

# Updates on the understanding and management of thyroid eye disease

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**Abstract:** Thyroid eye disease (TED) is a complex disease associated with myriad clinical presentations, including facial disfigurement, vision loss, and decreased quality of life. Traditionally, steroid therapy and/or radiation therapy were commonly used in the treatment of active TED. While these therapies can help reduce inflammation, they often do not have a sustainable, significant long-term effect on disease outcomes, including proptosis and diplopia. Recent advances in our understanding of the pathophysiology of TED have shifted the focus of treatment toward targeted biologic therapies. Biologics have the advantage of precise immune modulation, which can have better safety profiles and greater efficacy compared to traditional approaches. For instance, the insulin-like growth factor-1 receptor (IGF-1R) has been found to be upregulated in TED patients and to colocalize with the thyroid-stimulating hormone receptor (TSHR), forming a signaling complex. Teprotumumab is an antibody targeted against IGF-1R. By inhibiting the IGF-1R/TSHR signaling pathway, teprotumumab may reduce the production of proinflammatory cytokines, hyaluronan secretion, and orbital fibroblast activation in patients with TED. Due to promising phase II and III clinical trial results, teprotumumab has become the first biologic US Food and Drug Administration (FDA)-approved for the treatment of TED. In addition, there are currently ongoing studies looking at the use of antibodies targeting the neonatal Fc receptor (FcRn) in various autoimmune diseases, including TED. FcRn functions to transport immunoglobulin G (IgG) and prevent their lysosomal degradation. By blocking the recycling of IgG, this approach may dampen the body's immune response, in particular the pathogenic IgG implicated in some autoimmune diseases. Advances in our understanding of the pathophysiology of TED, therefore, are leading to more targeted therapeutic options, and we are entering an exciting new phase in the management of TED. This review will cover recent insights into the understanding of TED pathophysiology and novel treatment options as well as ongoing studies of new potential treatment options for TED.

**Keywords:** thyroid eye disease, thyroid-associated ophthalmopathy, Graves ophthalmopathy, biologics, targeted therapy

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## Introduction

Thyroid eye disease (TED) is a complex autoimmune disease which can lead to significant ocular symptoms, facial disfigurement, vision loss, and decreased quality of life. It affects 16 per 100,000 females and 2.9 per 100,000 males.<sup>1</sup> Female gender, age, smoking, and radioactive iodine therapy (RAI) have all been associated with increased risk for TED.<sup>2</sup>

Clinical assessment of TED is typically characterized by grading disease activity and severity. The disease typically begins with an acute inflammatory or active phase, lasting on average 18 months, although this period may vary significantly. Traditionally, steroid therapy and/or radiation therapy was commonly used to decrease inflammation in the active disease phase. The natural course of the disease is for the inflammation to

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subside over time, at which point the patient enters a more chronic or stable phase characterized by fibrosis, although orbital congestion and other factors contribute to cross over between these “phases.” Once the disease is thought to be relatively quiescent and stable, treatment often includes surgical correction of the residual proptosis, strabismus, and eyelid deformities. 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, which is graded as mild, moderate to severe, or sight threatening.

Recently, advances in the understanding of the pathogenesis of TED have helped elucidate the mechanisms of disease pathways and allowed for the identification of new molecular targets for therapy. In the last few years, there has been a paradigm shift in the management of TED with targeted therapy, including biologic agents which target key receptors implicated in the downstream pathogenesis and immune dysregulation.

### Pathophysiology

TED is characterized by inflammation and remodeling of the orbital soft tissues and periorbital areas. A long-held view of TED focused on orbital fibroblasts and their particularly robust responses to cytokines.<sup>3</sup> More recently, Douglas and colleagues<sup>4</sup> identified a subset of CD34+ fibrocytes that infiltrate the orbit and express high levels of thyroid-stimulating hormone receptor (TSHR). These cells can differentiate into fat cells or myofibroblasts, which may account for the phenotypic diversity of TED.

Considerable research has also gone into the role of TSHR in TED. While its role in hyperthyroidism associated with Graves’ disease is well established, the link between TSHR and orbital tissue remodeling is less clear. While higher cell surface levels of TSHR have been found in orbital tissues from cases of active TED,<sup>5</sup> a direct causal relationship between TSHR and disease activity has been difficult to establish. This has led to the exploration of other potential molecular mediators of the underlying disease process.

