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Advances in the Treatment of Thyroid Eye Disease Associated Extraocular Muscle Myopathy and Optic Neuropathy

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Abstract

Purpose of Review—To review emerging treatments for thyroid eye disease (TED) associated extraocular muscle myopathy and dysthyroid optic neuropathy (DON).

Recent Findings—Emerging targeted biologic therapies may alter the disease course in TED. Teprotumumab, a type I insulin-like growth factor receptor inhibitor, is the most recent addition to the treatments available for TED-associated extraocular muscle myopathy causing diplopia. Small studies also suggest a potential therapeutic benefit for DON. Various recent studies have also expanded our knowledge on conventional TED therapies.

Summary—The therapeutic landscape of TED and its sequelae has evolved in recent years. New targeted therapies have the potential to reduce the extraocular muscle and orbital volume expansion which can lead to diplopia and vision loss from optic nerve compression. Longer term efficacy and durability data is needed to determine the role biologics, such as teprotumumab, should play in the treatment of TED patients compared to the current standard of care.

Keywords

Thyroid eye disease (TED); Graves ophthalmopathy (GO); Compressive optic neuropathy (CON); Dysthyroid optic neuropathy (DON); Teprotumumab; Diplopia

Introduction

Thyroid eye disease (TED), also known as thyroid associated orbitopathy (TAO) or Graves ophthalmopathy (GO), is an autoimmune inflammatory disease which can be challenging

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Author Contribution

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Compliance with Ethical Standards

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to treat [1]. TED typically begins with an acute inflammatory or active phase, lasting on average 18 months [2–4]. Over time, inflammation subsides and the disease transitions into a chronic or stable phase where tissue remodeling ceases and proptosis, eyelid retraction, and diplopia can improve, but often persist. Risk factors for TED include smoking, female gender, age, radioactive iodine treatment, and vitamin D deficiency [5–8]. Additionally, recent studies report that diabetes mellitus and obstructive sleep apnea are significantly associated with progression to dysthyroid optic neuropathy (DON) [8, 9•, 10]. Most TED patients are hyperthyroid (> 90%), but up to 10% can be hypothyroid or euthyroid [1].

TED is primarily a clinical diagnosis; common clinical signs include upper lid retraction, conjunctival injection, eyelid edema, ocular motility changes, and proptosis. Patients typically present with symptoms of eye pain, blurry or double vision, photophobia, tearing, and cosmetic complaints [1, 11, 12]. Clinical assessment of TED is characterized by grading disease activity and severity. The clinical activity score (CAS) is used to assess disease activity based on 1–7 clinical findings including spontaneous orbital pain, gaze-evoked orbital pain, eyelid swelling, eyelid erythema, conjunctival redness, chemosis, or caruncle/plica inflammation. A score of 3 or more is considered active disease [13]. The severity of TED is a function of the degree of diplopia, proptosis and soft tissue changes and their impact on the patient's quality of life [14]. Most patients have mild TED while about 25% of patients will require medical or surgical intervention due to moderate-to-severe disease [15]. Three to five percent of patients may develop sight-threatening disease, due to DON or exposure keratopathy [16, 17].

Imaging such as orbital ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) can aid in diagnosis. Extraocular muscle belly enlargement, typically tendon-sparing, and orbital volume expansion are hallmarks of the disease. The inferior, medial, superior, and lateral rectus muscles are involved at rates of 57–77%, 61–75%, 51%, and 42–50%, respectively [18, 19]. DON findings may include optic nerve (ON) crowding, ON stretch, intracranial fat prolapse, and muscle index over 50%. MRI signal intensity values, using the short tau inversion recovery (STIR) sequence, have been shown to increase proportionally to increases in disease activity. Thus, quantifiable measures obtained via MRI, such as muscle volumes and signal intensity ratio values, may be valuable in disease monitoring [20]. Alternatively, B-scan ultrasonography can be used to visualize EOM swelling and orbital tissue expansion. While ultrasonography provides an inexpensive, simple, and radiation sparing means of assessing EOM size, ultrasonography is not preferred because results are highly operator dependent, and CT or MRI are superior methods of visualizing the posterior orbit [21–24]. Laboratory testing is not diagnostic but total T3, free T4, and TSH are indicated to screen for thyroid dysfunction and support the TED diagnosis. Thyroid-stimulating inhibitory immunoglobulins (TSI) levels can also aid in the diagnosis of TED and monitor disease progression, as studies suggest that TSI levels correlate with disease activity and clinical severity in TED [11, 25–27].

