Medical management of thyroid eye disease – A paradigm shift

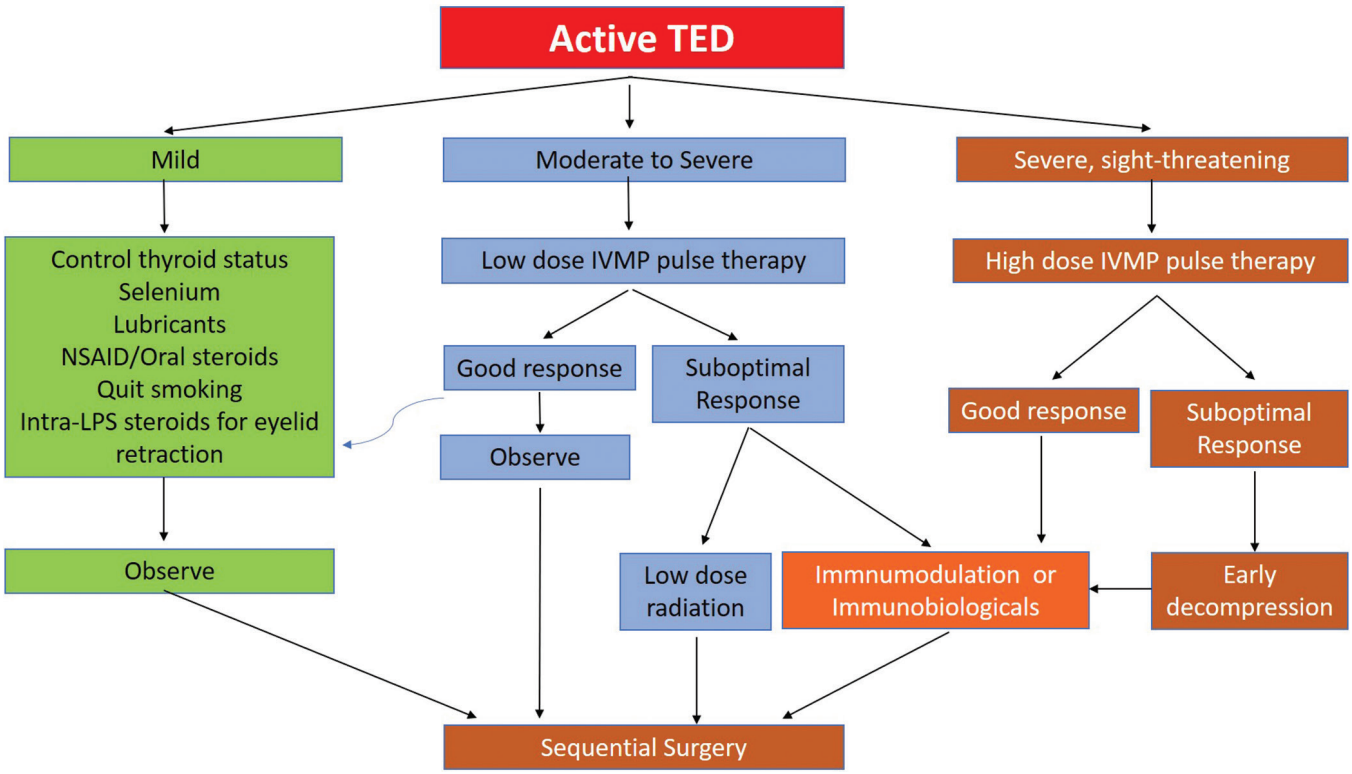
Thyroid eye disease (TED), also known as thyroid-associated orbitopathy or Graves' orbitopathy, is a potentially sight-threatening, disabling, and disfiguring, chronic autoimmune inflammatory disorder, predominantly involving the orbital fat and extraocular muscles.

Activation of orbital fibroblasts that express insulin-like growth factor-1 receptors (IGF-1R) and thyroid-stimulating hormone (TSH) receptor is integral to the genesis of inflammation and its consequences in TED. Orbital fibroblasts represent a heterogeneous population of cells with the multifarious potential for terminal differentiation into adipocytes or myofibroblasts.[1] Activation of orbital fibroblasts leads to the recruitment of T and B lymphocytes, mast cells and macrophages, upregulation of proinflammatory cytokines (IL-6, IL-12, IL-17, IFN-c, and TNF-a),[2] and augmentation of glycosaminoglycan (GAG) production. Deposition of GAG and neo-adipogenesis results in enlargement of the extraocular muscles and physical expansion of the orbital fat.[1,3-5] This, coupled with an element of lingering inflammation and consequent fibrosis manifests some of the typical clinical features of TED such as exophthalmos, eyelid retraction, ocular motility restriction, strabismus, and compressive optic neuropathy.[3-5]

