Future Projections in Thyroid Eye Disease

Giuseppe Barbesino,1 Mario Salvi,2 and Suzanne K. Freitag3

1Thyroid Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
2Graves’ Orbitopathy Center, Endocrinology, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy
3Ophthalmic Plastic Surgery Service, Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA

Correspondence: Giuseppe Barbesino, MD, Thyroid Unit, Massachusetts General Hospital, Harvard Medical School, WACC730S, 15 Parkman St, Boston, MA 02114, USA. Email: gbarbesino@mgh.harvard.edu

Abstract

Background and Aims: This review aims to summarize current and emerging therapies for treatment of thyroid eye disease (TED), in the light of novel understanding of pathogenetic mechanisms, leading to new treatment options and clinical trials.

Methods: We reviewed and analyzed peer-reviewed literature reporting recent translational studies and clinical trials in the treatment of TED. Searches were made at www.pubmed.gov with keywords “thyroid eye disease,” “Graves’ ophthalmopathy,” “thyroid orbitopathy,” and “Graves’ orbitopathy.”

Results: Surgery is reserved for rehabilitation in chronic TED or for emergent compressive optic neuropathy. Oral and intravenous glucocorticoid therapy has been used for decades with variable efficacy in acute TED, but results may be temporary and side effects significant. Nonsteroidal oral immunosuppressive agents offer modest benefit in TED. Several immunomodulatory monoclonal antibodies, including rituximab and tocilizumab, have shown efficacy for inactivating TED. Recently, teprotumumab, an insulin-like growth factor 1 receptor (IGF-1R) inhibitor, has demonstrated significant improvement in proptosis, clinical activity score, diplopia, and quality of life in patients with active TED, with good tolerability. Newly proposed TED therapies, currently in preclinical and clinical trial phases, include thyroid-stimulating hormone receptor (TSHR) inhibitor drugs, RVT-1401, local anti-vascular endothelial growth factor therapy, IGF-1R drugs delivered subcutaneously and orally, and desensitization to the TSH receptor with modified TSH receptor peptides.

Conclusion: New, albeit incomplete, understanding of the molecular mechanisms of TED has led to new promising therapies and offered improved outcomes in TED patients. Their full role and their relationship to classical immune suppression should be clarified in the next few years.

Key Words: thyroid eye disease, Graves’ disease, thyroid autoimmunity, glucocorticoids, teprotumumab; insulin-like growth factor 1 receptor, TSHR receptor

Abbreviations: CAS, clinical activity score; CsA, cyclosporine A; EBRT, external beam radiation therapy; GC, glucocorticoid; GD, Graves’ disease; IGF-1R, insulin-like growth factor 1 receptor; IVGC, intravenous glucocorticoid; OGC, oral glucocorticoid; MMF, mycophenolate mofetil; QoL, quality of life; RTX, rituximab; TCZ, tocilizumab; TED, thyroid eye disease; TRAb, thyroid-stimulating hormone receptor antibodies; TSHR, thyroid-stimulating hormone receptor; VEGF, vascular endothelial growth factor.

