%). Teprotumumab is strictly contraindicated around pregnancy because of inhibition of IGF-1 signaling. Given its long half-life (20 days), a 6-month waiting period after completion of therapy is recommended before conception. Safety and effectiveness have not been established in pediatric patients; however, owing to growth hormone pathway inhibition, it should be avoided in this patient population. Finally, teprotumumab should be used with caution in patients with inflammatory bowel disease or uncontrolled diabetes.

Limitations of the previously listed RCTs include the fact that teprotumumab was assessed only in the treatment of naive TED patients and was not compared to IV steroids, the prior standard of care. More information regarding the long-term outcomes and predictors of response is needed. Finally, whether teprotumumab results in meaningful reduction in rates of rehabilitative surgery is still unknown.

Considerations around choice of therapy

The 2016 EUGOGO guidelines recommended that IV steroids be considered as first-line therapy for active moderate to severe TED. Since then, phase 2 and 3 clinical trials led to FDA approval of teprotumumab for TED and additional biologic agents have been assessed in RCTs. Comparisons of therapies are limited by study heterogeneity of inclusion criteria, outcome measures, and follow-up data. New guidelines are needed to establish a new treatment algorithm for active moderate to severe TED.

Until then, a number of factors should be considered. First, the main manifestations of TED in any given patient may guide therapeutic choice, as the various therapies have differential effects on disease parameters. Teprotumumab significantly improves proptosis, double vision, CAS, and QoL at 24 weeks' follow-up with 72-week data reporting durability in the majority of proptosis and diplopia responders. Steroids and tocilizumab are mainly effective in reducing soft-tissue inflammation and CAS score, with little effect on diplopia or proptosis, at 12- and 16-week follow-up, respectively. However, the anti-inflammatory effect of tocilizumab was not durable at 40 weeks and long-term durability of CAS improvement in RCTs is lacking for steroids. Rituximab may also decrease inflammation when used early in active disease, but has no meaningful impact on diplopia and proptosis. ORT primarily ameliorates diplopia at the 24-week follow-up, and is most effective when used early in active progressive disease. Therefore, while it is reasonable to consider all of the listed options for active TED, teprotumumab is reported to be the most effective for patients with significant proptosis and/or diplopia. When diplopia is the main manifestation, ORT may also be considered in patients with early progressive disease, with the recognition that the majority of patients will still need rehabilitative surgery. When soft-tissue inflammation is the main manifestation, teprotumumab or steroids should be considered, with ORT, tocilizumab, and rituximab also showing some efficacy in RCTs.

Second, comorbidities may affect the choice of therapy. The potential for cardiovascular disease or hepatotoxicity may limit steroid use. Susceptibility to infection would make steroids, tocilizumab, and rituximab less desirable. Preexisting uncontrolled diabetes would limit the use of steroids, teprotumumab, and ORT. A history of inflammatory bowel disease and diabetes would require close monitoring with teprotumumab. The timing of future pregnancy would be a factor to consider when prescribing teprotumumab. The timing from the onset of TED may affect the efficacy of treatment, such as with rituximab and ORT, showing improved efficacy when used early in the disease. The presence of hypertension or preexisting retinopathy would make ORT less attractive. Patient age would preclude the use of

teprotumumab in those younger than 18 and ORT in those younger than 35.

Finally, cost and availability influence the choice of therapy. Cost-benefit analyses of targeted therapies are lacking; however, the high cost of biologics is an important consideration and limits access to patients without insurance. Furthermore, variability and restrictions to insurance coverage can influence their use. Additionally, access to biologic medications such as teprotumumab may be limited because of drug availability or provider expertise. Moreover, teprotumumab is currently available only in the United States; therefore, the future international role of teprotumumab remains to be seen. Taking this into context, IV steroids are the more cost-effective option for patients presenting primarily with soft-tissue inflammatory signs, without significant proptosis or diplopia, particularly for patients without insurance coverage or those living outside the United States.