The biphasic natural history of TED as described over six decades ago by Francis Rundle[6,7] has an initial active, inflammatory, progressive component, followed by a static, noninflammatory, fibrotic sequelae.[8,9] The clinical course, however, is heterogenous with numerous permutations of severity and duration of inflammation and functional derangement. TED is described as a function of two variables – activity and severity. Baseline activity and severity can be measured on the European Group on Graves' Orbitopathy (EUGOGO), Vision, Inflammation, Strabismus, Appearance (VISA), NOSPECS (No physical signs or symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle signs, Corneal involvement, and Sight loss), and Clinical Activity Score (CAS). EUGOGO scale [Supplementary Tables 1 and 2] is currently favored as the basis for designing primary management.[10]

Current Management Algorithm

The current management algorithm is shown in Fig. 1. Although mild inactive cases are symptomatically and conservatively managed, aggressive primary medical management is indicated in patients with moderate to severe, active, and sight-threatening TED. Early medial endoscopy-assisted transnasal orbital decompression is indicated in patients with sight-threatening dysthyroid optic neuropathy (DON) unresponsive to medical management. Sequential surgery (orbital decompression, extraocular



Low-dose intravenous methylprednisolone (IVMP) pulse therapy includes IVMP 500 mg on 3 consecutive days as a loading dose, followed by 500 mg thrice weekly X 5, and a cumulative dose of 4000 mg. In sight-threatening DON, high-dose IVMP (1000 mg on 3 consecutive days and 500–1000 mg weekly X 6) is indicated. Immunomodulation includes oral Azathioprine 50 mg BD or Oral Mycophenolate Mofetil 500 mg BD for 6 months or more

Figure 1: Standard sequential management in active TED

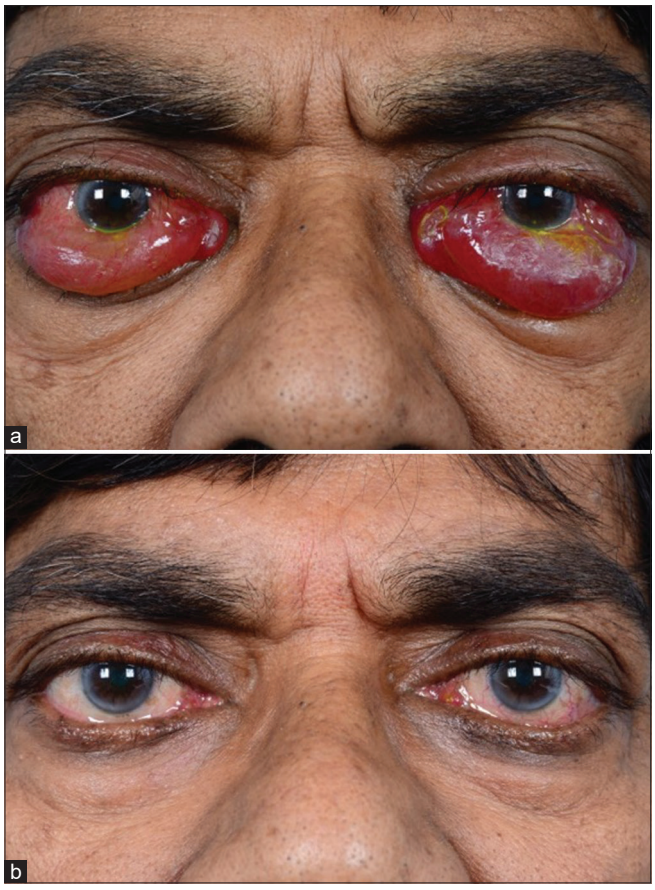


Figure 2: A 45-year-old male with active TED with CAS 7, exophthalmos, ocular motility restriction, and optic disc edema (a), with resolution in activity (CAS 1), exophthalmos, ocular motility restriction, and optic disc edema 6 months later following IVMP and oral Azathioprine (b)

muscle surgery, correction of eyelid retraction) is planned in patients with >6 months of stable, inactive TED for cosmetic or functional indications.

