Approach to the Management of Thyroid Eye Disease

Sabrina Yu, MD and Vivian T. Yin, MD, MPH

Introduction

Thyroid Eye Disease (TED), also known as Graves’ orbitopathy, is an autoimmune condition characterized by inflammation of the extraocular muscles, orbital fat and periocular tissues.¹ As the most common orbital disease worldwide, its prevalence is estimated to be between 0.5%–2% and it disproportionately affects females 4:1.² Although the majority of TED cases occur in patients with Graves’ disease (80%–90%), it can also be seen with patients with Hashimoto’s thyroiditis (10%), euthyroid individuals (5%–10%) and thyroid cancer.³ At the time of initial Graves’ disease diagnosis, 25% of patients have clinically detectable orbital involvement that is often mild.⁴ The natural history of TED typically consists of an initial active inflammatory period lasting 6–36 months, which then plateaus and is followed by a quiescent fibrotic phase with stabilization of disease.⁵

About the Authors

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Clinical Phenotypes

Similar to the wide range in duration of the disease, the clinical manifestation of TED can also be highly variable with no single pathognomonic diagnostic finding. The most commonly observed and often early sign is lid retraction (38%–90%) followed by von Graefe's sign (36%–80%). Von Graefe's sign is a dynamic finding described as upper eyelid lag as the eye tracks a moving object downward, and is distinct from lid lag which is a static finding and occurs less frequently in TED. Proptosis (exophthalmos) (60%) and restriction in extraocular mobility (40%) are the most commonly seen orbital signs. On neuroimaging, extraocular muscles (EOM) can show enlargement and inflammation, with the order of involvement starting with inferior rectus, followed by medial rectus, superior rectus, and finally lateral rectus. Fat expansion can also be noted on neuroimaging. The combination of EOM enlargement and fat expansion produces compression at the orbital apex causing compression optic neuropathy, leading to vision loss. Less commonly, significant fat expansion alone can lead to severe proptosis and stretching of the optic nerve leading to optic neuropathy. Other inflammatory periocular changes can include edema and/or erythema of the lid, conjunctiva (chemosis and injection), caruncle, and plica. The patient can experience excessive tearing or dry eye symptoms as part of direct meibomian gland dysfunction (MGD) or lagophthalmos (incomplete closure of the eye) from lid retraction.

Diagnosis and Disease Grading

The heterogeneity of TED findings can make diagnosis difficult at times, especially in mild cases. In 1994, Bartley and Gorman proposed a diagnostic criterion for TED including eyelid retraction with one of these characteristics: thyroid dysfunction or regulation (antibodies), exophthalmos; optic nerve dysfunction, or EOM involvement, after exclusion of other orbital diseases. In cases where no lid retraction is noted, thyroid dysfunction or regulation must be present. More recently, the North American Society of Academic Orbital Surgeons (NASAOS) proposed that the diagnostic criteria include serological evidence of autoimmune thyroid disease, clinical features in the orbit and eyelid consistent of TED, and imaging findings of fusiform, tendon-sparing enlargement of ≥1 extraocular muscle. Serum markers can include thyroid stimulating antibody (TSAb) and thyroid blocking antibodies (TBAbs) including anti-thyroid peroxidase antibody (TPOAb), TSH receptor antibody (TSHRAb), and thyroglobulin antibody (TGAb).

Dysthyroid optic neuropathy can also be difficult to identify, as no single clinical sign is completely reliable. Generally, optic nerve function is assessed with visual acuity; colour vision; presence of disc edema; relative afferent pupillary defect; absence of spontaneous venous pulsations; and abnormal visual fields.

Neuroimaging may be used for diagnosis and to facilitate management. CT of orbits can facilitate surgical planning, and MR imaging can potentially

Figure 1. A. Coronal CT without contrast showing bilateral enlargement of the inferior rectus, medial rectus and superior rectus-levator complex with sparing of lateral rectus. No apical crowding. B. Coronal CT without contrast showing apical crowding. C. Axial MRI T2 flair showing enlargement of bilateral medial and lateral rectus with tendon sparing and enhancement indicating inflammation with the muscles. Neuroimaging used for diagnosis; courtesy of Sabrina Yu, MD & Vivian T. Yin, MD.
help delineate active inflammation in extraocular muscles (Figure 1). It is recommended that all Graves’ disease patients be screened for TED at each visit and connected to ophthalmology early, with urgency of referral dependent on clinical presentation.9