TED is thought to result from loss of immune tolerance to autoantigens including thyroid stimulating hormone-receptor (TSH-R) and insulin-like growth factor-I receptor (IGF-IR) [28]. Self-reactive T-cells then activate plasma cells, which produce autoantibodies that bind these antigens in the thyroid gland and other tissues. In the orbit, TSH-R and IGF-IR

co-localize on the membranes of CD34+ fibrocytes. When these receptors are activated by autoantibody binding, the fibrocytes can (1) increase inflammation, (2) increase deposition of extracellular matrix, and (3) differentiate into myofibroblasts or adipocytes [29–31]. The resultant tissue expansion and inflammation produce the characteristic clinical findings seen in TED [32].

Due to advancements in our understanding of the pathophysiology of TED, there have been significant advancements in management. In 2020, teprotumumab became the first drug approved by the US Food and Drug Administration (FDA) for the treatment of TED in adults [33]. Pivotal clinical trials reported improvements in CAS score, proptosis, diplopia, extraocular muscle size, and quality-of-life scores associated with teprotumumab treatment [34••, 35]. This article reviews the neurologic manifestations of TED and the treatment options for TED-associated extraocular muscle myopathy causing diplopia and DON with a focus on the evidence for targeted therapies which can potentially reverse the disease course.

Neurologic Manifestations

Myopathy of the extraocular muscles causes diplopia in roughly 50% of TED patients and is mostly restrictive in nature, meaning that stiffening of the extraocular muscles limits eye movement opposite to the direction of muscle action [11]. This is thought to occur secondary to myofibroblast-mediated tissue remodeling, inflammatory muscle swelling, and fibrosis [36]. Patients experience binocular double vision that varies with the direction of gaze and focal distance. Depth perception can also be affected. Diplopia is often classified using the Gorman diplopia score (GDS): absent (0), intermittent (1), inconstant (at the extremes of gaze) (2), or constant (3) [37]. Prism diopter measurements can more accurately quantify the amount of extraocular muscle restriction leading to diplopia [38].

Recent epidemiologic studies have found that of patients with TED, an estimated 3–5% present with DON [16, 17]. Though rare, DON is a medical emergency, and timely management is necessary to prevent permanent vision loss. DON is thought to be primarily caused by ON compression at the narrow orbital apex by swollen extraocular muscles [19, 39–41]. This may result in ON ischemia or inhibition of axoplasmic flow and irreversible ON damage. DON may also occur secondary to axial tension on the ON in rare cases of TED without significant extraocular muscle involvement [41–43]. Patients will experience symptoms ranging from blurred vision to profound vision loss in one or both eyes. Neurologists can assess ON health by evaluation of best corrected visual acuity (BCVA), a relative afferent pupillary defect (RAPD) in unilateral or asymmetric cases, and color vision testing, which can be an early indicator of ON dysfunction. Orbital imaging can assess for ON compression if the clinical exam is suspicious. Should there be any concern for sight-threatening disease, emergent evaluation by ophthalmology is indicated for additional testing, including visual field (VF) testing and optic nerve and orbital imaging.

TED Treatment Overview

The European Group on Graves' Orbitopathy (EUGOGO) published their clinical practice guidelines for the treatment of TED in 2021 [44••]. These state that for patients with active moderate-to-severe TED, the combination of intravenous (IV) methylprednisolone

(IVMP) and mycophenolate mofetil (MMF) is recommended as first-line therapy. Second-line treatments include a second course of IVMP at a higher starting dose, oral prednisone combined with cyclosporine or azathioprine, orbital radiotherapy (ORT) combined with oral or IV glucocorticoids, teprotumumab, rituximab (RTX), and tocilizumab (TCZ). These guidelines are influenced by lack of European Medicines Agency (EMA) approval for teprotumumab and therefore reflect availability more than efficacy.

Conventional Therapies

Until recently, the mainstay of treatment for active, moderate-to-severe TED consisted of oral or IV corticosteroids with or without MMF or ORT [45]. IV corticosteroids are typically used over oral steroids due to studies demonstrating their superior efficacy and side effect profile [46]. The recommended regimen is IVMP 500 mg weekly for six doses followed by 250 mg weekly for six doses, with higher dosing for severe disease with constant or inconstant diplopia (750 mg weekly for 6 weeks then 500 mg weekly for 6 weeks), not to exceed 8 g to avoid life-threatening hepatotoxicity [46, 47•, 48]. Second-line, oral glucocorticoids (1 mg/kg tapered over 4–6 months) [46, 49] are still used worldwide either alone or after a course of IVMP. MMF is a reversible inhibitor of inosine monophosphate dehydrogenase that inhibits lymphocyte activity [50] and has a favorable safety and efficacy profile [44••, 51•, 52•, 53, 54]. Two large, randomized control trials (RCT) recently evaluated the efficacy of MMF for the treatment of TED. One study assessed MMF plus IVMP compared to IVMP monotherapy in 174 cases of active moderate-to-severe TED and found that CAS, proptosis, diplopia, adverse event (AE) burden, and rate of reactivation were improved over the IVMP group [52•]. The second study assessed MMF compared to IVMP in 164 cases of active, moderate-to-severe disease and found that patients in the combined therapy group had an improved rate of response (defined as improvement in at least two clinical parameters including eyelid swelling, CAS, proptosis, lid width, diplopia, and extraocular motility) at 24 and 36 weeks [51•]. ORT in combination with glucocorticoids is recommended as a second-line treatment for moderate-to-severe active TED, particularly in the presence of diplopia and/or restriction of extraocular motility [44••].

