Approach to the Management of Thyroid Eye Disease

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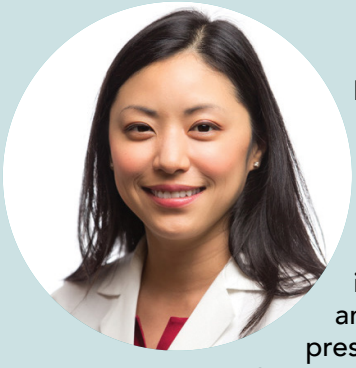

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Introduction

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]

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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%).[6] 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.[7] 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.[8]

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

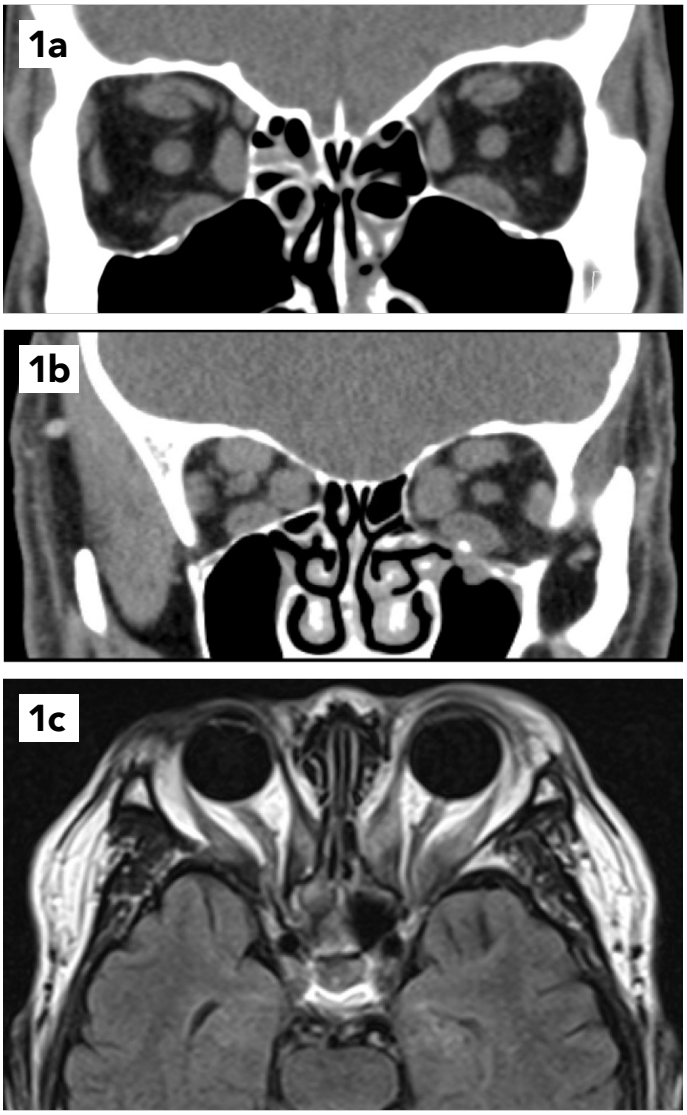

Figure 1. A. Coronal CT without contrast showing bilateral enlargement of the inferior rectus, medial rectus and superior rectus-levator complex with sparing of lateral rectus. No apical crowding. **B.** Coronal CT without contrast showing apical crowding. **C.** Axial MRI T2 flair showing enlargement 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 pentoxyphilline.[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 congestion[16] 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, periocular 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

	Grade	Subjective	Objective
VISA	Vision /1	Visual acuity Colour	Best correct visual acuity (BCVA) HRR colour test Optic nerve edema/pallor
	Inflammation /10	Retrobulbar ache Lid swelling Diurnal variation	Caruncle edema Chemosis Conjunctival injection Lid erythema Lid edema
	Strabismus /3	Diplopia Head turn/tilt	> 45° = 0 30–35° = 1 15–30° = 2 < 15° = 3
	Appearance /3	Lid stare Lid sensitivity Bulging eye Tearing Ocular irritation	Lid retraction, scleral show, lagophthalmos, exophthalmos, corneal erosion/ulcer, SLK, IOP primary, and upgaze