In addition to the challenges of diagnosis, the variable course of the disease makes disease grading necessary in order to manage TED patients based on best evidence. There are two types of TED classifications based on the severity or activity of disease. The Clinical Activity Score (CAS) and vision, inflammation, strabismus, and appearance score (VISA)2 evaluate disease activity (Table 1). In contrast, the European Group on Graves’ Orbitopathy (EUGOGO) classifies disease severity broadly into mild (<2 mm lid retraction; mild soft tissue involvement; <3 mm exophthalmos; transient/no diplopia); moderate-to-severe (lid retraction >2 mm; moderate/severe soft tissue involvement; exophthalmos >3 mm; diplopia), and sight-threatening (dysthyroid optic neuropathy and/or corneal breakdown).10 As with all grading systems, none is perfect for all scenarios. The choice of grading system is dependent on purpose and ease of use; however, the key factor is consistency in order to track patients over time.

### Conventional Treatments

Traditionally, the management of TED is dependent on the severity of disease. However, in all patients with TED, it is important to optimize modifiable risk factors. Smoking is the strongest modifiable risk factor. Smoking shows a dosage-dependant correlation with the development of proptosis and diplopia, disease progression and reduced efficacy of treatment.11 Euthyroid status should be established and maintained early, as both hypothyroidism and hyperthyroidism have been shown to exacerbate TED.10 However, in some studies radioactive iodine treatment has been shown to worsen and increase the risk of developing TED in patients with Grave’s disease.12 Consideration for prophylaxis corticosteroid treatment should be discussed with the patient and managed in conjunction with an ophthalmologist.

In patients with mild disease, supportive management includes artificial tears and ointments for dry eye, and prisms or ocular occlusion for diplopia.9 In a randomized, controlled trial (RCT) from the European Group on Graves’ Orbitopathy, selenium was shown to improve quality of life (QOL), eyelid aperture and soft tissue involvement compared to pentoxysphylline.13 However, it remains unclear if supplementation is effective in populations that are not deficient in selenium, as is the case in North America.

In moderate-to-severe disease, glucocorticoids have historically been the mainstay of treatment to suppress orbital inflammation. In recent years, the use of intravenous methylprednisolone (IVMP) has become more common, as it has been shown to achieve more rapid improvement without the same degree of side effects than longer-term oral steroid use.10 The recommended regimen is a total dose of 4.5 g IVMP divided as 0.5 g weekly for six weeks, then 0.25 g weekly for a further six weeks.14 An individualized approach should be adopted in determining when to discontinue steroids or switch to another agent, although generally IVMP pulse should not continue beyond 12 weeks.9

In the treatment of optic neuropathy, urgent decompression and high-dose IVMP (1,000–15,000 mg/kg) is advised.15 Orbital injection of triamcinolone for the treatment of TED is controversial. Some studies have shown benefit in decreasing orbital congestion16 and lid retraction;17 however, there is risk of retinal embolic phenomenon with orbital injection.18 Furthermore, real-life clinical response has not been as promising as the results seen in the literature.

The use of orbital radiation in treating TED remains variable. Although it is well tolerated, multiple systematic meta-analyses have reached varying conclusions regarding its efficacy.19,20 Radiation can be considered in the early, active phase of the disease and appears most beneficial for dysthyroid optic neuropathy, periorbital inflammatory changes and progressive diplopia.21 The optimal dose and fractionation schedule is unclear, with 20 Gy over two weeks commonly administered, although alternatively lower-dose 1 Gy per week over 20 weeks may be equally effective.22 Radiotherapy should be avoided in Type 2 diabetics to prevent retinopathy, and in patients < 35 for secondary malignancy risk. Radiotherapy has only been studied with oral steroids to date and there is no published data to date on its efficacy in combination with intravenous glucocorticoids. Currently, two multicentre RCTs are underway to compare the efficacy of combined radiotherapy and IVMP vs monotherapy IVMP, in both early progressive TED and dysthyroid optic neuropathy (thyroideyedisease.org).