ORT in combination with glucocorticoids is thought to suppress orbital fibroblasts activity during rapidly worsening periods of active disease [48, 55]. Other immunosuppressive agents such as cyclosporine, azathioprine, and methotrexate are generally second-line therapeutic options without convincing RCT data [44••]. While further studies are needed to determine the long-term efficacy of combined ORT and steroid therapy, the current best evidence suggests that patients with early, active, moderate-to-severe disease benefit most [56].

Biologics

While conventional therapies like steroids are effective at reducing inflammation, they have not been shown to significantly reverse the proptosis and restrictive strabismus characteristic of more advanced TED [57, 58]. The recent approval of teprotumumab for the treatment of TED has changed the therapeutic landscape. Teprotumumab is a human monoclonal antibody antagonist of the IGF-IR. In the phase 3 RCT of 83 patients with active moderate-to-severe TED, IV teprotumumab (10 mg/kg followed by 20 mg/kg every 3 weeks × 7

doses) resulted in an improvement in proptosis of ≥ 2 mm in 83% of patients compared to 10% in the placebo group at 24 weeks follow-up [34••]. Currently, there are no studies comparing teprotumumab to IV steroids and/or ORT or other conventional therapies.

Other biologics that have been evaluated for TED therapy include rituximab (RTX), a CD-20 inhibitor, and tocilizumab (TCZ), an IL-6 receptor antagonist. RTX was evaluated in 2 small RCTs that compared treatment outcomes in patients treated with rituximab or IVMP. The two studies collectively assessed 57 patients with one study finding a significant improvement in CAS reduction over the IVMP group, while the other study did not [59, 60]. A follow-up analysis of the studies found that the study with a significant result had patients with a shorter disease duration, lower age, and lower baseline thyrotropin receptor antibodies (TRAb) [61]. Interestingly, previous studies did not demonstrate a significant improvement in diplopia or proptosis with RTX [60, 62, 63]. It is also worth noting that RTX has been associated with the development of DON and is not recommended in patients at risk of DON, though the quality of evidence is low [44••].

Tocilizumab was evaluated in a RCT including 32 active, moderate-to-severe TED patients refractory to at least 3 doses of IVMP or an increase in CAS ≥ 1 after IVMP [64•]. The patients were randomized to either four doses of monthly 8 mg/kg TCZ or placebo. CAS improved by≥2 points in 93% versus 59%, respectively, at 16 weeks. However, CAS reduction was not found to be significant at week 40. Additional studies are needed to assess the long-term efficacy of TCZ.

Treatment of TED-Associated Extraocular Muscle Myopathy

Management of diplopia due to extraocular muscle myopathy can be challenging due to its variability throughout the course of TED. The activity and severity of disease as well as patient preferences and medical history guide treatment selection. Here we will review therapeutic options for TED-associated diplopia (Table 1) and summarize our treatment recommendations.

Active TED-Associated Extraocular Muscle Myopathy

Corticosteroids—Corticosteroids are the first-line treatment for active moderate-to-severe TED [44••]. Kahaly et al. showed that IV steroids were superior to oral steroids for the treatment of constant diplopia at 12 weeks (56.5% vs 33.3% improvement in GDS), but not for inconstant or intermittent diplopia [46]. Bartalena et al. compared cumulative dosages of IVMP at 2.25 g, 4.98 g, and 7.47 g and did not find any significant differences in diplopia improvement by GDS [65]. Meta-analysis of available RCTs demonstrated that IV steroids improve GDS in approximately 33% of patients [48]. However, most of these studies did not have a placebo comparison, and thus it is unclear how much of the improvement in GDS was from steroid therapy versus the natural course of TED. Periorbital steroid injections have been reported as an alternative treatment option [44••]. One RCT of 41 moderate-to-severe TED patients, diagnosed within 6 months, reported that patients treated with 4 weekly periorbital triamcinolone acetate injections had an increase in the area of binocular vision without diplopia (105.93% vs 1.30% improvement) on Goldmann perimetry and a decrease in extraocular muscle size (− 18.3% vs + 5.2%) as measured on CT scan

compared to placebo at 24 weeks [66]. These results suggest that patients with early onset of TED-associated diplopia may benefit from periorbital steroids, though larger studies are needed to confirm these results.