Thyroid eye disease (TED) is characterized by swelling and inflammation of orbital and periorbital tissues with widely varying manifestations. Visual dysfunction can result from diplopia, caused by extraocular muscle restriction, or from visual loss from exposure keratopathy or compressive optic neuropathy. Even when visual function is spared, TED can adversely affect quality of life (QoL) with eye pain, photophobia, tearing, and cosmetic changes ranging from eyelid retraction to disfiguring proptosis. Understanding the pathogenesis of TED has been challenging, due to difficult access to target tissues and lack of high-fidelity animal models. Since TED is closely associated with Graves’ hyperthyroidism, a role for thyroid-stimulating hormone receptor (TSHR) antibodies (TRAb) has been long postulated (1). TED was initially thought to be a classical acute or subacute autoimmune inflammatory condition driven by a T-and B-cell response, elicited by orbital autoantigens, such as the TSHR, and mediated by a multiplicity of soluble factors (2). Hence, nonselective immunosuppressive therapy has typically been used with variable success, with the intent to smother the active inflammatory process, and potentially prevent less reversible anatomic changes, such as proptosis, which result from chronic inflammation leading to fibrosis. Orbital decompression, strabismus, and eyelid surgery have been used primarily for rehabilitative purposes and, on occasion, to urgently relieve optic nerve compression or severe exposure keratopathy. Given the limited success of available treatments, patients are typically counseled that a complete return of visual function and appearance to their preexisting state is unlikely. Recent data, however, have suggested that a nonclassical immunological mechanism may be central to TED pathogenesis. The TSHR in orbital tissues may indeed not only be a classical autoantigen passively being targeted by a typical cellular and humoral autoimmune response. According to newer evidence, Graves’ TRAb can functionally activate the TSHR in concert with the insulin-like growth factor 1 receptor (IGF-1R) on orbital fibrocytes (3-5). The coexistence of IGF-1R–stimulating autoantibodies has been proposed, but the evidence for this remains incomplete (6). Indeed, the 2 receptors appear to be physically and functionally complexed in orbital fibrocytes. The activation of both TSHR and IGF-1R in orbital fibroblasts and fibrocytes leads to their differentiation into adipocytes, capable of secreting...
inflammatory cytokines and hyaluronic acid, and proliferate. Given the central role of the IGF-1R pathway, IGF-1R inhibition through a monoclonal antibody (teprotumumab) has been tested in 2 randomized placebo-controlled trials (7, 8). Teprotumumab has demonstrated efficacy in improving many TED manifestations, particularly proptosis, a feature typically minimally affected by traditional medical therapies. Preliminary evidence from observational studies also suggests that teprotumumab may be effective in chronic TED (9-11). These findings offer hope that TED manifestations can now be partially or completely reversed, rather than simply inactivated by medical therapy. The goal of this review is to summarize current and emerging treatment options for TED during this exciting time of increasing and more effective options.

Current Landscape of Treatment for TED

In considering available treatments for TED, we must recognize that the available evidence is limited by several factors. TED is rare, so that the recruitment of large series of patients is difficult. TED is heterogeneous, and its many manifestations may worsen or improve independently of one another, making the establishment of clinically relevant and comprehensive measures difficult to establish. Most of the clinical assessment is based on subjective or semiquantitative measures at best, making the comparison between studies performed in different centers difficult. The inflammatory symptoms in TED undergo spontaneous improvement of variable degree after the initial flare, making the use of placebo-treated controls critical in evaluating the efficacy of any treatment. Many of the available studies, especially those addressing the use of glucocorticoids (GC) have been performed in eras in which the criteria for clinical evidence were looser than now, and placebo controlled data with GC are scarce. Evidence on the short term efficacy of steroids has been obtained from dose-response studies, which have shown variable effects on the natural course of disease (12, 13). Thus, GC have become standard of care in many centers and countries, making the performance of placebo-controlled studies with novel agents more difficult from the ethical standpoint. A summary of randomized controlled studies discussed in this minireview is presented in Table 1.

Surgery

The surgical treatment of TED traditionally has been reserved for patients with inactive disease (eg, after medical treatment) or for emergency treatment of sight-threatening complications (compressive optic neuropathy and severe anterior eye surface exposure) that are not responsive to medical treatment. The operations most often performed on patients with TED include orbital decompression, strabismus surgery, and eyelid surgery, which includes eyelid recession and blepharoplasty.

Orbital Decompression

Orbital decompression surgery involves removal of bone from 1 or multiple orbital walls and/or orbital fat to increase orbital volume and reduce the pressure exerted from expanded extraocular muscles and/or orbital fat. Indications for this surgery include compressive optic neuropathy, disfiguring or extreme proptosis, significant exposure keratopathy or globe subluxation, or uncontrollable elevation of intraocular pressure. This procedure is performed in the inactive phase of TED unless there is an emergent indication.