In summary, treatment options continue to evolve. Of all the RCTs reviewed, teprotumumab is the first drug to demonstrate a significant improvement in all clinical parameters: proptosis, diplopia, CAS, and QoL. However, there are many considerations when selecting therapy, including the main manifestations of TED, patient comorbidities, and the cost and availability of therapies. RCTs comparing IV steroids to teprotumumab are warranted and several questions regarding teprotumumab's efficacy and duration in certain populations need answers. Until then, teprotumumab should be considered, along with IV steroids, as a first-line therapy for active moderate to severe TED in the United States. New guidelines are needed to determine a new TED treatment algorithm, incorporating targeted therapies.

Moderate-Severe Inactive Thyroid Eye Disease

Surgical rehabilitation is carried out in the "inactive" phase of TED because fibrotic disease is thought to be resistant to medical therapy. There is also a risk of worsening orbital inflammation if surgery is performed in the active phase. Therefore, it is common practice to ensure stable disease is present for at least 6 months. Exceptions to this delay include surgical interventions for sight-threatening disease.

Surgical management of stable TED is customized to individual patient needs and their unique presentation. The sequence of surgery considers 4 components of TED: 1) proptosis, 2) restrictive strabismus, 3) eyelid abnormality (retraction), and 4) cosmetic concerns (fat bags, rhytids, etc). Therefore, rehabilitative surgery is staged in the following order, though not all patients require all stages.

Orbital Decompression

The principle of orbital decompression is to expand the orbital space by widening the bony orbit and/or removing excessive orbital fat to address proptosis. This also relieves symptoms of orbital congestion and mechanical pressure on the optic nerve. The medial, lateral, and inferior orbital walls as well as orbital fat are amenable to decompression. Decompression of the orbital roof is fraught with serious potential complications and is typically avoided. Surgical complications include diplopia (5%-25%, depending on the technique) and vision loss (< 0.5%) [55, 56], though these risks have been minimized with advances in surgical techniques.

Strabismus Surgery

Strabismus surgery adjusts the extraocular muscles and maximizes the area of single binocular vision. Strabismus surgery is performed following orbital decompression, if needed, because decompression carries a risk of inducing diplopia. Surgical success is inversely related to the degree of fibrosis and scarring in the extraocular muscles.

Eyelid Surgery

Eyelid retraction, the most common TED manifestation, is corrected with eyelid retraction repair, with the exact approach varying depending on the severity. Nonsurgical treatment with botulinum toxin (i.e., Botox) to the levator muscle or hyaluronic acid gel filler can be effective as a temporizing measure. Aesthetic concerns can be addressed with a combination of lasers, fillers, botulinum toxin, and eyelid surgery, as the last step of surgical rehabilitation.

Sight-Threatening Thyroid Eye Disease

Sight-threatening orbitopathy, though present only in 3% to 5% of patients, is the most devastating complication of TED [30].

Exposure keratopathy

During active disease, corneal protection can be achieved with frequent topical lubrication. A moisture chamber or goggles can be used at night-time for nocturnal lagophthalmos. In nonresponsive cases, a tarsorraphy may be necessary.

Compressive optic neuropathy

CON is a medical emergency. Management options for CON include corticosteroids, external beam radiation, and surgical decompression, or a combination of these

interventions. The 2016 EUGOGO guidelines recommend IV steroids (500-1000 mg of methylprednisolone for 3 consecutive days) as first-line therapy [20]. This course can be repeated after a week and is effective in approximately 40% of patients [57, 58]. If CON is refractory to high-dose IV glucocorticoids, or there is rapid deterioration in visual function, surgical decompression is typically recommended to mechanically relieve the optic nerve compression [20, 58]. Recently, case reports demonstrated that tocilizumab [59] and teprotumumab [60, 61] were effective in treating CON. Sears et al. measured objective improvements in visual acuity, relative APD, color vision, proptosis, and visual field testing as early as 4 weeks after initiating teprotumumab for steroid-resistant CON, with orbital magnetic resonance imaging showing improvement in extraocular muscle size and optic nerve compression at 8 weeks [60]. Slentz and colleagues measured an objective improvement in visual acuity, proptosis, optic nerve edema, and optical coherence tomography retinal nerve fiber thickening 2 weeks after initiating teprotumumab for steroid-naive CON [61]. While these reports suggest biologic therapies may be considered as treatment options for CON, additional studies and long-term data are needed to validate these findings.