Orbital Radiotherapy—Several RCTs have demonstrated the efficacy of ORT (20 Gy in 10 fractions over 2 weeks per eye) over sham irradiation in improving diplopia and ductions, with a response rate of 50–60% based on improvement of GDS by ≥ 1 [67, 68]. However, other RCTs have shown no significant difference in area of diplopia fields and CAS score between ORT and placebo [69, 70]. Additional studies and meta-analyses of existing information are needed to make accurate conclusions on the efficacy of ORT on diplopia in TED patients.

Mycophenolate Mofetil—A recent RCT assessed MMF plus IVMP compared to IVMP monotherapy in 164 patients and did not find a significant difference in diplopia improvement [51•], while another RCT of 174 patients reported significantly improved diplopia using MMF compared to IVMP (90.4% vs 62.6% with GDS improvement ≥ 1) [52•].

Rituximab—Recent studies demonstrated efficacy in decreasing CAS score but have not shown convincing evidence for improving eye motility or diplopia [62, 63].

Tocilizumab—In a RCT of 32 active moderate-to-severe TED patients refractory to at least 3 doses of IVMP, there was no significant benefit in diplopia at 16 and 40 weeks despite improvement in CAS score [64•].

Teprotumumab—In the phase 3 RCT of treatment naïve patients with active moderate-to-severe TED, teprotumumab was associated with diplopia improvement by ≥ 1 on the GDS in 68% versus in 29% with placebo [34••]. Preliminary long-term data from the phase 2 and 3 clinical trials, 72 weeks after starting treatment, demonstrated maintenance of diplopia improvement in 69% and 58% of diplopia responders, respectively [71••, 72]. Additionally, 53% of patients had complete resolution of diplopia at 24 weeks in the teprotumumab group vs 28% of patients in the placebo group. Importantly, it is not known what percentage of patients avoided strabismus surgery due to teprotumumab use. In a retrospective study of patients with moderate-to-severe disease refractory to previous therapies, there was improvement in diplopia (≥ 1 on GDS) in 61% of patients at mean follow-up of 30 weeks [73].

Stable TED-Related Diplopia

Non-surgical options such as prisms can be considered for small to moderate angle deviations, typically < 15 prism diopters (PD) [74]. Botulinum toxin (BT) injections can also be considered in patients who wish to avoid surgery and have deviations larger than what prisms can correct for [75, 76]. A retrospective study of 22 TED patients treated with BT for diplopia demonstrated that a third of patients (most effective in patients with a 20 PD deviation or less) avoided surgical intervention after a follow-up ranging from 6 months to 1 year. An additional 27% had a reduced deviation that altered their surgical plan [75].

Strabismus Surgery—Strabismus correction has been reported to be required in 4 to 29% of TED patients [15, 77, 78]. Measurements of strabismus should be stable for at least 6 months before surgery is considered [79]. The primary goal of strabismus surgery is to achieve binocular single vision on primary gaze and typically involves diminishing extraocular muscle restriction by recessing the involved muscle. Large-angle deviation strabismus surgeries have lower success rates with reported reoperation rates up to 45% for strabismus greater than 25 PD [77]. Patients should be counseled prior to surgery and have realistic expectations, as binocular single vision may not be achievable in all directions of gaze with surgery alone.

Teprotumumab—Early reports suggest teprotumumab may be considered for chronic TED and related diplopia [80•, 81•, 82••]. A retrospective study of 31 patients with stable TED (> 2 years) treated with teprotumumab demonstrated a significant improvement in diplopia (≥ 1 grade on GDS) in 67% of patients with 47% of patients having complete resolution of diplopia. Additionally, volumetric analysis of 15 patients who had pre- and post-treatment CT scans demonstrated a significant reduction in extraocular muscle volume before and after treatment (mean reduction of 2011 mm^3 in the study orbit) [82••]. The authors suggest that despite the dormant appearance of chronic TED, orbital fibroblasts continually turnover hyaluronic acid and other extracellular matrix macromolecules weekly to maintain tissue integrity [83]. Therefore, they suggest that teprotumumab may reduce the downstream signaling that leads to tissue expansion in TED and may be effective for chronic TED. Additional studies are needed to confirm these results and assess the long-term efficacy and rate of strabismus surgery avoidance after teprotumumab therapy.