Nonspecific immunomodulation with low-dose pulse intravenous methylprednisolone (IVMP), followed by sequential oral immunomodulation forms the basis of current medical management of TED.[11] IVMP shows pronounced and sustained effect in active TED and has a definite edge over oral steroids. In moderate, active TED, 72% responded to IVMP as compared to only 49% to oral steroids.[12] IVMP is most effective in reducing inflammation and ocular motility dysfunction. Oral immunomodulators (azathioprine or mycophenolate mofetil) used with corticosteroids produce a synergistic and sustained response.[13,14] In our series of 81 patients (117 eyes) with active TED managed with low-dose IVMP pulse therapy coupled with oral azathioprine or mycophenolate mofetil, 59% (69 of 117) showed improvement in exophthalmos (mean, 2.7 mm), 60% (45 of 75) showed resolution of diplopia in the primary position and downgaze, and 80% (94 of 117) demonstrated remission in disease activity (CAS reduction from a mean of 7.1 ± 1.1 pretreatments to 1.2 ± 0.4 posttreatment) [Fig. 2].

Newer Trends

Local injections

Eyelid retraction in TED is typically managed by the levator recession. Temporary measures include botulinum toxin

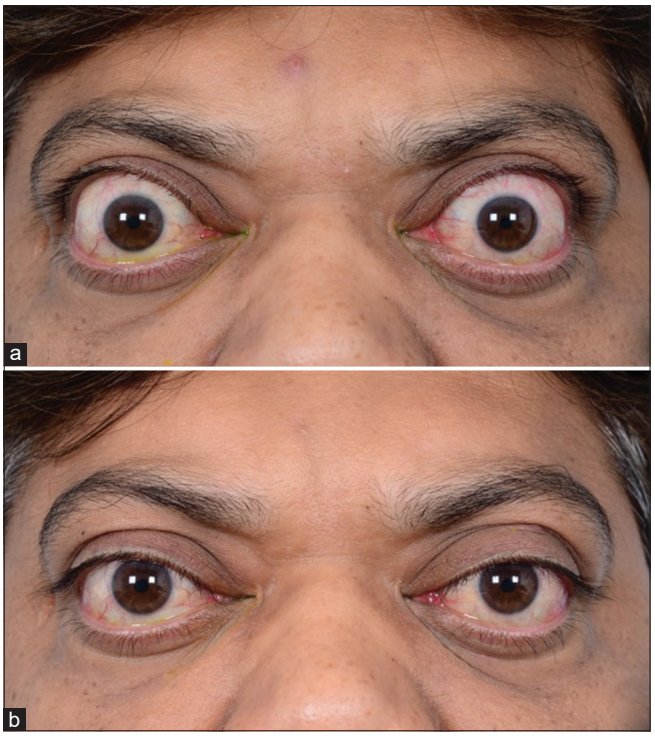


Figure 3: A 50-year-old male with inactive TED with bilateral eyelid retraction (a), following two injections of Triamcinolone 10 mg to the levator, showing resolution of eyelid retraction (b) 3 months later