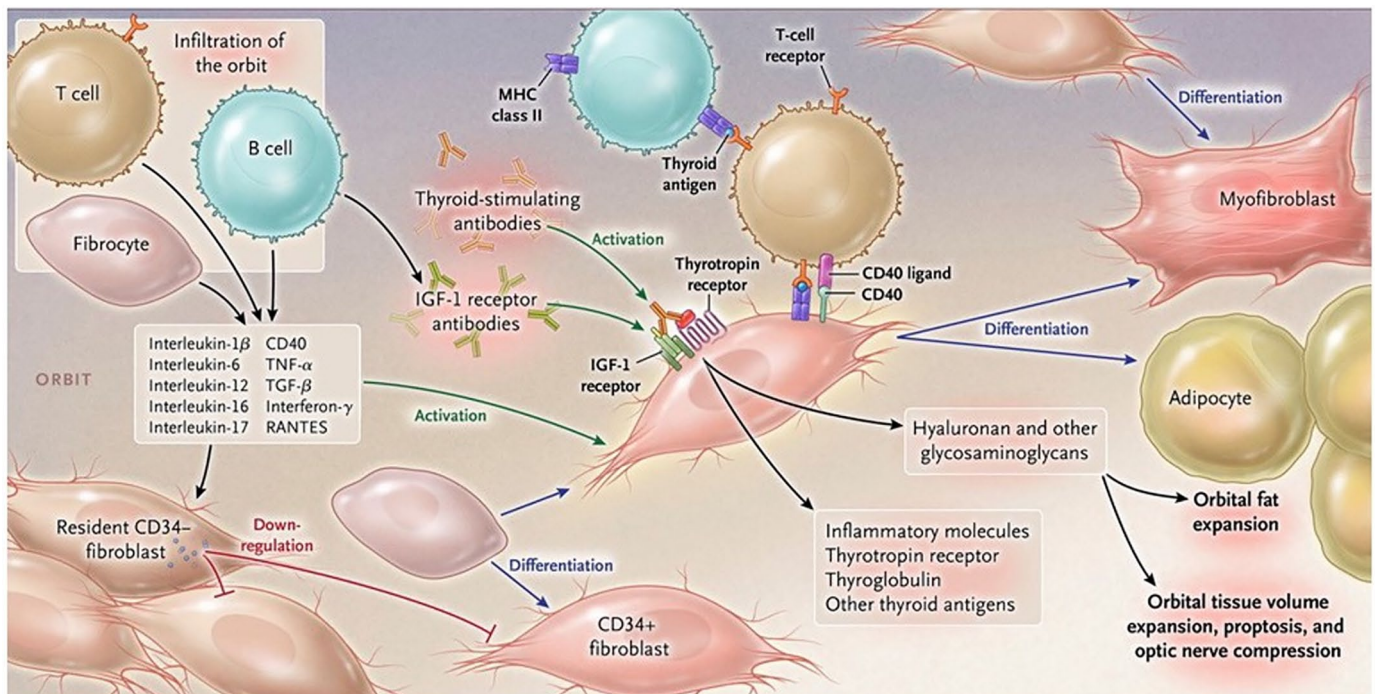
One of the candidate molecules is insulin-like growth factor-1 (IGF-1), a widely expressed cell surface protein found in most tissues in the human body. IGF-1 pathways are implicated in many autoimmune diseases, including TED.<sup>6,7</sup> The IGF-1 pathway acts synergistically with TSH

to enhance the growth of thyroid cells.<sup>8,9</sup> Further studies have shown that anti IGF-1 receptor (IGF-1R) antibodies are present in patients with Graves’ disease but absent in healthy patients.<sup>10</sup> The IGF-1R and TSHR colocalize to the perinuclear and cytoplasmic compartments in fibroblasts and thyrocytes.<sup>5</sup> Autoantibody activation of the TSHR/IGF-1R complex leads to downstream expression of genes and cytokines implicated in orbital tissue reactivity and remodeling (see Figure 1).<sup>5,10</sup> Cytokines recruit inflammatory cells into the orbit and stimulate fibroblasts to secrete glycosaminoglycans, including hyaluronan, which increases adipose and muscle expansion and tissue inflammation.<sup>11</sup> The activated orbital fibroblasts can also proliferate and differentiate into adipocytes and myofibroblasts, which further increase orbital tissue volume.<sup>11</sup>

Furthermore, B and T lymphocytes have been implicated in TED pathophysiology. Memory B cells provide enhanced antibody production when stimulated and present antigens to T cells.<sup>12</sup> Stimulated T cells secrete various cytokines including interleukin-4 (IL-4) and interferon- $\gamma$ .<sup>12</sup> T helper cells (Th cells) cytokine profiles have been detected in TED orbital fat and extraocular muscles, with Th1 cells dominating in the active phase and Th2 cells in the late phase.<sup>12-14</sup> Continued advances in our understanding of TED help to identify potential targets for therapeutic development.

### Clinical manifestations

The diagnosis of TED is made based on the characteristic clinical picture in the setting of systemic thyroid dysfunction. However, up to 20% of patients can present with eye symptoms prior to thyroid dysfunction, 40% concurrently, and 40% after the development of systemic findings.<sup>15,16</sup> Among patients with TED, 90% develop hyperthyroidism, 4–5% develop hypothyroidism, and 5–6% may remain euthyroid.<sup>17</sup> Eyelid retraction is the most common clinical sign, present in up to 90% of patients.<sup>18</sup> Other signs that are suggestive of TED include proptosis, lid lag of the upper eyelid on down gaze (von Graefe sign), eyelid edema, eyelid erythema, increased resistance to retropulsion, bulbar conjunctival injection, chemosis, and restrictive strabismus. In some cases, the clinical presentation is mild with minimal eyelid retraction, dry eyes, or chronic conjunctival injection and irritation. More severe signs include exposure keratopathy and compressive optic neuropathy (CON).