Double vision is a common complication of orbital decompression surgery, occurring in 20% to 34% of patients (14, 15). Preservation of a strip of periorbital tissue along the medial wall may reduce this risk (14, 15). For a balanced orbital decompression, a simultaneous lateral wall decompression allows the globe to maintain its mid-orbit location and helps prevent diplopia. Fat removal decompression may be performed in combination with bony wall decompression. Rarely, surgeons may perform fat removal as the primary decompression procedure. This may be more effective in patients with type I fat predominant–type TED (16).

Strabismus Surgery

Diplopia occurs in approximately 36% of patients with TED (17). The most commonly affected extraocular muscles are the inferior and medial recti, sometimes resulting in an obvious eso- or hypotropia. Diplopia may be intermittent or constant and may occur in primary gaze, peripheral directions of gaze, or all directions. The least invasive treatments for diplopia involve occlusion of 1 eye or prism correction. Strabismus surgery may be performed to realign the eyes with a goal of binocular vision in as many directions of gaze as possible. This should only be undertaken when TED is inactive, once multiple sets of measurements confirm stable disease.

Eyelid Surgery

Eyelid surgery in TED may be performed to recess upper and/ or lower eyelids to provide more complete coverage of the ocular surface, allowing dry eye symptom improvement. It might also be performed to improve eyelid position or remove excess skin or hypertrophied and prolapsed eyelid fat pads. Upper eyelid retraction is independent of globe position and proptosis and often persists after surgical or medical proptosis reduction. Lower eyelid retraction is more closely related to globe position and may be expected to improve when the globe is medically or surgically moved posteriorly in patients with minimal underlying eyelid laxity (18, 19). Patients with significant lower eyelid retraction may require lower eyelid recession with placement of a posterior spacer graft.

Simultaneous Surgical Procedures

In recent years, several authors have proposed that combinations of usually staged eye surgeries be performed during the same surgical event. This concept was first reported by Choi et al in 2016 in a series of 27 patients undergoing orbital decompression. Three patients underwent successful simultaneous strabismus surgery, and eyelid retraction surgery was successfully performed simultaneously in 10 cases (20). Bernardini et al described a series of 40 patients undergoing orbital decompression, with 23 patients having simultaneous eyelid retraction repair, and 26 and 32 patients, respectively, having upper and lower cosmetic blepharoplasty. None required additional eyelid surgery, and 17% needed strabismus surgery for new-onset diplopia (21). Quaranta-Leoni et al described a series of 45 patients undergoing orbital decompression plus simultaneous strabismus and/or eyelid surgery and compared them with control groups having similar procedures in a traditional multistep fashion, with similar outcomes in the simultaneous vs staged groups (22). Although these
Table 1. Summary of randomized controlled studies on medical treatment of thyroid eye disease discussed in the text