	Points	Parameters
CAS *inactive if < 3* *active if ≥ 3*	1	Spontaneous retrobulbar pain
	1	Pain on attempted upgaze or downgaze
	1	Eyelid erythema
	1	Eyelid edema
	1	Conjunctival hyperemia
	1	Conjunctival chemosis
	1	Inflammation of caruncle or plica
Follow-Up	1	Increase of > 2 mm proptosis
	1	Decrease of extraocular movement in any direction ≥ 5°
	1	Decrease of visual acuity > 1 Snellen line

	Severity	Description
EUGOGO	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

	Class	Description
NO SPECS	0	No physical signs or symptoms
	I	Only signs, no symptoms (lid retraction)
	II	Soft tissue involvement (conjunctival/caruncle injection and chemosis, eyelid erythema, edema)
	III	Proptosis
	IV	Extraocular muscle signs
	V	Corneal involvement
	VI	Sight loss (optic nerve involvement)

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.*

Agent	Company	Mechanism of action	Route	Phase	Country Sites
Batoclimab (IMVT-401)	Immunovant	Anti-neonatal Fc receptor monoclonal antibody	SC	III	US, Belgium, Hungary, Latvia, Spain
VRDN-001	Viridian	Monoclonal antibody, IGF-1R inhibitor	IV	II/III	Canada Italy, Netherlands, UK, US
Linsitinib	Sling Therapeutic	Small molecule IGF-1R inhibitor	PO	II/III	Canada, Italy, Spain, UK, US

Table 2. Ongoing clinical trials in drug therapy for thyroid eye disease; *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.[23] 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.[24] 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[25] and dysthyroid optic neuropathy.[26] However, a small percentage of patients may require a second course of treatment.[27,28] 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,[29] with subsequent consistent real-world data showing inactivation in 74% of treated patients.[30] 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.[9] No benefit was observed with azathioprine, and there is inconclusive evidence on rituximab in treating TED.[9]

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.

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Financial Disclosures

V.Y.: Co-principal investigator for clinica trial on Linsitinib (Sling Therapeutics).

S.Y.: None declared.