**Figure 1.** Pathophysiology of thyroid eye disease. In TED, B-lymphocytes, T-lymphocytes, and CD34+ fibrocytes infiltrate the orbit. CD34+ fibroblasts, originating from bone marrow-derived fibrocytes, further differentiate into myofibroblasts or adipocytes. Both CD34+ and residential CD34- fibroblasts are present within the orbit, and depending upon microenvironment-mediated signaling, can produce cytokines, including IL-1 $\beta$ , IL-6, IL-8, IL-16, TNF- $\alpha$ , RANTES, and CD40 ligand, which activate orbital fibroblasts. CD34+ fibroblasts express low levels of TSH-R, thyroglobulin, and additional thyroid antigens. TSIs activate the TSH-R/IGF-1R complex inducing inflammatory molecule expression and glycosaminoglycan synthesis. Furthermore, immunoglobulins directed against IGF-1R induce orbital fibroblast signaling, thereby increasing cytokine and hyaluronan production, and subsequent orbital tissue expansion, leading to proptosis and compression of the optic nerve. Adipogenesis also leads to orbital fat expansion.<sup>11</sup> Copyright © (2016) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Abbreviations: IGF-1R, insulin-like growth factor-1 receptor; IL, interleukin; MHC, major histocompatibility complex; RANTES, Regulated on Activation, Normal T Cell Expression and Secreted); TED, thyroid eye disease; TGF- $\beta$ , transforming growth factor beta; TNF- $\alpha$ , tumor necrosis factor alpha; TSH-R, thyroid-stimulating hormone receptor; TSI, thyroid-stimulating immunoglobulins.

Two subtypes of TED have been described, although it is clear that many patients have characteristics of both subtypes.<sup>19</sup> Type 1 disease comprises approximately two-thirds of cases, with an indolent presentation evolving slowly over months. This is characterized by predominant adipose tissue proliferation resulting in proptosis and focal levator muscle inflammation leading to retraction. Type I disease tends to affect younger patients under the age of 40 years, females, and nonsmokers. Type 2 disease develops more rapidly, is characterized by extraocular muscle enlargement, and tends to affect older patients greater than 60 years, males, and smokers. These patients tend to develop more severe inflammatory features, including congestion and edema of the conjunctiva and eyelids, restrictive strabismus with diplopia, and CON.

Laboratory testing for TED is aimed at screening for dysthyroid states. Testing usually includes

TSH, free thyroxine (T<sub>4</sub>), total or free triiodothyronine (T<sub>3</sub>), anti-TSHR antibody, and/or antithyroid peroxidase antibody levels. Two assays are available to measure TSHR antibody activity: the TSH-binding inhibition immunoglobulin (TBII) and the thyroid-stimulating immunoglobulin (TSI). The TBII assays detect immunoglobulins that competitively inhibit the binding of TSH to recombinant TSHR, while TSI assays are based on measurement of cyclic adenosine monophosphate (cAMP) production stimulated by TSHR activation. Elevated TSI levels have been found to be better associated with clinically active TED than TBII levels and may also be associated with the development of CON.<sup>20,21</sup>

Orbital imaging can be used to aid in the diagnosis of TED, particularly when the clinical picture or laboratory values are not characteristic. Orbital

**Table 1.** Disease severity classification adapted from the European Group on Graves' Orbitopathy (EUGOGO).<sup>53</sup>

Stage	Symptoms and Findings
Mild	Mild eyelid retraction (<2 mm), mild soft tissue involvement, mild exophthalmos (<3 mm above normal), transient or no diplopia, corneal exposure responsive to lubricants
Moderate to severe	Eyelid retraction (≥2 mm), moderate or severe soft tissue involvement, exophthalmos (≥3 mm above normal), inconstant or constant diplopia, impact on daily functions of life
Sight-threatening	Dysthyroid optic neuropathy, corneal breakdown

computed tomography (CT) scan or magnetic resonance imaging (MRI) can assess for Type 1 *versus* Type 2 disease, presence of CON, degree of proptosis, and rule out other potential diagnoses in equivocal cases. Extraocular muscle involvement usually adheres to a consistent pattern involving the muscle belly but sparing the tendon, with the inferior rectus muscle most commonly involved, followed by the medial rectus, superior rectus, lateral rectus, and oblique muscles. However, any pattern of extraocular muscle involvement may be possible.

TED is graded by activity and severity. Activity refers to the soft tissue changes and inflammatory symptoms. It is often assessed by the clinical activity score (CAS) or vision, inflammation, strabismus, and appearance (VISA) classification. Disease severity refers to the extent of involvement and is commonly classified as mild, moderate, or severe (see Table 1).