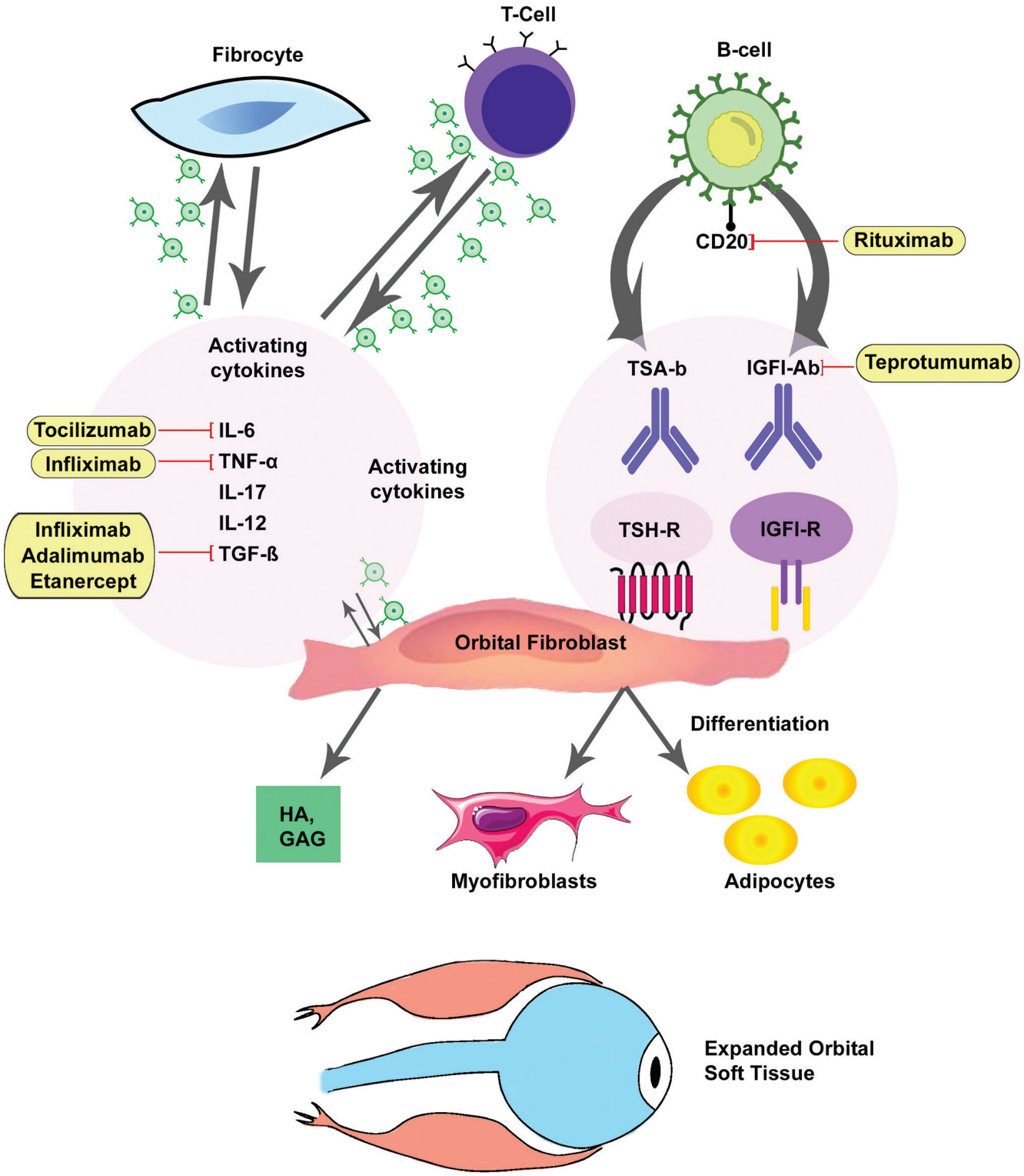
injection or fillers. As an alternative, injection of triamcinolone 10 mg transconjunctivally into the levator has shown excellent results in the resolution of eyelid retraction in both the active and inactive phases of TED [Fig. 3]. This may help minimize the need for surgical intervention for eyelid retraction.[15]

Immunobiologicals

The newer trend in the management of TED is to use immunobiologicals for specifically targeted immunomodulation [Fig. 4]. Rituximab is a humanized chimeric monoclonal antibody that targets CD20 on B cells and its precursors.[16] A randomized controlled trial comparing it with IVMP in active, moderate-to-severe TED showed a 100% response, with no reactivation at 24 weeks and fewer rehabilitative surgeries in the treated group.[16] A controlled trial in North America comparing rituximab to placebo, however, did not show a significant difference.[17]

IL-6 is a pleiotropic cytokine that plays a role in B cell activation and the production of antibody-producing plasma cells. Tocilizumab, a recombinant, humanized, monoclonal antibody against the IL-6 receptor, has shown promising results. It improved clinical activity score in all patients, proptosis in 72%, extraocular motility in 83%, and diplopia in 54%.[18] Besides, it seems effective in vision-threatening and corticosteroid-refractory TED as well.[19] Etanercept; a TNF-α receptor blocker, adalimumab a fully human monoclonal antibody against TNF,[20] and infliximab; a chimeric monoclonal antibody that targets TNF-α,[21] have shown encouraging results in small case series.

A landmark breakthrough is the introduction of specific IGF-1R blocker teprotumumab.[6,22,23] It has been demonstrated that eight infusions of teprotumumab over 24 weeks were



Modified from Hodgson NM, Rajaii F. Current Understanding of the Progression and Management of Thyroid Associated Orbitopathy: A Systematic Review. Ophthalmology and Therapy. 2020 Mar; 9 (1):21-33

Figure 4: A complex interaction of the immune system, proinflammatory cytokines, and autoantibodies on orbital fibroblasts leading to the clinical characteristics of TED and sites of action of target therapy

associated with clinical improvement in patients with moderate-to-severe, active TED, shown by reductions in CAS, proptosis, subjective diplopia, and improved quality of life.[22] The reduction in proptosis was comparable to orbital decompression.[22] The results were further confirmed by phase 3 trial, OPTIC (Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study), and the

drug has received Food and Drug Administration (FDA) approval.[23]