Choice of TED-Associated Extraocular Muscle Myopathy Therapy Summary

Early diagnosis and treatment are key to halt the progression of the underlying disease resulting in extraocular muscle myopathy and diplopia. The severity and chronicity of diplopia are important factors for determining therapy. In the active phase, if mild or intermittent diplopia is attributed to soft tissue inflammation, many of the therapies reviewed can effectively decrease orbital inflammation and improve symptoms, particularly in the short term. Once inconstant or constant diplopia develops, teprotumumab or ORT with steroids can be considered as studies suggest they may be effective at improving diplopia. The authors currently consider teprotumumab a first-line therapy for active moderate-to-severe TED with inconstant or constant diplopia. IVMP and MMF or ORT are alternative treatment options, depending on patient history, insurance approval, and risk factors. Studies specifically evaluating severe, constant, or long-standing diplopia are lacking. It is unknown if any of the current therapies available will result in meaningful reductions in rates of strabismus surgery. Additionally, studies to-date have mostly used the GDS as a measure of response; however, RCTs using more accurate measurements of motility, such as PDs of deviation, are needed.

When diplopia is stable or long-standing, strabismus surgery is still the therapeutic mainstay. While early studies support the use of teprotumumab for chronic TED-associated diplopia, higher quality evidence is needed to support this recommendation. Teprotumumab can still be considered as a treatment option for patients with diplopia that are poor surgical

candidates, resistant to other therapies, or understand the limited data and long-term evidence supporting teprotumumab's use in the stable phase. It is possible that combination therapy may prove useful in patients with large-angle deviations where reoperation rates with surgery alone are high.

Treatments for Dysthyroid Optic Neuropathy

The standard of care in DON has traditionally involved (1) pulsed high-dose IV corticosteroids as the first-line treatment; (2) ORT with or without steroids; or (3) surgical decompression in refractory patients or those at increased risk of vision loss. As new targeted treatments emerge, it is currently unknown if the treatment paradigm for DON may shift [47•]. Table 2 details all recent studies evaluating DON treatments.

Pulsed IV Corticosteroids

EUGOGO guidelines recommend high-dose IVMP (0.5–1.0 g) for three consecutive days or on every second day, titrated based on improvements in visual function measured with BCVA and VF testing [44••, 84]. Urgent orbital decompression is recommended for no improvement or worsening visual function after 1 week or limited improvement after 2 weeks of treatment. These recommendations are mostly supported by a small RCT that compared orbital decompression and high-dose IVMP therapy consisting of 1g IVMP daily for 3 days, repeated after 1 week and followed by an oral steroid taper [84]. The study found that 83% of patients treated with decompression failed treatment and required additional IVMP or ORT. Additionally, 56% of patients treated with IVMP failed and required surgical decompression or ORT. Finally, the study determined that treatment outcomes were not significantly different between patients in the IVMP and decompression groups, which led the authors to conclude that IVMP should be the first-line treatment for DON [84]. Limitations to the RCT include the small sample size and the invasive and outdated surgical approach studied. Of note, previous studies have reported that IVMP is less effective in patients with ON swelling, CAS over 5, and severe visual field defects (≤ 6.31 dB) [84].

Orbital Radiation Therapy

There are several retrospective studies that have found differing efficacy in DON response to ORT, which is likely due to patient selection [85–89], as ORT is less likely to be effective in DON patients with long-standing disease [90, 91, 92•, 93]. Another important factor is the synergistic effect of corticosteroids. A retrospective study of 104 DON patients found that 94% of patients that received concurrent ORT and oral prednisone (1 mg/kg/day for 2 weeks with taper over several weeks) did not require orbital decompression during the active phase of disease [92•]. After 40 weeks of follow-up, 37% of patients required decompression. This study and others support ORT with oral steroids as an effective option for DON [94–96]; however, EUGOGO provides no guidelines on the use of ORT in DON [44••].

Surgical Decompression

Orbital decompression is reserved for cases of DON that are refractory to medical therapy [97, 98] or for severe, rapidly worsening DON. A retrospective study comparing patients who received IVMP monotherapy versus both IVMP and surgical decompression

demonstrated that patients with mild DON with better initial BCVA responded well to corticosteroids alone, whereas patients with worse BCVA required both corticosteroids and surgical decompression [99].

Mycophenolate Mofetil

A retrospective study of moderate-to-severe TED patients detailed the response to treatment of 10 DON patients treated with MMF (median treatment duration of 76 weeks, follow-up of 4 years) either during or shortly after a course of IVMP (Table 2). The study found that 90% (9/10), 100% (7/7), and 100% (4/4) of patients showed clinical efficacy (defined as an absence of relapse: no decline in BCVA, no need for further steroids, no increase in CAS of ≥ 2) at 24 weeks, 52 weeks, and 78, respectively [54]. The authors suggest that the combination of MMF and IVMP may reverse DON with long-term efficacy. However, a comparison study of MMF and IV steroids versus IV steroids alone is needed to determine if the addition of MMF is necessary in DON treatment. Furthermore, this study had a small sample size, high attrition rate, and included different concurrent treatments. Therefore, further studies are needed to determine the efficacy of MMF in DON. Of note, the recent EUGOGO guidelines do not provide guidance on the use of MMF in DON [44••].