It is also important to note that systemic treatments for Grave's disease can have an impact on TED. Management of systemic disease usually includes antithyroid drugs (ATD), RAI, or thyroidectomy. RAI has been associated with the development or worsening of orbitopathy in 15–20% of patients.<sup>22</sup> Furthermore, it is difficult to achieve a precise RAI dose to balance the control of hyperthyroidism with avoidance of hypothyroidism. In one study of high dose treatment for Graves' disease, RAI resulted in permanent hypothyroidism in up to 80% of patients.<sup>23</sup> Total thyroidectomy also raises the issue of post-operative hypothyroidism and need for lifelong thyroid hormone replacement therapy. In addition, surgery carries potential complications such as hypoparathyroidism and vocal cord paralysis. However, thyroidectomy in patients with thyrotoxic goiters

may be associated with an improvement of ophthalmopathy.<sup>24</sup> A prospective randomized controlled trial (RCT) is currently analyzing the efficacy of thyroidectomy *versus* ATD in TED patients who have suffered their first relapse of disease or who have shown no improvement after 6 months of ATD therapy.<sup>25</sup>

## Management for active TED

### *Nonspecific therapies*

Treatment for TED depends on the patient's disease activity and severity and often requires a multidisciplinary approach. For mild TED, treatment includes ocular surface optimization with lubricants, minimizing risk factors that can exacerbate disease such as smoking, and controlling thyroid hormone levels. Selenium, an antioxidant, has also been found to be helpful in patients with mild disease. In cell culture, selenium has been found to lower the levels of hyaluronan, suppress the production of inflammatory cytokines such as IL-1 $\alpha$  and IL-8, and prevent cell death by necrosis and apoptosis in TED fibroblasts.<sup>26–28</sup> In an RCT, selenium given at 100 mcg twice a day for 6 months was found to be associated with improved quality of life, reduced soft tissue inflammation, and slowed progression in patients with TED.<sup>29</sup> However, the study drew patients from selenium deficient areas. It is unclear if the same beneficial effects would be found in areas without deficient selenium, such as the United States.

*Corticosteroids.* Traditionally, systemic corticosteroids were employed in the treatment of active, moderate to severe TED.<sup>30</sup> Intravenous (IV) corticosteroids have been found to be more effective and better tolerated than oral corticosteroids.<sup>31,32</sup>

Kahaly and colleagues<sup>31</sup> found that patients treated with IV methylprednisolone 500 mg weekly for six doses followed by 250 mg weekly for six doses showed a response rate of 77% *versus* 51% of those treated with oral prednisone. Bartalena and colleagues investigated three different cumulative doses of IV steroids, and found that ophthalmic improvement was more common with the higher dose regimens (52% in the 7.47 g group, 35% in the 4.98 g group, and 28% in the 2.25 g group). However, differences among the three groups were no longer seen at 24 weeks, and major adverse events were slightly more common in the highest dose group.<sup>33</sup> Hepatotoxicity is a potentially fatal complication of IV corticosteroid therapy in patients receiving a cumulative dose greater than 8 g of methylprednisolone.<sup>34</sup> Contraindications to steroid therapy include recent hepatitis, liver dysfunction, cardiovascular morbidity, severe hypertension, poorly controlled diabetes, and severe steroid-responsive glaucoma.<sup>30</sup>

In addition, corticosteroid prophylaxis (either oral prednisone at cumulative dose of 1.54 g or IV methylprednisolone at 1.5 g) is effective at reducing the risk of RAI-induced TED.<sup>35–37</sup> A lower dose of oral prednisone (0.2 mg/kg body weight) has also been found to be equally effective.<sup>37</sup>

In patients with either poor response to systemic steroids or with complications related to systemic steroid use, intraorbital injections of triamcinolone acetonide 20 mg and dexamethasone 4 mg have been utilized in active TED with promising results.<sup>38,39</sup> Bagheri and colleagues<sup>39</sup> showed an improvement of CAS from 5.2 to 1.6 after four monthly injections, proptosis reduction of 1.2 mm on average, and 100% and 68.2% improvement in upper and lower lid, respectively. Of the patients, 8.8% in the study developed intraocular pressure issues.<sup>39</sup> Subconjunctival injections of triamcinolone acetonide 20 mg have also been reported in the treatment of upper eyelid retraction with reported 68–100% success rates in improving eyelid edema and retraction, especially in the acute, congestive phase.<sup>40–42</sup>

**Orbital radiation.** Orbital radiotherapy (ORT) has also been used as an adjunctive or, less commonly, as primary therapy for active TED for decades due to its effectiveness in reducing inflammation and the radio-sensitivity of orbital lymphocytes.<sup>43,44</sup> Proper patient selection is critical, as

patients with early and progressing, active, moderate-to-severe TED have the highest response rates.<sup>45</sup> ORT is typically dosed at 20 Gy administered over 10 days. Two RCTs comparing ORT to sham irradiation in moderately severe TED showed a response rate of 50–60%, as defined by improvement in a composite ophthalmic score.<sup>46,47</sup> The main outcome improved was the diplopia score, with no significant effect on proptosis, CAS, or lid aperture.<sup>46,47</sup> The long-term benefit from ORT is unclear, as a recent prospective RCT found no clinically significant improvement in volume of extraocular muscles and fat, proptosis, or retraction with ORT at 6 and 12 months in patients with mild-to-moderate TED.<sup>48</sup> A review of 5 observational studies and 9 RCTs concluded with level 1 evidence that proptosis, eyelid retraction, and soft tissue changes do not improve with ORT.<sup>49</sup>