References

1. Szelog J, Swanson H, Sniegowski MC, et al. Thyroid eye disease. Mo Med. 2022;119(4):343-350.
2. Dolman PJ. Grading severity and activity in thyroid eye disease. Ophthalmic Plast Reconstr Surg. 2018 Jul;34(4S):S34-40.
3. Bahn RS. Graves' Ophthalmopathy. N Engl J Med. 2010 Feb 25;362(8):726-738.
4. Bartalena L, Fatourechi V. Extrathyroidal manifestations of Graves' disease: a 2014 update. J Endocrinol Invest. 2014 Aug;37(8):691-700.
5. Menconi F, Profilo MA, Leo M, et al. Spontaneous improvement of untreated mild Graves' ophthalmopathy: Rundle's curve revisited. Thyroid. 2014 Jan;24(1):60-66.
6. Gaddipati RV, Meyer DR. Eyelid retraction, lid lag, lagophthalmos, and von Graefe's sign. Ophthalmology. 2008 Jun;115(6):1083-1088.
7. Bartley GB, Gorman CA. Diagnostic criteria for Graves' ophthalmopathy. Am J Ophthalmol. 1995 Jun;119(6):792-5.
8. McKeag D, Lane C, Lazarus JH, et al. Clinical features of dysthyroid optic neuropathy: a European group on Graves' orbitopathy (EUGOGO) survey. Br J Ophthalmol. 2007 Apr 1;91(4):455–8.
9. Burch HB, Perros P, Bednarczuk T, et al. Management of thyroid eye disease: a consensus statement by the American Thyroid Association and the European Thyroid Association. Eur Thyroid J. 2022 Dec 1;11(6):e220189.
10. Bartalena L, Baldeschi L, Boboridis K, et al. 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.
11. Pfeilschifter J, Ziegler R. Smoking and endocrine ophthalmopathy: impact of smoking severity and current vs lifetime cigarette consumption. Clin Endocrinol.1996 Oct;45(4):477-481.
12. Träisk F, Tallstedt L, Abraham-Nordling M, et al. Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or idine-131. J Clin Endocrin Metab. 2009 Oct 1;94(10):3700-3707.
13. Marcocci C, Kahaly GJ, Krassas GE,, et al. Selenium and the course of mild Graves' orbitopathy. N Engl J Med. 2011 May 19;364(20):1920-2031.
14. 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 Sep;90(9):5234-5240.
15. Bartalena L, Krassas GE, Wiersinga W, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. J Clin Endocrinol Metab. 2012 Dec 1;97(12):4454-4463.
16. Ebner R. Treatment of thyroid associated ophthalmopathy with periocular injections of triamcinolone. Br J Ophthalmol. 2004 Nov 1;88(11):1380-1386.
17. Xu DD, Chen Y, Xu HY. Long-term effect of triamcinolone acetonide in the treatment of upper lid retraction with thyroid associated ophthalmopathy. Int J Ophthalmol 2018 Aug 18;11(8):1290-1295.
18. Dolman PJ, Wirth MA. Glucocorticoids for thyroid eye disease. Int Ophthalmol Clin. 2021;61(2):63-78.
19. Bradley EA, Gower EW, Bradley DJ, et al. Orbital radiation for Graves ophthalmopathy. Ophthalmology. 2008 Feb;115(2):398-409.
20. Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, et al. Treatment modalities for Graves' ophthalmopathy: systematic review and metaanalysis. J Clin Endocrin Metab. 2009 Aug 1;94(8):2708-2816.
21. Dolman PJ, Rath S. Orbital radiotherapy for thyroid eye disease: Curr Opin Ophthalmol. 2012 Sep;23(5):427-32.
22. Kahaly GJ, Rösler HP, Pitz S, et al. Low-versus high-dose radiotherapy for Graves' ophthalmopathy: a randomized, single blind trial. J Clin Endocrin Metab. 2000 Jan 1;85(1):102-108.
23. Smith TJ, Kahaly GJ, Ezra DG, Fleming, et al. Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med. 2017 May 4;376(18):1748-1761.
24. Kahaly GJ, Douglas RS, Holt RJ, et al. Teprotumumab for patients with active thyroid eye disease: a pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials. Lancet Diabetes Endocrinol. 2021 Jun;9(6):360-372.
25. Ugradar S, Shi L, Wang Y, et al. Teprotumumab for non-inflammatory thyroid eye disease (TED): evidence for increased IGF-1R expression. Eye. 2021 Sep;35(9):2607-2612.
26. Sears CM, Wang Y, Bailey LA, et al. Early efficacy of teprotumumab for the treatment of dysthyroid optic neuropathy: A multicenter study. Am J Ophthalmol Case Rep. 2021 Sep;23:101111.
27. Smith T. Evaluation of United States thyroid eye disease patients receiving an additional course of teprotumumab treatment over 2 years. Thyroid. 2022 Oct 1;32(S1):P-1-A-135.
28. Douglas RS, Kahaly GJ, Ugradar S, et al. Teprotumumab efficacy, safety, and durability in longer-duration thyroid eye disease and re-treatment. Ophthalmol. 2022 Apr;129(4):438-449.
29. Pérez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, et al. Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant Graves orbitopathy: a randomized clinical trial. Am J Ophthalmol. 2018 Nov;195:181-190.
30. Pérez-Moreiras JV, Varela-Agra M, Prada-Sánchez MC, et al. Steroid-resistant Graves' orbitopathy treated with tocilizumab in real-world clinical practice: a 9-year single-center experience. J Clin Med. 2021 Feb 11;10(4):706.