Biologics—Several biologics have been investigated for the treatment of DON [47•, 58]; however, studies have been limited to case reports or case series. There is currently no consensus regarding use of these treatment options in DON.

Rituximab—EUGOGO guidelines recommend avoiding RTX in cases of DON due to the potential for a post-treatment cytokine syndrome that could cause worsened periorbital edema and decreased vision [44••, 62]. Several patients in recent studies assessing the response to RTX in moderate-to-severe TED developed DON during treatment [62, 100–102].

Tocilizumab—Recent studies report mixed efficacy of TCZ for the treatment of DON. Pascual-Camps et al. demonstrated successful reversal of DON in a single patient with VF defects and improved BCVA from 20/200 to 20/40 after primary treatment with TCZ, with 1-year follow-up [103]. Another case report demonstrated improvement in VA and color vision after TCZ therapy in a patient with recalcitrant DON; however, this patient experienced recurrence of DON at 10 months requiring retreatment [104•]. A small (n = 7) observational study of TCZ monotherapy or combination therapy with methotrexate, reported no significant improvement in BCVA over baseline [105]. Lastly, a series of 3 patients with DON treated with IVMP and concurrent TCZ showed rapid improvement in CAS, proptosis, and VA, though one case relapsed 2 months following treatment [106]. Overall, these studies are small, included different concurrent treatments, and lack controls. Therefore, further studies are needed to determine the efficacy of TCZ for DON.

Teprotumumab—The phase 2 and 3 clinical trials on teprotumumab for TED therapy excluded patients with prior ORT, decompression for TED, optic neuropathy in the last 6 months, corticosteroid treatment with a cumulative dose of> 1 g, and prior treatment with RTX or TCZ [34••, 35]. Since teprotumumab's approval, several reports have demonstrated

improvement of DON in refractory TED or for poor surgical candidates treated with teprotumumab as first-line therapy [107, 108•, 109••, 110–112]. In the first report by Sears et al., a patient with unilateral DON, refractory to ORT and a poor surgical and steroid candidate, experienced improvement in BCVA, color vision, and visual fields after 2 infusions of teprotumumab [108•]. In the literature, a total of 19 cases of refractory DON (all patients failed therapy with IVMP, ORT, and/or surgical decompression) have been managed with teprotumumab (Table 2) [81•, 107, 108•, 109••, 110–112]. Of these cases, most patients saw an early improvement in visual function, CAS, or proptosis within 2 infusions. Non-responders all had long-standing DON with severe vision loss. The authors proposed that the lack of improvement was due to irreversible optic atrophy [81•, 109••]. These studies highlight the potential utility of teprotumumab in DON patients, particularly when refractory to other therapies and prior to irreversible ON compromise.

Choice of DON Therapy Summary

The current gold standard for DON therapy is high-dose IVMP. Urgent orbital decompression is recommended for no improvement or worsening visual function after 1 week or limited improvement after 2 weeks of medical treatment. The authors believe teprotumumab can also be considered in cases of mild DON if immediate therapy and close follow-up is possible. ORT with oral steroids has demonstrated good efficacy at avoiding decompression and can also be considered. When DON is long-standing with ON atrophy, it is unlikely that any treatment will significantly improve BCVA. Additional studies on TCZ and MMF are needed for the authors to adopt these therapies; however, they can be considered under certain circumstances or in refractory disease.

Conclusion

TED is a complex condition where early diagnosis and co-management with an ophthalmologist are key to prevent and potentially reverse functional ocular sequelae, and novel biologics have increased therapeutic options. Teprotumumab or IV steroids with or without ORT or MMF should be considered for patients with active moderate-to-severe TED. When diplopia due to extraocular myopathy is a significant manifestation, only teprotumumab and ORT have shown significant improvements in diplopia, with teprotumumab demonstrating long-term durability. When diplopia is stable, surgery is the mainstay of therapy, though early reports suggest that teprotumumab may also be effective. Similarly, the treatment options for DON are expanding from high-dose IVMP, ORT with steroids, and surgery to include teprotumumab. More RCTs, comparison studies, and long-term data are needed to better understand which therapeutic option is most effective for the different phenotypes of TED. Nevertheless, this is an exciting time for the treatment of TED as several emerging targeted therapies are in the pipeline that may continue to change the paradigm of TED management.