Treatment with a combination of radiotherapy and corticosteroids can be more effective than either treatment alone.<sup>32,50</sup> A prospective randomized study showed that ORT with oral prednisone (100 mg/day for 7 days, followed by a gradual taper over 5–6 months) was more effective than ORT alone in active TED, as assessed by a drop in the ophthalmopathy index.<sup>50</sup> When comparing ORT with oral prednisone (100 mg/day followed by 5 month taper) and ORT with IV methylprednisolone (15 mg/kg for four cycles followed by 7.5 mg/kg for four cycles) in active, moderate-to-severe TED, the ORT with IV steroids group resulted in a greater decrease in CAS (2.8 *versus* 2), fewer surgical procedures at follow-up (7% *versus* 22%), and fewer side effects (56.1% *versus* 85.4%).<sup>51</sup> Both groups were equally effective in improving diplopia by about 50%, reducing proptosis by 1.3–1.6 mm and improving lid width by 1.5–2.1 mm.<sup>51</sup> Furthermore, delivery of ORT concurrently with steroids in moderate-to-severe TED has also been found to improve clinical scores, decrease cumulative dose of steroids needed, and reduce overall length of therapy when compared to sequential treatment.<sup>52</sup> Contraindications to ORT include diabetic retinopathy, severe hypertension, and age less than 35 years.<sup>44,53</sup> Potential side effects of radiation include cataract formation and radiation retinopathy.

**Mycophenolate mofetil.** Mycophenolate mofetil (MMF) acts to inhibit the proliferation of T and B lymphocytes and suppress antibody production. In a RCT comparing MMF (500 mg twice a day for 24 weeks) with corticosteroids (IV methylprednisolone 0.5 g a day, 3 days a week, followed

by an oral prednisone taper) in active, moderate-to-severe TED, the MMF group showed a better response in CAS, diplopia, and proptosis at 24 weeks as well as a lower rate of disease reactivation on follow up.<sup>54</sup> In addition, the MINGO study (a multicenter, randomized, observer-masked trial) found that the addition of MMF 360 mg twice a day for 24 weeks to IV methylprednisolone (500 mg/week for 6 weeks followed by 250 mg/week for 6 weeks) is superior to steroids alone in improvement of a composite ophthalmic index including eyelid swelling, CAS, proptosis, lid width, diplopia, and eye muscle motility in patients with active, moderate-to-severe TED.<sup>55</sup> Significantly fewer patients in the combination group relapsed at 36 weeks follow up.<sup>55</sup> There was no difference in the rate of adverse events between the combination and monotherapy groups.<sup>55</sup>

**Cyclosporine.** Cyclosporine is a lipophilic polypeptide that inhibits calcineurin and prevents the secretion of interleukin-2 by CD4 + T-lymphocytes. As a single agent, cyclosporine's effect on severe TED is debatable.<sup>56</sup> However, a prospective, RCT has found the combination of cyclosporine (at 7.5 mg/kg/day) and oral prednisone (60 mg for 2 weeks, 40 mg for 2 weeks, 30 mg for 2 weeks, then 20 mg for 2 weeks) to be effective in improving proptosis and visual acuity (VA) in patients who do not respond to corticosteroids alone and those with TED-associated CON.<sup>56</sup> In a case series of 14 patients with severe TED and CON, all patients on cyclosporine (2 mg/kg twice daily) and corticosteroids (IV methylprednisolone 10 mg/kg every 48 h  $\times$  3, followed by oral prednisone taper 30, 25, 20, 17.5, 15 mg) recovered their pre-morbid visual acuities and visual fields.<sup>57</sup> Common side effects of cyclosporine include hypertension and nephrotoxicity.

**Azathioprine.** Azathioprine is a cytostatic agent that inhibits DNA synthesis, thus preventing cell proliferation. It has been used in combination with steroids and ORT for the treatment of active TED. In a double-blind RCT, azathioprine (100–200 mg/day for 48 weeks) was found to reduce morbidity, reduce CAS, and improve diplopia when combined with radiotherapy (20 Gray in 10–12 fractions) and/or corticosteroids (prednisone 80, 60, 40, 20, 10, 5 mg taper over 24 weeks) in patients with active moderate-to-severe TED.<sup>58</sup> A retrospective study including 88 active TED patients showed that mean CAS improved by 4 points and 44% of patients had resolution of

diplopia in primary gaze after treatment with the combination of azathioprine (200 mg/day tapered to 50 mg/day for 6 months), corticosteroids (IV methylprednisolone 10 mg/kg followed by oral prednisolone 0.5 mg/kg/day tapered to 0.2 mg/kg/day), and ORT (20 Gray total).<sup>59</sup> Major side effects include bone marrow suppression, hepatic toxicity, and pancreatitis.