An Eye to the Future: Upcoming Therapies

Emerging biologic targeted therapies are promising but will need to prove substantial benefit, a low side effect profile, or a more cost-effective alternative to enter the TED therapeutic landscape.

Thyrotropin Receptor Antagonists

Small-molecule TSHR antagonists have been tested in preclinical models. These could attenuate orbital fibroblast activation by TSI, as allosteric inhibition of the TSHR G protein signaling has been shown to silence the TSHR [62]. A small-molecule TSHR antagonist (ANTAG3) has been shown to inhibit TSI-induced signaling and TSHR activation in the thyroid gland of mice and could thus potentially inhibit TSHR signaling in orbital fibroblasts [63]. Additional animal studies have reported new small-molecule TSHR antagonists that are highly selective TSHR inhibitors [64]. While these studies are still in preclinical development, their potential as targeted therapeutic options for TED is exciting.

Enhancement of Immunoglobulin G Catabolism

IMVT-1401 is a fully human monoclonal antibody inhibiting FcRn-mediated recycling of immunoglobulin G (IgG). FcRn is the primary protein preventing the degradation of IgG antibodies, thereby prolonging their half-life. IMVT-1401 disrupts the IgG-FcRn interaction to increase catabolism of IgG and is thought to remove pathogenetic autoantibodies against the TSHR and IGF-1R. In an open-label, single-arm phase 2a clinical trial (NCT03922321), 7 patients with moderate/severe active TED were treated weekly for 6 weeks. Initial results demonstrated a 65% reduction in total IgG, 57% of patients had ≥ 2 point improvement in CAS, and 67% of patients with baseline diplopia improved, with no serious adverse events [65]. A larger phase 2b double-blind study is under way with a plan to enroll 77 patients with moderate/severe active TED. IMVT-1401 is being developed as a subcutaneous injection for the treatment of TED and other autoimmune disorders.

Other Therapies

Belimumab (monoclonal antibody against B-cell activating factor) is under investigation in a European RCT in patients with TED (EudraCT 2015-002127-26). Immunomodulators such as fingolimod (a sphingosine-1-phosphate receptor antagonist) [66] and iscalimab (an anti-CD40 antibody) [67], antibodies that block the TSHR, as well as microbiome manipulation are other novel therapies under investigation.

Clinical Case Discussion

Case 1

On diagnosis of CON, the patient underwent emergent right orbital decompression with high-dose IV steroids followed by a standard 12-week course of IV steroids combined with ORT for her active TED. Despite these interventions, she developed CON in her left eye requiring left orbital decompression. After 9 months of stable inactive disease, she underwent additional rehabilitative surgery for double vision and eyelid retraction.

This case illustrates a number of points. First, the patient was initially misdiagnosed with allergic conjunctivitis and bacterial conjunctivitis, the most common incorrect diagnoses for mild active TED. Second, the delay in diagnosis could have contributed to her developing more severe TED, with pain, disfigurement, restrictive strabismus, and decreased QoL. Third, her left eye progressed to sight-threatening disease despite IV steroids and ORT, demonstrating that sometimes these treatments cannot prevent vision loss or halt disease progression. Selenium was added as adjuvant therapy, given its relatively benign safety profile in short-term use, even though its efficacy has been proven only in mild active TED, and it has not been studied

in moderate/severe active disease. Although the patient recovered well after several rehabilitative surgeries (Fig. 1C), her treatment course lasted more than 2 years. This case is an example of the typical delay in diagnosis, sometimes incomplete response to nonspecific medical therapies, and the serious ocular sequelae that can result.

Case 2

Surgical decompression and biologic therapies were discussed as treatment options for CON of the left eye and steroid-resistant active TED. The patient received teprotumumab, 10 mg/kg followed by 20 mg/kg every 3 weeks × 8 doses. Her extraocular movement improved, proptosis decreased by 3.5 mm, and inflammatory symptoms decreased (Fig. 2C). Her vision improved quickly to 20/25 OU and color vision normalized. Side effects included hives and rashes after infusions responsive to diphenhydramine hydrochloride, muscle cramps, diarrhea, autophony, and hyperglycemia responsive to medical therapy.