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Not applicable.

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Table 1

Recent literature summary of thyroid eye disease-related diplopia treatments

Author	Year	Design	Intervention	Patient type	Sample size	Follow-up (weeks)	Results
Diniz	2021	Cross-sectional cohort	Teprotumumab (10 mg/kg IV × 1 dose, 20 mg/kg × 7 doses every 3 weeks)	TED (all activity and stages)	21	~30	No significant differences for ductions between different grades and stages of disease, greater improvement in strabismus for active stage of disease
Ugradar	2021	Retrospective study	Teprotumumab (10 mg/kg IV × 1 dose, 20 mg/kg × 7 doses every 3 weeks)	Chronic stable TED 2(> years)	31	~21	67% had clinically significant diplopia response, 47% had complete diplopia resolution following treatment
Bagheri	2020	Prospective case series	Periorbital TA 20 mg + DEX 4 mg × 3–4 injections every 4 weeks	Active TED refractory to systemic steroids	17	24–28	Improved CAS score, improvement in supraduction
Wang	2020	Retrospective study	Periorbital TA 40 mg + DEX 2.5 mg every 4 weeks[a]	Steroid-naïve, active TED	386	24	Eye motility improvement in 30.21%
Gorman	2020	RCT	ORT (20 Gy × 10 doses over 2 weeks)[b]	Active moderate-to-severe TED	42	24 and 48	No significant differences between orbits at 24 and 48 weeks
Lee	2020	Retrospective study	Analysis of safety data of 2 prior RCTs for mycophenolate	Active moderate-to-severe TED	170	12, 24, 36	Low rate of mild-to-moderate adverse events with promising efficacy
Vannucchi	2020	Prospective case series	RTX (100 mg IV × 1 dose)	Active moderate-to-severe TED	17	24	No significant improvement in diplopia
Deltour	2020	Retrospective study	RTX (1000 mg × 2 doses every 2 weeks)	Active moderate-to-severe TED	40	24	No significant improvement in diplopia or oculomotor motility
Douglas	2020	RCT	Teprotumumab (10 mg/kg IV × 1 dose, 20 mg/kg × 7 doses every 3 weeks)	Active moderate-to-severe TED	83	24	Diplopia response in 68% of treatment group compared to 29% in placebo group
Rajendram	2018	RCT	24 weeks oral prednisolone+ORT (20 Gy × 10–12 doses over 2–3 weeks)+azathioprine (100–200 mg PO every day for 48 wks)[c]	Active moderate-to-severe TED	126	12 and 48	No benefit of radiotherapy on top of oral prednisolone
Kahaly	2018	RCT	IVMP (500 mg × 6 doses every week, 250 mg × 6 doses every week)±MMF	Active moderate-to-severe TED	164	12, 24, 36	Improved composite ophthalmic score at 24 and 36 weeks, but no differences in diplopia-specific improvement
Perez-Moreiras	2018	RCT	TCZ (8 mg/kg IV × 4 doses every 4 weeks)	Active moderate-to-severe TED	32	16, 40	No significant benefit observed for diplopia

TED thyroid eye disease, *TA* triamcinolone acetate, *DEX* dexamethasone, *IVMP* intravenous methylprednisolone, *RTX* rituximab, *MMF* mycophenolate mofetil, *TCZ* tocilizumab, *ORT* orbital radiotherapy, *RCT* randomized control trial

[a] treated until symptoms stopped improving

[b] initially one orbit received radiation and sham radiation to the other with reversal of treatment 6 months later

[c] after 24 weeks treatment was randomized to radiotherapy vs sham and azathioprine vs placebo in 2 × 2 design