**Methotrexate.** Methotrexate is an antimetabolite that inhibits folic acid synthesis, thus suppressing the proliferation of T and B lymphocytes. In the treatment of TED, it has been trialed alone or in combination with corticosteroids or orbital radiation.<sup>60–64</sup> In active, moderate-to-severe TED patients unresponsive to steroids or unable to tolerate steroid-related side effects, two retrospective case series have found that methotrexate at a weekly dose of 7.5 or 10 mg led to a clinically significant improvement in VISA and CAS scores as well as ocular motility.<sup>60,61</sup> No significant change was seen in exophthalmos or eyelid position.<sup>60,61</sup> A retrospective study of 72 severe TED patients with CON treated with methylprednisolone alone *versus* methylprednisolone with methotrexate showed the combination group saw a statistically significant improvement in VA and VISA score at 3 months, but this was not sustained at 6, 12, or 18 months.<sup>64</sup> No difference was seen in ocular motility, proptosis, or exposure keratopathy.<sup>64</sup> Gastrointestinal side effects (such as nausea, vomiting, and stomatitis) and hepatotoxicity are common potential adverse reactions to methotrexate.

#### Targeted therapies

In recent years, advances in our understanding of the immunological pathogenesis of TED have shifted the focus of management to novel biological therapies (see Table 2). These treatments have the advantage of targeting immune cells and receptors implicated in the pathogenesis of TED, with potentially better safety profile and greater efficacy compared to traditional approaches.<sup>73–78</sup>

**Rituximab.** Rituximab is a monoclonal antibody against CD20 that depletes the population of autoreactive B cells by both the antibody- and complement-mediated pathways.<sup>79</sup> Two RCTs demonstrated mixed results in improvement of CAS for active, moderate-to-severe TED.<sup>65,66</sup> Salvi and colleagues<sup>65</sup> showed superiority of rituximab (1000 mg IV weekly  $\times$  2) *versus* IV methylprednisolone in improving CAS at 24 weeks in 32

**Table 2.** Summary of biologic therapies for TED.

Small Molecule Therapies	Target	Dosing	Findings	Side Effects
Rituximab	CD20	Two infusions of 1000 mg each two weeks apart	Mixed results in improvement of clinical activity score (CAS), proptosis, and motility <sup>65,66</sup>	Exacerbation of inflammatory bowel disease, arthralgias, hypotension
Adalimumab	TNF- $\alpha$	Subcutaneous injections of initial 80 mg dose, then biweekly 40 mg doses for a total of 10 weeks	6/10 showed decrease in inflammation, no changes in proptosis or extraocular motility <sup>67</sup>	Sepsis (1/10)
Infliximab	TNF- $\alpha$	Infusions at 5 mg/kg each dose over 2 h	Case reports showed improvement in visual acuity and CAS after 1 dose and complete resolution in three cases after 3 doses <sup>68,69</sup>	Infections, malignancies (especially lymphoma), drug-induced lupus
Tocilizumab	IL-6	Three infusions at 8 mg/kg given every 4 weeks	93% with $\geq 2$ -point improvement in CAS, mean proptosis reduction of 1.5 mm, no change in diplopia <sup>70</sup>	High recurrence rate, transaminitis, pyelonephritis
Teprotumumab	IGF-1R	Initial infusion at 10 mg/kg, followed by seven infusions at 20 mg/kg given every 3 weeks	Reduced proptosis in 79–83% of patients, improved CAS in 69%, reduced diplopia in 68% <sup>71,72</sup>	Most common: muscle spasms fatigue, nausea, diarrhea, hyperglycemia, hearing impairment, and alopecia. 5–12% with serious adverse events requiring early withdrawal.
<b>Emerging Therapies</b>				
IMVT-1401 (Phase II clinical trials)	FcRn	Subcutaneous injections of two weekly 680 mg doses followed by four weekly 340 mg doses	4/7 with $\geq 2$ -point improvement of CAS, 3/7 with improved proptosis, 65% reduction in IgG levels (ASCEND-GO 1 clinical trial, NCT03922321)	No serious adverse events
TSHR Antagonist (Preclinical)	TSHR	N/A	N/A	N/A

patients. Of the patients in the rituximab arm, 13% showed lid fissure reduction of 3 mm or greater *versus* 0% in the methylprednisolone arm.<sup>65</sup> No improvement in mean proptosis or diplopia was found in either group.<sup>65</sup> Stan and colleagues<sup>66</sup> showed no difference between rituximab (500 mg  $\times$  1) *versus* placebo in 25 patients in CAS, proptosis, diplopia or lid retraction at 24 or 52 weeks.

The study populations in the two studies differed in average duration of TED (4 months *versus* 12 months), percentage of smokers included (59% *versus* 16%), and baseline CAS score ( $\geq 3$  *versus*  $\geq 4$ ). One case report of a patient with severe TED with CON found that rituximab was unable to stop the progression of disease.<sup>80</sup> Furthermore, the patient's ophthalmopathy continued to deteriorate despite rituximab, and he ultimately required surgical decompression.<sup>80</sup> Larger, prospective randomized

trials are needed to validate the efficacy of rituximab in TED. Notably, the rates of adverse events from rituximab therapy were high (8/13 patients and 13/15 patients) and included infusion reactions, hypotension, myalgias, transaminitis, aggravation of inflammatory bowel disease, transient loss of vision, and arthralgias.<sup>65,66</sup>