| Population                        | Treatment                  | Treatment patients, n | Control patients, n | Duration, weeks | Main outcome measure | Response in cases | Response in controls | Reference                        |
|-----------------------------------|----------------------------|------------------------|---------------------|-----------------|----------------------|-------------------|---------------------|----------------------------------|
| Active, moderate to severe TED    | IVGC                       | 25                     | OGC                 | 12              | Composite index      | 72%               | 49%                 | Aktaran et al, 2007 (29)         |
| Active, moderate to severe TED    | IVGC                       | 41                     | OGC                 | 22              | Composite index      | 88%               | 63%                 | Marcocci et al, 2001 (30)        |
| Active, severe TED                | IVGC                       | 35                     | OGC                 | 12              | Composite index      | 77%               | 51%                 | Kahaly et al, 2005 (13)          |
| Active, moderate to severe TED    | IVGC + 7.47 g Total        | 52                     | OGC + 4.98 or 2.25 g total | 12              | Overall ophthalmic assessment, QoL | 52%               | 35%, 28%                | Bartalena et al, 2012 (12)       |
| Active, moderate to severe TED    | MMF + IVGC, OGC            | 80                     | IVGC, OGC           | 24              | Composite index      | 79%               | 81%                 | Ye et al, 2017 (34)              |
| Active, moderate to severe TED    | MMF + IVGC                 | 83                     | IVGC                | 36              | Response rate at 12 weeks, relapse rate at 36 weeks, based on Composite Index | 63%, 12%*         | 49%, 19%                      | Kahaly et al, 2018 (35)          |
| Moderate to severe TED            | OGC + Cyclosporine A       | 20                     | OGC                 | 52              | Activity Score, Change in proptosis | Mean proptosis change -3 mm, mean AS change -6.0 | Mean proptosis change -1 mm, AS change -1.1 | Kahaly et al, 1986 (37)          |
| Severe TED                        | Cyclosporin A              | 18                     | OGC                 | 12              | NO-SPECS Class change | 22%               | 61%                 | Prummel et al, 1989 (38)         |
| TED                               | Azathioprine               | 10                     | No treatment        | 52              | Proptosis, lid aperture, visual acuity | No changes*       | No changes*                  | Perros, 1990 (88)                |
| Active, moderate to severe TED    | Rituximab                  | 11                     | Placebo             | 24              | CAS improvement      | 31%*              | 25%                 | Stan et al, 2015 (48)            |
| Active, moderate to severe TED    | Rituximab                  | 16                     | IVGC                | 24              | CAS improvement      | 100%              | 69%                 | Salviet al, 2015 (49)            |
| Glucocorticoid resistant, moderate to severe TED | Tocilizumab | 15                     | Placebo             | 16              | CAS improvement      | 93%               | 59%                 | Perez-Moreiras et al, 2018 (58) |
| Active, moderate to severe TED    | Tepronatumab               | 42                     | Placebo             | 24              | CAS improvement + change in proptosis | 69%               | 20%                 | Smith et al, 2017 (8)            |
| Active, moderate to severe TED    | Tepronatumab               | 41                     | Placebo             | 24              | CAS improvement + change in proptosis | 83%               | 10%                 | Douglas et al, 2020 (7)          |
| Moderate to severe TED with hypercholesterolemia | Atorvastatin + IVGC | 44                     | IVGC                | 24              | Composite Index      | 51%               | 28%                 | Lanzolla et al, 2021 (41)        |

Abbreviations: CAS, clinically activity score; IVGC, intravenous glucocorticoids; OGC, oral glucocorticoids; QoL, quality of life; TED, thyroid eye disease.

*Not statistically significant vs controls.
novel approaches of combined surgery are not yet widely adopted by TED surgeons, they provide they offer the opportunity of a faster achievement of surgical goals and improve patient satisfaction.

Systemic Medical Therapy

Glucocorticoids

Oral GC (OGC) have been employed in TED since the 1950s (23). Based on a variety of parameters and the short-term clinical activity score (CAS), the response rate is estimated at 40% to 60% (24). Relapses at the end of OGC or even during treatment are common. Intravenous GC (IVGC) pulse therapy (methylprednisolone) was introduced in the late 1980s to exploit the immunosuppressive effect of GC while reducing their side effects (25). Early protocols have varied widely, with early studies using up to 3 g of methylprednisolone weekly (25, 26) plus or minus oral prednisone between pulses (27). In these uncontrolled studies, the response rate has been estimated at 75% to 80%, therefore higher than with OGC alone (24, 28). Randomized studies (13, 29, 30) and a meta-analysis comparing IVGC vs OGC (31) showed roughly an 80% response rate with IVGC vs 50% to 60% with OGC. Disease inactivation requires 4.5 to 7.5 g cumulative dose of methylprednisolone, with the higher dose effective in improving overall disease severity (12). Protocols employing cumulative doses of IVGC equivalent to >8 g methylprednisolone were associated with several cases of severe and even fatal liver toxicity (32) and should not be used ordinarily. In summary, IVGC remain the most widely studied medical treatment for TED. The data suggest significant, immediate benefits in the active phase of the disease, mostly on inflammatory changes with little effect on diplopia and virtually none on proptosis. The scarcity of placebo-controlled studies is also a major problem, as the disease tends to undergo spontaneous improvement. IVGC are associated with significant side effects. Most important, the durability and the long-term effect on the natural history of TED have not been established. Given their low cost, the ease of use, and the current unavailability of teprotumumab in most countries, IVGC currently remain the first-line treatment for TED worldwide.