This case was a therapeutic challenge because of active sight-threatening disease recalcitrant to IV steroids. Teprotumumab was given in the hopes of halting active progressive disease and delaying orbital decompression during the peak of coronavirus disease 2019 quarantine and hospital restrictions in April 2020. The patient had a significant improvement both in CON and active TED symptoms. Following treatment, her rashes, GI symptoms, and muscle cramps resolved. Her ear symptoms, which developed after the sixth infusion and persisted after the final infusion visit, are being monitored and are expected to resolve, as per the data in the clinical trials. She will be monitored for 6 months to ensure durable resolution of active TED prior to undergoing further rehabilitative surgery in the stable phase, if needed.

Conclusion

TED is a complex autoimmune disease that can result in vision loss, disfigurement, and decreased QoL. Developments in our understanding of the pathophysiology of TED have led to a paradigm shift in TED management. Traditionally, corticosteroids, radiation therapy, and surgical correction were the mainstays of treatment. In 2020, the FDA approved teprotumumab for the treatment of TED after pivotal phase 2 and 3 RCTs showed significant improvement in proptosis, diplopia, QoL, and CAS. Teprotumumab is a promising therapy for patients with active moderate to severe TED, particularly for patients with proptosis and/or diplopia. Long-term efficacy studies are still needed to better assess the durability of all treatment options available. Several emerging treatments are in the pipeline, as research has shifted to the development of additional targeted molecular therapies. It remains to be determined how new therapeutic options will continue to change the treatment paradigm of TED.

Additional Information

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References

1. Eckstein AK, Lösch C, Glowacka D, et al. Euthyroid and primarily hypothyroid patients develop milder and significantly more asymmetrical Graves ophthalmopathy. *Br J Ophthalmol*. 2009;**93**(8):1052-1056.
2. Chin YH, Ng CH, Lee MH, et al. Prevalence of thyroid eye disease in Graves' disease: a meta-analysis and systematic review. *Clin Endocrinol (Oxf)*. 2020;**93**(4):363-374.
3. Enzmann DR, Donaldson SS, Kriss JP. Appearance of Graves' disease on orbital computed tomography. *J Comput Assist Tomogr*. 1979;**3**(6):815-819.
4. Bartalena L, Tanda ML. Clinical practice. Graves' ophthalmopathy. *N Engl J Med*. 2009;**360**(10):994-1001.
5. Tanda ML, Piantanida E, Liparulo L, et al. Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. *J Clin Endocrinol Metab*. 2013;**98**(4):1443-1449.
6. Perros P, Crombie AL, Matthews JN, Kendall-Taylor P. Age and gender influence the severity of thyroid-associated ophthalmopathy: a study of 101 patients attending a combined thyroid-eye clinic. *Clin Endocrinol (Oxf)*. 1993;**38**(4):367-372.
7. Khong JJ, Finch S, De Silva C, et al. Risk factors for Graves' orbitopathy; the Australian Thyroid-Associated Orbitopathy Research (ATOR) Study. *J Clin Endocrinol Metab*. 2016;**101**(7):2711-2720.
8. Perros P, Žarković M, Azzolini C, et al. PREGO (presentation of Graves' orbitopathy) study: changes in referral patterns to European Group On Graves' Orbitopathy (EUGOGO) centres over the period from 2000 to 2012. *Br J Ophthalmol*. 2015;**99**(11):1531-1535.
9. Estcourt S, Hickey J, Perros P, Dayan C, Vaidya B. The patient experience of services for thyroid eye disease in the United Kingdom: results of a nationwide survey. *Eur J Endocrinol*. 2009;**161**(3):483-487.
10. Wiersinga WM, Smit T, van der Gaag R, Koornneef L. Temporal relationship between onset of Graves' ophthalmopathy and onset of thyroidal Graves' disease. *J Endocrinol Invest*. 1988;**11**(8):615-619.