**Adalimumab.** Adalimumab, an antitumor necrosis factor-alpha (TNF- $\alpha$ ) agent, was evaluated for the treatment of active TED in a small retrospective study. Four out of 10 patients reported subjective improvements in diplopia, pain, and swelling; however, there were no significant objective improvements in proptosis or extraocular movement restriction.<sup>67</sup>

**Infliximab.** Infliximab is a monoclonal antibody that targets TNF- $\alpha$ . Its use in cases of steroid-resistant, severe TED has been reported with

improvement in VA and CAS after one dose in one case report and complete resolution in three cases after three doses.<sup>68,69</sup>

**Tocilizumab.** An IL-6 monoclonal antibody, tocilizumab has been proposed as a potential treatment for TED. IL-6 is a proinflammatory cytokine implicated in the disease process of TED and is found in high concentrations in TED patients.<sup>81,82</sup> IL-6 has been found to stimulate the expression of TSHR in orbital fibroblasts.<sup>83</sup> Tocilizumab therapy consists of four infusions given every 4 weeks for a total of 16 weeks, although subcutaneous injections have also been tried and found to be effective.<sup>84</sup> A randomized clinical trial showed that tocilizumab significantly reduced CAS by 2 points or greater in 93% of patients with moderate-to-severe, corticosteroid-resistant TED at week 16 *versus* 59% in the placebo group.<sup>70</sup> There was no improvement in diplopia.<sup>70</sup> However, the recurrence rate was high, and improvement of CAS was not significant at 40 weeks of follow-up. Furthermore, side effects—such as infections, hypercholesteremia, neutropenia, and transaminitis—were common, with more than one adverse event occurring in 60% of treated patients *versus* 24% of placebo.<sup>85</sup>

**Teprotumumab.** Teprotumumab, an antibody targeted against the IGF-1R, is the first U.S. Food and Drug Administration (FDA) approved therapy for TED. Initial *in vitro* experiments showed that teprotumumab inhibited not only IGF-1R but also TSHR signaling, thus reducing the production of proinflammatory cytokines.<sup>86</sup> The teprotumumab regimen consists of 8 infusions administered every 3 weeks, with initial dosing of 10 mg/kg for the first infusion, followed by 20 mg/kg for the remaining infusions. Teprotumumab was studied in phase II and III clinical trials to evaluate its efficacy in the treatment of active, moderate-to-severe TED. In the phase II study, the treatment group showed significant improvements in proptosis and CAS score compared to placebo at 6, 12, 18, and 24 weeks.<sup>71,72</sup> Proptosis improved by  $\geq 2$  mm in 79% of the treatment group *versus* 22% of the placebo group, and 40% of patients in the treatment group had a reduction of  $\geq 4$  mm.<sup>71</sup> CAS score reduced to 0 or 1 in 69% of the treatment group *versus* 21% of the placebo group.<sup>71</sup> In addition, patients reported significant improvements on the Graves' ophthalmopathy-specific quality-of-life questionnaire (GO-QOL).<sup>71</sup> The OPTIC phase III trial confirmed teprotumumab's efficacy. Proptosis improved in

83% of the teprotumumab group *versus* 10% of the placebo group, with the mean improvement in proptosis after the full course of teprotumumab 3.32 mm.<sup>72</sup> Diplopia improved by 1 grade or more in 68% of the treatment group *versus* 29% of placebo.<sup>72</sup> CAS reduced to 0 or 1 in 59% of the treatment group *versus* 21% of placebo.<sup>72</sup>

**Durability data.** Preliminary long-term data from the phase II and III clinical trials demonstrated maintenance of proptosis response 72 weeks after their initial infusion in 53% and 56% of proptosis responders, respectively. In addition, 69% and 58% of diplopia responders maintained at least one grade or more improvement in diplopia 72 weeks after their initial infusion in the phase II and III studies, respectively.<sup>87,88</sup>

Studies are ongoing to determine the efficacy of teprotumumab in patients with longer disease duration or who may need retreatment. The OPTIC X clinical trial (NCT03461211) enrolled patients who were proptosis nonresponders in the earlier OPTIC trials, those who received placebo in OPTIC, and patients who met criteria for retreatment due to relapse in the follow-up period (defined as a loss of at least 2 mm of their week 24 proptosis improvement or substantial increase in the number of inflammatory signs). Preliminary results show that 89% of the OPTIC placebo patients (who had average of 12 months duration of TED) were proptosis responders, >60% of patients who relapsed after OPTIC experienced at least 2 mm of proptosis improvement with additional treatment, and of the 5 OPTIC nonresponders, two benefited from an additional course of teprotumumab in the OPTIC-X study.