Table 2

Recent literature summary of dysthyroid optic neuropathy treatments

Author	Year	Design	Intervention	Patient type	Sample size	Follow-up (weeks)	Results
Précausta	2017	Case series	RTX (1000 mg IV × 2 doses every 2 weeks)	DON	6	79.3	Significant improvement in CAS, BCVA, and VF, but decompression was needed
Pascual-Camps	2018	Case report	TCZ (8 mg/kg IV × *N* doses every 4 weeks)	DON	1	52	Improved VF and BCVA after 2 infusions that remained stable at 1-year follow-up
Gold	2018	Retrospective study	ORT (20 Gy × 10 doses over 2 weeks) + prednisone (1 mg/kg × 14 doses everyday) or orbital decompression	DON	104	162.4	Most (93%) ORT patients responsive to steroids did not require decompression in the acute phase of disease and only 36.7% of ORT patients had elective surgery
Insull	2019	Case series	RTX (100 mg IV × 1 doses) + as needed IVMP (mean cumulative dose 2.3 g)	TED and DON	12	25.2	Significant improvement in CAS and VISA score with one patient requiring decompression for DON 2 mo after RTX treatment
Ito	2019	Retrospective study	IVMP (10 mg/kg × 3 doses everyday × 2–3 cycles) + ORT (20 Gy × 10 doses over 2 weeks)	TED and DON	77	25	DON, high TSAb, and lower standard deviation of T2 signal intensity were significant risk factors for disease recurrence after concurrent ORT and steroid therapy
Nicosia	2019	Retrospective study	IVMP (500 mg × 2 doses every week) + ORT (20 Gy × 10 doses over 2 weeks)	TED and DON	40	56	Improved BCVA in 27.5% and 21% of patients required decompression for recurrent disease at last follow-up
Yong	2019	Retrospective study	IVMP (500–1000 mgx3 doses everyday × 1–5 cycles) ±MTX (12.5–15 mg POx24 doses every week)	DON	72	72	Significantly better BCVA and VISA at 3 months in patients on IVMP + MTX
Sanchez-Bilbao	2020	Retrospective study	TCZ (8 mg/kg IV every 4 weeks or 162 mg s.c. every week)	TED and DON	48	64.4	Significantly improved BCVA and CAS
Kaplan	2020	Case report	TCZ (8 mg/kg IV × 11 doses every 4 weeks)	DON	1		CAS improvement in TED refractory to IVMP and decompression
Maldiney	2020	Case series	TCZ (8 mg/kg IV × 6–8 doses every 4 weeks)	DON	3		Improvement in BCVA and reduced EOM swelling on MRI
Zhang	2020	Case series	RTX (500 mg IV xl dose)	DON	2	104	Developed DON at 2-month follow-up; both needed surgery
Choi	2020	Retrospective study	ORT (24 Gy in 12 fractions)	TED and DON	62	24	Resolution of DON in 76.9% of ORT treated patients
Garip-Kuebler	2020	Retrospective study	IVMP (500 mg × 8 doses every 3–4 days, 250 mg × 4 doses every 3–4 days)	DON	25		Better initial BCVA (0.3 logMAR) was predictive of better response to IVMP
Sears	2020	Case series	Teprotumumab (10 mg/kg IV × 1 dose, 20 mg/kg × 7 doses every 3 weeks)	DON	10	15	Improvement in BCVA, APD, or both after two infusions in 70% of patients
Slentz	2021	Case report	Teprotumumab (10 mg/kg IV × 1 dose, 20 mg/kg × 7 doses every 3 weeks)	DON	1	25	Improvement of CAS, VF, and extraocular muscle size

Author	Year	Design	Intervention	Patient type	Sample size	Follow-up (weeks)	Results
Chiou	2021	Case series	Teprotumumab (10 mg/kg IV × 1 dose, 20 mg/kg × 7 doses every 3 weeks)	DON	2	6	Improvement in VF in mild DON previously treated with IVMP
Diniz	2021	Case series	Teprotumumab (10 mg/kg IV × 1 dose, 20 mg/kg × 7 doses every 3 weeks)	TED and DON	21	30	Improved BCVA, VF, and color vision
Lopez	2021	Case report	Teprotumumab (10 mg/kg IV × 1 dose, 20 mg/kg × 7 doses every 3 weeks) + oral prednisone (80 mg daily)	DON	1	6	Improved BCVA, APD color, and VF in TED previously treated with oral steroids
Hwang	2021	Case report	Teprotumumab (10 mg/kg IV × 1 dose, 20 mg/kg x7 doses every 3 weeks)	DON	1	24	Improved BCVA, APD VF, and color after two infusions in TED previously treated with steroids
Quah Qin	2021	Retrospective study	IVMP + MMF	TED and DON	20	78	Significant improvement in CAS, diplopia, and BCVA of 90% at 24 weeks that was stable to 78 weeks
Ozzello	2021	Case report	Teprotumumab (10 mg/kg IV × 1 dose, 20 mg/kg × 7 doses every 3 weeks)	DON	1	6	Improved proptosis and extraocular muscle swelling in chronic TED

DON dysthyroid optic neuropathy, *TED* thyroid eye disease, *RTX* rituximab, *TCZ* tocilizumab, *ORT* orbital radiotherapy, *MMF* mycophenolate mofetil, *IVMP* intravenous methylprednisolone, *MTX* methotrexate, *CAS* clinical activity score, *BCVA* best corrected visual acuity, *VF* visual field, *EOM* extraocular muscle, *TSAb* thyroid stimulating antibody, *VISA* vision, inflammation, strabismus and appearance score, *APD* afferent pupillary defect