11. Rundle FF. Management of exophthalmos and related ocular changes in Graves' disease. *Metabolism*. 1957;**6**(1):36-48.
12. Patel A, Yang H, Douglas RS. A new era in the treatment of thyroid eye disease. *Am J Ophthalmol*. 2019;**208**:281-288.
13. Bahn RS. Graves' ophthalmopathy. *N Engl J Med*. 2010;**362**(8):726-738.
14. Smith TJ. The putative role of fibroblasts in the pathogenesis of Graves' disease: evidence for the involvement of the insulin-like growth factor-1 receptor in fibroblast activation. *Autoimmunity*. 2003;**36**(6-7):409-415.
15. Smith TJ, Koumas L, Gagnon A, et al. Orbital fibroblast heterogeneity may determine the clinical presentation of thyroid-associated ophthalmopathy. *J Clin Endocrinol Metab*. 2002;**87**(1):385-392.
16. Tsui S, Naik V, Hoa N, et al. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in Graves' disease. *J Immunol*. 2008;**181**(6):4397-4405.
17. Chen H, Mester T, Raychaudhuri N, et al. Teprotumumab, an IGF-1R blocking monoclonal antibody inhibits TSH and IGF-1 action in fibrocytes. *J Clin Endocrinol Metab*. 2014;**99**(9):E1635-E1640.
18. Smith TJ. Is there potential for the approval of monoclonal antibodies to treat thyroid-associated ophthalmopathy? *Expert Opin Orphan Drugs*. 2018;**6**(10):593-595.
19. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. *Clin Endocrinol (Oxf)*. 1997;**47**(1):9-14.
20. Bartalena L, Baldeschi L, Boboridis K, et al; European Group on Graves' Orbitopathy (EUGOGO). The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J*. 2016;**5**(1):9-26.
21. Bartalena L, Baldeschi L, Dickinson AJ, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. *Thyroid*. 2008;**18**(3):333-346.
22. Marcocci C, Kahaly GJ, Krassas GE, et al; European Group on Graves' Orbitopathy. Selenium and the course of mild Graves' orbitopathy. *N Engl J Med*. 2011;**364**(20):1920-1931.
23. Marcocci C, Bartalena L, Tanda ML, et al. Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: results of a prospective, single-blind, randomized study. *J Clin Endocrinol Metab*. 2001;**86**(8):3562-3567.
24. Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. *J Clin Endocrinol Metab*. 2005;**90**(9):5234-5240.
25. Bartalena L, Krassas GE, Wiersinga W, et al; European Group on Graves' Orbitopathy. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. *J Clin Endocrinol Metab*. 2012;**97**(12):4454-4463.
26. Zhao LQ, Yu DY, Cheng JW. Intravenous glucocorticoids therapy in the treatment of Graves' ophthalmopathy: a systematic review and meta-analysis. *Int J Ophthalmol*. 2019;**12**(7):1177-1186.
27. Gao G, Dai J, Qian Y, Ma F. Meta-analysis of methylprednisolone pulse therapy for Graves' ophthalmopathy. *Clin Exp Ophthalmol*. 2014;**42**(8):769-777.
28. Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. *J Clin Endocrinol Metab*. 2011;**96**(2):320-332.
29. Bartalena L, Veronesi G, Krassas GE, et al; European Group on Graves' Orbitopathy (EUGOGO). Does early response to intravenous glucocorticoids predict the final outcome in patients with moderate-to-severe and active Graves' orbitopathy? *J Endocrinol Invest*. 2017;**40**(5):547-553.
30. Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. *Endocr Rev*. 2000;**21**(2):168-199.
31. Le Moli R, Baldeschi L, Saeed P, Regensburg N, Mourits MP, Wiersinga WM. Determinants of liver damage associated with intravenous methylprednisolone pulse therapy in Graves' ophthalmopathy. *Thyroid*. 2007;**17**(4):357-362.
32. Riedl M, Kolbe E, Kampmann E, Krämer I, Kahaly GJ. Prospectively recorded and MedDRA-coded safety data of intravenous methylprednisolone therapy in Graves' orbitopathy. *J Endocrinol Invest*. 2015;**38**(2):177-182.
33. Donaldson SS, Bagshaw MA, Kriss JP. Supervoltage orbital radiotherapy for Graves' ophthalmopathy. *J Clin Endocrinol Metab*. 1973;**37**(2):276-285.
34. Chundury RV, Weber AC, Perry JD. Orbital radiation therapy in thyroid eye disease. *Ophthalmic Plast Reconstr Surg*. 2016;**32**(2):83-89.
35. Bartalena L, Marcocci C, Chiovato L, et al. Orbital cobalt irradiation combined with systemic corticosteroids for Graves' ophthalmopathy: comparison with systemic corticosteroids alone. *J Clin Endocrinol Metab*. 1983;**56**(6):1139-1144.
36. Mourits MP, van Kempen-Harteveld ML, García MB, Koppeschaar HP, Tick L, Terwee CB. Radiotherapy for Graves' orbitopathy: randomised placebo-controlled study. *Lancet*. 2000;**355**(9214):1505-1509.
37. Prummel MF, Terwee CB, Gerding MN, et al. A randomized controlled trial of orbital radiotherapy versus sham irradiation in patients with mild Graves' ophthalmopathy. *J Clin Endocrinol Metab*. 2004;**89**(1):15-20.
38. Gorman CA, Garrity JA, Fatourechi V, et al. A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for Graves' ophthalmopathy. *Ophthalmology*. 2001;**108**(9):1523-1534.
39. Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, Ezrachi D, Shimon I, Leibovici L. Treatment modalities for Graves' ophthalmopathy: systematic review and metaanalysis. *J Clin Endocrinol Metab*. 2009;**94**(8):2708-2716.
40. Bradley EA, Gower EW, Bradley DJ, et al. Orbital radiation for graves ophthalmopathy: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2008;**115**(2):398-409.
41. Marcocci C, Bartalena L, Bogazzi F, Bruno-Bossio G, Lepri A, Pinchera A. Orbital radiotherapy combined with high dose systemic glucocorticoids for Graves' ophthalmopathy is more effective than radiotherapy alone: results of a prospective randomized study. *J Endocrinol Invest*. 1991;**14**(10):853-860.