Conclusion

There is an increasing understanding of the various facets of TED.[24-27] The debilitating functional manifestations of TED are multifactorial and are difficult to treat optimally with conventional modalities. With the unraveling of the pathophysiology of TED at the molecular level, there are several new options for powerful targeted therapy that have shown the potential to alter the natural history of the disease, both in terms of its activity and severity, resulting in better functional and aesthetic recovery, and a reduced need for rehabilitative surgeries.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Santosh G Honavar

Editor, Indian Journal of Ophthalmology,
Centre for Sight, Hyderabad, Telangana, India.
E-mail: santosh.honavar@gmail.com

References

1. Hodgson NM, Rajaii F. Current understanding of the progression and management of thyroid associated orbitopathy: A systematic review. Ophthalmol Ther 2020;9:21-33.
2. Shan SJ, Douglas RS. The pathophysiology of thyroid eye disease. J Neuroophthalmol 2014;34:177-85.
3. Dik WA, Virakul S, van Steensel L. Current perspectives on the role of orbital fibroblasts in the pathogenesis of Graves' ophthalmopathy. Exp Eye Res 2016;142:83-91.
4. Krieger CC, Neumann S, Place RF, Marcus-Samuels B, Gershengorn MC. Bidirectional TSH and IGF-1 receptor cross talk mediates stimulation of hyaluronan secretion by Graves' disease immunoglobins. J Clin Endocrinol Metab 2015;100:1071-7.
5. Smith TJ, Koumas L, Gagnon A, Bell A, Sempowski GD, Phipps RP, *et al*. Orbital fibroblast heterogeneity may determine the clinical presentation of thyroid-associated ophthalmopathy. J Clin Endocrinol Metab 2002;87:385-92.
6. Patel A, Yang H, Douglas RS. A new era in the treatment of thyroid eye disease. Am J Ophthalmol 2019;208:281-8.
7. Rundle FF, Wilson CW. Development and course of exophthalmos and ophthalmoplegia in Graves' disease with special reference to the effect of thyroidectomy. Clin Sci 1945;5:177-94.
8. Douglas RS, Gupta S. The pathophysiology of thyroid eye disease: Implications for immunotherapy. Curr Opin Ophthalmol 2011;22:385-90.
9. Bothun ED, Scheurer RA, Harrison AR, Lee MS. Update on thyroid eye disease and management. Clin Ophthalmol 2009;3:543-51.
10. Yang DD, Gonzalez MO, Durairaj VD. Medical management of thyroid eye disease. Saudi J Ophthalmol 2011;25:3-13.
11. Strianese D, Rossi F. Interruption of autoimmunity for thyroid eye disease: B-cell and T-cell strategy. Eye 2019;33:191-9.
12. Aktaran S, Akarsu E, Erbağci I, Araz M, Okumuş S, Kartal M. Comparison of intravenous methylprednisolone therapy vs. oral methylprednisolone therapy in patients with Graves' ophthalmopathy. Int J Clin Pract 2007;61:45-51.
13. Rajendram R, Taylor PN, Wilson VJ, Harris N, Morris OC, Tomlinson M, *et al*. Combined immunosuppression and radiotherapy in thyroid eye disease (CIRTED): A multicentre, 2 × 2 factorial, double-blind, randomised controlled trial. Lancet Diabetes Endocrinol 2018;6:299-309.
14. Ye X, Bo X, Hu X, Cui H, Lu B, Shao J, *et al*. Efficacy and safety of mycophenolate mofetil in patients with active moderate-to-severe Graves' orbitopathy. Clin Endocrinol (Oxf) 2017;86:247-55.
15. Joos ZP, Sullivan TJ. Peri-levator palpebrae superioris triamcinolone injection for the treatment of thyroid eye disease-associated upper eyelid retraction. Clin Exp Ophthalmol 2017;45:651-2.
16. Salvi M, Vannucchi G, Currò N, Campi I, Covelli D, Dazzi D, *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;100:422–31.
17. 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;100:432-41.
18. Pérez-Moreiras JV, Alvarez-López A, Gómez EC. Treatment of active corticosteroid-resistant graves' orbitopathy. Ophthalmic Plast Reconstr Surg 2014;30:162-7.
19. Sy A, Eliasieh K, Silkiss RZ. Clinical response to tocilizumab in severe thyroid eye disease. Ophthalmic Plast Reconstr Surg 2017;33:e55-7.
20. Ayabe R, Rootman DB, Hwang CJ, Ben-Artzi A, Goldberg R. Adalimumab as steroid-sparing treatment of inflammatory-stage thyroid eye disease. Ophthalmic Plast Reconstr Surg 2014;30:415-9.
21. Durrani OM, Reuser TQ, Murray PI. Infliximab: A novel treatment for sight-threatening thyroid associated ophthalmopathy. Orbit 2005;24:117-9.
22. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, *et al*. Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med 2017;376:1748-61.
23. Douglas RS, Kahaly GJ, Patel A, Sile S, Thompsom EHZ, Perdok R, *et al*. Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med 2020;382:341-52.
24. Pradhan A, Ganguly A, Naik MN, Nair AG, Desai S, Rath S. Thyroid eye disease survey: An anonymous web-based survey in the Indian subcontinent. Indian J Ophthalmol 2020;68:1609-14.
25. Delampady K, Reddy SV, Yadav SB. Assessing the quality of life in Indian Graves' orbitopathy patients and validation of Hindi version of GO-QOL questionnaire. Indian J Ophthalmol 2020;68:1617-21.
26. Gupta R, Thomas R, Almukhtar F, Kiran A. Visual morbidity in thyroid eye disease in Asian Indian patients. Indian J Ophthalmol 2020;68:1622-7.
27. Muralidhar A, Das S, Tiple S. Clinical profile of thyroid eye disease and factors predictive of disease severity. Indian J Ophthalmol 2020;68:1629-34..

Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_2386_20

Cite this article as: Honavar SG. Medical management of thyroid eye disease – A paradigm shift. Indian J Ophthalmol 2020;68:1515-8.

Supplementary Table 1: Activity and severity assessments in TED

Measures of activity based on the classical features of inflammation

Clinical activity score (CAS) is the sum of all items present

1. Spontaneous retrobulbar pain
2. Pain on attempted up- or downgaze
3. Redness of the eyelids
4. Redness of the conjunctiva
5. Swelling of the eyelids
6. Inflammation of the caruncle and/or plica
7. Conjunctival edema

A CAS >3/7 indicates active TED at baseline

Patients assessed after follow-up (1-3 months) can be scored out of 10 by including items 8-10

8. Increase of >2 mm in proptosis
9. The decrease in a uniocular ocular excursion in any one direction of >8°
10. Decrease of acuity equivalent to 1 Snellen line

A CAS >4/10 indicates active TED on follow-up

Measures of severity based on functional impairment:

1. Lid aperture (distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed and with distant fixation)
2. Swelling of the eyelids (absent/equivocal, moderate, severe)
3. Redness of the eyelids (absent/present)
4. Redness of the conjunctivae (absent/present)
5. Conjunctival edema (absent/present)
6. Inflammation of the caruncle or plica (absent/present)
7. Exophthalmos (measured in mm using the same Hertel exophthalmometer and same intercanthal distance for an individual patient)
8. Subjective diplopia score (0 - no diplopia; 1 - intermittent, i.e., diplopia in the primary position of gaze, when tired or when first awakening; 2 - inconstant, i.e., diplopia at extremes of gaze; 3 - constant, i.e., continuous diplopia in primary or reading position)
9. Eye muscle involvement (ductions in degrees)
10. Corneal involvement (absent/punctate keratopathy/ulcer)
11. Optic nerve involvement (best-corrected visual acuity, color vision, optic disc, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected)

From: Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marcocci C *et al*. European Group on Graves' Orbitopathy (EUGOGO). Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol. 2008 Mar; 158(3):273-85

Supplementary Table 2: Classification of severity in TED

Severity	Clinical Features
Mild TED, whose features have only a minor impact on daily life, insufficient to justify immunosuppressive or surgical treatment.	Lid retraction <2 mm Mild soft-tissue involvement Exophthalmos <3 mm No diplopia or transient diplopia Exposure keratopathy responsive to lubrication
Moderate-to-severe TED, whose eye disease has a sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive).	Lid retraction >2 mm Moderate to severe soft-tissue involvement Constant or inconstant diplopia Exophthalmos >3 mm
Sight-threatening TED	Presence of optic neuropathy Presence of corneal decompensation

From: Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marcocci C *et al*. European Group on Graves' Orbitopathy (EUGOGO). Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol. 2008 Mar; 158(3):273-85