Additional surgical intervention for rehabilitation purposes occurs on an elective basis once the disease is in the quiet phase, with a staged approach to address proptosis first with orbital decompression, then ocular misalignment with strabismus surgery, and lastly, eyelid retraction repair with levator-muller recession.9

### Immunomodulatory Therapies

In recent years, there has been a proliferation of new therapies for modifying the course of TED. The first
### VISA

**Grade**
- Vision /1
  - Visual acuity
  - Colour

**Subjective**
- Best correct visual acuity (BCVA)
- HRR colour test
- Optic nerve edema/pallor

**Objective**
- Caruncle edema
- Chemosis
- Conjunctival injection
- Lid erythema
- Lid edema

### Inflammation /10

- Retrobulbar ache
- Lid swelling
- Diurnal variation

### Strabismus /3

- Diplopia
- Head turn/tilt

### Appearance /3

- Lid stare
- Lid sensitivity
- Bulging eye
- Tearing
- Ocular irritation

### CAS

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<td>Pain on attempted upgaze or downgaze</td>
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<tr>
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<td>Eyelid erythema</td>
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<tr>
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<td>Eyelid edema</td>
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<tr>
<td>1</td>
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<td>1</td>
<td>Inflammation of caruncle or plica</td>
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### Follow-Up

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<td>Decrease of extraocular movement in any direction ≥5°</td>
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<td>1</td>
<td>Decrease of visual acuity &gt;1 Snellen line</td>
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### EUGOGO

**Severity**

- **Mild**
  - <2 mm lid retraction
  - Mild soft tissue involvement
  - >3 mm exophthalmos
  - Transient/no diplopia
  - Corneal exposure responsive to lubrication

- **Moderate-to-Severe**
  - ≥2 mm lid retraction
  - Moderate-severe soft tissue involvement
  - ≥3 mm exophthalmos
  - Diplopia

- **Impaired function**
  - Dysthyroid optic neuropathy
  - Corneal breakdown

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<td>I</td>
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<td>II</td>
<td>Soft tissue involvement (conjunctival/caruncle injection and chemosis, eyelid erythema, edema)</td>
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<td>V</td>
<td>Corneal involvement</td>
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<td>Sight loss (optic nerve involvement)</td>
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Table 1. Four thyroid eye disease scoring systems. VISA grades both disease activity and severity. CAS measures disease activity. EUGOGO and NOSPECS classify disease severity; courtesy of Dr. Sabrina Yu & Dr. Vivian T. Yin.
on the market in the United States was teprotumumab, a monoclonal antibody that binds to and inhibits the IGF-1 receptor, blocking signalling in the autoimmune activation of orbital fibroblasts. It was approved by the FDA in January 2020 for the treatment of active moderate-to-severe TED. In a pooled RCT from two centres, there was a mean improvement in proptosis of 3 mm vs <0.5 mm, with 62% of patients achieving disease inactivation (CAS ≤1) at 24 weeks following every three-week infusion. Response at 72-week follow-up was maintained. Real-world data indicates that this therapy may be effective in a more diverse population than was studied in the initial clinical trials, including patients with chronic thyroid orbitopathy and dysthyroid optic neuropathy. However, a small percentage of patients may require a second course of treatment. Although teprotumumab is currently not Health Canada approved, clinical trials for a Phase 3 study will include Canadian sites. In addition, other candidate drugs targeting similar pathway are ongoing in Canada (Table 2).

Another emerging immunomodulatory agent for the treatment of TED is tocilizumab, a monoclonal antibody that blocks the interleukin-6 receptor. A multicentre RCT in Spain reported impressive findings of nearly ten-fold greater odds of CAS reduction of ≥2 points in steroid-resistant patients, with subsequent consistent real-world data showing inactivation in 74% of treated patients. Tocilizumab is Health Canada approved for use in rheumatoid arthritis, giant cell arteritis and juvenile idiopathic arthritis, and costs 20–30 times less than teprotumumab. Most surprisingly, early data from the Université de Montréal shows efficacy in the reversal of optic neuropathy in patients not amendable for decompression, in addition to 91% achieving CAS ≤1 at last follow-up (unpublished data).

Additionally, several adjunct and alternative agents have been studied in TED. The recent EUGOGO guidelines recommended combination therapy of IVMP and mycophenolate as first-line therapy; however, there are inconsistent findings from RCTs to conclude its impact. No benefit was observed with azathioprine, and there is inconclusive evidence on rituximab in treating TED.

### Conclusion

TED can be a challenging and complex disease to evaluate and manage. Glucocorticoids continue to be the conventional mainstay for treating moderate-to-severe TED. However, a number of new molecules targeting TED pathways may alter the treatment of TED to focus on disease modification at an earlier stage.

### Correspondence

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### Financial Disclosures

V.Y.: Co-principal investigator for clinical trial on Linsitinib (Sling Therapeutics).  
S.Y.: None declared.

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Table 2. Ongoing clinical trials in drug therapy for thyroid eye disease; courtesy of Dr. Sabrina Yu & Dr. Vivian T. Yin.
References