**Adverse events.** The most common adverse events across both studies were mild to moderate, including muscle spasms, fatigue, nausea, diarrhea, hyperglycemia, hearing impairment, and alopecia.<sup>71,72</sup> In the teprotumumab group, 5–12% of patients had serious adverse events that resulted in early withdrawal from the study, with half of them categorized as likely unrelated to the treatment (such as pneumothorax, urinary retention, and *Escherichia* sepsis).<sup>71,72</sup> However, recent studies suggest that hearing impairment may be more prevalent than previously reported.<sup>89</sup> The authors' own experience with teprotumumab therapy is closer to 65% (17 of 26 patients) of patients complaining of otologic symptoms (tinnitus, ear plugging, autophony, hearing loss), with four patients developing



objective sensorineural hearing loss and 3 patients developing a patulous eustachian tube. Of the affected patients, 55% reported persistent symptoms even after discontinuation of therapy. Until the risk factors for hearing dysfunction are better understood, the authors recommend baseline audiogram and patulous eustachian tube testing with audiology evaluation prior to starting teprotumumab and repeat testing if otologic symptoms develop. The authors also recommend ENT involvement and stopping teprotumumab therapy if significant objective hearing loss develops during therapy. Another adverse event reported is the development or exacerbation of pre-existing inflammatory bowel disease after initiating teprotumumab therapy, underlining the importance for clinicians to exercise caution in this particular population.<sup>90,91</sup>

*Teprotumumab for compressive optic neuropathy.* Teprotumumab has been utilized successfully in disease activity and stages not described in the clinical trials. Several case reports describe its efficacy treating severe TED cases with CON, with improvements in VA, relative afferent pupillary defect (RAPD), CAS, Humphrey visual fields, proptosis, and extraocular muscle size after two to three infusions.<sup>92-95</sup> In a case series of 10 patients with active and chronic TED and CON, 70% of patients showed improvement of VA, RAPD, or both after two infusions.<sup>96</sup> On average, patients had 4.7 mm of proptosis reduction and 5.25 points of CAS improvement, and of the seven patients with color vision deficits, six had normalization of their color vision.<sup>96</sup>

*Teprotumumab for chronic TED.* Teprotumumab can also be used to treat stable, chronic TED.<sup>97-99</sup> A retrospective study of 31 patients with TED for longer than 2 years with CAS  $\leq 3$  and without any changes in exam showed a mean reduction in proptosis by 3 mm, improvement in CAS by 1.8, and improvement in Gorman diplopia score (GDS) by 0.5.<sup>98</sup> Analysis of pre- and post-therapy imaging revealed reductions in volume of both extraocular muscles and fat.<sup>98</sup> Another study including 21 patients in various stages (active *versus* stable) and grades (mild, moderate, severe, DON) of TED found that there were no significant differences in CAS, proptosis, ductions, or lid position in the clinical subgroups after teprotumumab treatment.<sup>99</sup>

Teprotumumab presents a promising new therapy for the management of TED. Recent studies

describing its success in conditions outside of those approved by the FDA are encouraging for broadening its therapeutic applications. Additional studies are needed to define the role of teprotumumab for severe and chronic TED.

### *Emerging therapies*

*IMVT-1401.* Recently, a monoclonal antibody targeting the neonatal Fc receptor (FcRn) has been proposed for the treatment of autoimmune diseases, including TED.<sup>100</sup> FcRn functions to transport immunoglobulin G (IgG) and prevents their lysosomal degradation.<sup>101</sup> IMVT-1401 disrupts the IgG-FcRn interaction to increase catabolism of IgG and may increase degradation of pathogenetic autoantibodies against the TSHR and IGF-1R. A small proof of concept phase IIa multicenter, open-label, single-arm clinical trial (ASCEND-GO 1, NCT03922321) evaluated two weekly 680 mg subcutaneous doses of IMVT-1401 followed by four weekly 340 mg subcutaneous doses of IMVT-1401 in seven adult patients with moderate-to-severe, active TED. IMVT-1401 is a subcutaneous injection that is administered weekly, allowing for the possibility of at-home treatment rather than in an infusion center. Initial results showed four of seven patients achieved an improvement in CAS by two or more points and three of seven patients achieved a reduction in proptosis after IMVT-1401 treatment. Mean reduction in total IgG levels was 65%. However, at the time of this writing, the phase IIb randomized, placebo-controlled trial (ASCEND-GO 2, NCT03938545) has been closed due to elevated total cholesterol and low-density lipoprotein (LDL) levels found in IMVT-1401 treated patients.

*TSHR antagonist.* Small molecule antagonists targeting TSHR have been developed and tested in preclinical studies.<sup>102</sup> These antagonists selectively inhibit TSH-stimulated signaling. They have been found to reduce serum free T4 levels by 44% and lower mRNAs for thyroperoxidase by 83%.<sup>102</sup> TSHR antagonists present a promising option for targeted therapy.

### **Conclusions**

In recent years, we have seen exciting developments in the understanding and management of TED. Traditionally, corticosteroids, radiation therapy, and surgical correction were the mainstays in TED management. Now, focus has shifted to the development of targeted molecular

therapies for TED. In particular, teprotumumab demonstrated efficacy at changing the natural disease course of TED by targeting fundamental pathways involved in its pathophysiology. Long term data on teprotumumab and emerging therapies for TED will continue to change the treatment paradigm of TED. Further studies are needed to confirm the long-term effects of these novel biologics and whether the therapies reduce the need for rehabilitative surgery.

### Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Sara Tullis Wester and Andrea Lora Kossler are advisors and consultants for Horizon Therapeutics. Andrea Lora Kossler is also a consultant for Immunovant.

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