42. Wakelkamp IM, Tan H, Saeed P, et al. Orbital irradiation for Graves' ophthalmopathy: is it safe? A long-term follow-up study. *Ophthalmology*. 2004;**111**(8):1557-1562.
43. Marcocci C, Bartalena L, Rocchi R, et al. Long-term safety of orbital radiotherapy for Graves' ophthalmopathy. *J Clin Endocrinol Metab*. 2003;**88**(8):3561-3566.
44. Marquez SD, Lum BL, McDougall IR, et al. Long-term results of irradiation for patients with progressive Graves' ophthalmopathy. *Int J Radiat Oncol Biol Phys*. 2001;**51**(3):766-774.
45. Schaefer U, Hesselmann S, Micke O, et al. A long-term follow-up study after retro-orbital irradiation for Graves' ophthalmopathy. *Int J Radiat Oncol Biol Phys*. 2002;**52**(1):192-197.
46. Tanda ML, Bartalena L. Efficacy and safety of orbital radiotherapy for graves' orbitopathy. *J Clin Endocrinol Metab*. 2012;**97**(11):3857-3865.
47. Kahaly GJ, Riedl M, König J, et al; European Group on Graves' Orbitopathy (EUGOGO). Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. *Lancet Diabetes Endocrinol*. 2018;**6**(4):287-298.
48. Salvi M, Vannucchi G, Currò N, et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. *J Clin Endocrinol Metab*. 2015;**100**(2):422-431.
49. Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. *J Clin Endocrinol Metab*. 2015;**100**(2):432-441.
50. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, et al; Tocilizumab in Graves Orbitopathy Study Group. Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant graves orbitopathy: a randomized clinical trial. *Am J Ophthalmol*. 2018;**195**:181-190.
51. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;**376**(18):1748-1761.
52. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;**382**(4):341-352.
53. Kahaly G. 48-week follow-up of a multicenter, randomized, double-masked, placebo-controlled treatment trial of teprotumumab in thyroid-associated ophthalmopathy. *Thyroid*. 2018;(Supp 1):A-1.
54. Douglas RS, Holt RJ, Vescio T, Smith TA, Kahaly G. Long-term assessment of proptosis and diplopia from the OPTIC trial of teprotumumab in thyroid eye disease (Abstract PA038). Abstract presented at: American Academy of Ophthalmology Virtual Meeting, November 13-15, 2020. https://secure.aao.org/aao/meeting-archive
55. Ramesh S, Eichhorn K, Leibowitz S, Goldberg R. Bony regrowth after deep lateral orbital decompression. *Ophthalmic Plast Reconstr Surg*. 2018;**34**(6):533-535.
56. Ramesh S, Nobori A, Wang Y, Rootman D, Goldberg RA. Orbital expansion in cranial vault after minimally invasive extradural transorbital decompression for thyroid orbitopathy. *Ophthalmic Plast Reconstr Surg*. 2019;**35**(1):17-21.
57. Currò N, Covelli D, Vannucchi G, et al. Therapeutic outcomes of high-dose intravenous steroids in the treatment of dysthyroid optic neuropathy. *Thyroid*. 2014;**24**(5):897-905.
58. Wakelkamp IM, Baldeschi L, Saeed P, Mourits MP, Prummel MF, Wiersinga WM. Surgical or medical decompression as a first-line treatment of optic neuropathy in Graves' ophthalmopathy? A randomized controlled trial. *Clin Endocrinol (Oxf)*. 2005;**63**(3):323-328.
59. Pascual-Camps I, Molina-Pallete R, Bort-Martí MA, Todolí J, España-Gregori E. Tocilizumab as first treatment option in optic neuropathy secondary to Graves' orbitopathy. *Orbit*. 2018;**37**(6):450-453.
60. Sears CM, Azad AD, Dosiou C, Kossler AL. Teprotumumab for dysthyroid optic neuropathy: early response to therapy. *Ophthalmic Plast Reconstr Surg*. Published online September 22, 2020. doi:. doi:10.1097/IOP.0000000000001831
61. Slentz DH, Smith TJ, Kim DS, Joseph SS. Teprotumumab for optic neuropathy in thyroid eye disease. *JAMA Ophthalmol*. 2021;**139**(2):244-247.
62. Neumann S, Nir EA, Eliseeva E, et al. A selective TSH receptor antagonist inhibits stimulation of thyroid function in female mice. *Endocrinology*. 2014;**155**(1):310-314.
63. Newmann S. Small molecule agonists and antagonists as potential new therapeutics targeting the TSH receptor. *Endocrine Abstracts*. 2017;**49**:NSA5.2.
64. Marcinkowski P, Hoyer I, Specker E, et al. A new highly thyrotropin receptor-selective small-molecule antagonist with potential for the treatment of Graves' orbitopathy. *Thyroid*. 2019;**29**(1):111-123.
65. Immunovant. March 30, 2020. Immunovant announces positive clinical results from ongoing phase 2a proof-of-concept study of IMVT-1401, a novel investigational anti-FcRn antibody delivered by subcutaneous injection, in thyroid eye disease. https://immunovant.com/immunovant-announces-positive-clinical-results-from-ongoing-phase-2a-proof-of-concept-study-of-imvt-1401-a-novel-investigational-anti-fcrn-antibody-delivered-by-subcutaneous-injection-in-thyroid-eye/. Accessed April 7, 2021.
66. Plöhn S, Hose M, Schlüter A, et al. Fingolimod improves the outcome of experimental Graves' disease and associated orbitopathy by modulating the autoimmune response to the thyroid-stimulating hormone receptor. *Thyroid*. 2019;**29**(9):1286-1301.
67. Kahaly GJ, Stan MN, Frommer L, et al. A novel anti-CD40 monoclonal antibody, iscalimab, for control of Graves hyperthyroidism—a proof-of-concept trial. *J Clin Endocrinol Metab*. 2020;**105**(3):dgz013.