Nonsteroidal Oral Agents

Immunosuppression with nonsteroidal agents has been studied either alone or as way to enhance the efficacy of GC. Mycophenolate mofetil (MMF) specifically targets activated T and B lymphocytes (33). In a randomized clinical trial of MMF vs an unusual mixture of IVGC and OGC, MMF was followed by a greater drop in average CAS (5.2 to 1.9) than GC (5.2 to 2.4), with a better safety profile (34). In another trial, comparing MMF in addition to IVGC vs IVGC alone, MMF showed benefit in a post hoc analysis only (35). Despite these limited data, the European Group on Graves’ Orbitopathy (EUGOGO) recommends MMF in adjunct to IVGC as first-line therapy for moderate to severe TED (36).

Cyclosporine A (CsA) and azathioprine also deserve mention. In a randomized controlled trial, OGC plus CsA were more effective than OGC alone (37). In another study of 36 subjects, CsA (response rate 22%) was inferior to OGC (response rate 66%) as primary treatment, but a follow-up treatment with combination OGC and CsA resulted in a response rate of approximately 60% in nonresponders from either OGC or CsA alone (38). However, CsA has significant neurological, renal, and cardiovascular side effects and is therefore seldom used.

In a randomized, controlled study, azathioprine was compared to placebo in patients receiving OGC (24 and 25 patients, respectively). Patients received azathioprine or placebo for up to 48 weeks, and they all received a taper of oral steroids in the first 24 weeks of the study. While there was no benefit of azathioprine over placebo at 24 weeks, a benefit was seen in patients continuing azathioprine for >24 weeks (odds ratio 5.2; 1.62 to 16.8), suggesting that the drug may be useful in maintaining the effects obtained with steroids (39). Given the paucity of data, azathioprine’s role in the treatment of TED remains uncertain.

Nonimmunosuppressive Oral Treatments

Epidemiological studies have suggested a lower risk of TED in Graves’ disease (GD) patients taking statins (40). In a Phase 2, open label, randomized clinical trial in patients with active TED and hypercholesterolemia, improvement of TED based on a composite evaluation of exophthalmos, CAS, eyelid aperture, and diplopia at 24 weeks was observed in 51% of patients (n = 41) treated with IVGC and atorvastatin compared to 28% in those treated with IVGC alone (n = 39) (41). The low response rate to IVGC in this study is unexplained, but the data are promising. Given the small size and short duration of this study, additional studies on statins are necessary. A recent retrospective, case-control study demonstrated that serum 25 hydroxyvitamin D [25(OH)D] levels were lower in TED patients than GD patients without TED (42). Although the study involved only 89 TED patients and 356 healthy controls, the results were statistically significant and suggest that vitamin D deficiency may be associated with TED development. Hence, further studies may be helpful in elucidating whether vitamin D supplementation could play a role in TED prevention or treatment.

Immunosuppression with Biologics

A number of immune cells and cytokines are thought to be involved in the pathogenesis of TED (43, 44). Several monoclonal antibodies able to interfere with cytokine signalling are available for treatment of moderate-to-severe TED, but only a few of these immunosuppressants have been tested in randomized clinical trials. In deciding among available therapies efficacy and safety carry the greatest weight, but costs may impose limits as well. In addition, specific clinical situations may suggest the choice of agents with greater activity on specific features of TED.

Rituximab

Rituximab (RTX) is a chimeric mouse-human monoclonal antibody targeting the CD20 antigen expressed by B cells. Treatment with RTX in TED patients induces B-cell depletion by direct lysis and likely interferes with their antigen presentation function and cytokine production (45). Early open label studies (46, 47) have found RTX effective in patients with active TED, both naive and those who were unresponsive to IVGC.

Two prospective randomized clinical trials of patients with active moderate-to-severe TED, one vs placebo in the United
States (48) and the other vs IVGC in Italy (49), have produced conflicting results. In the US study of 25 patients, with mean baseline CAS = 5.1, RTX (n = 12) failed to inactivate TED, whereas in the Italian study of 31 patients with mean baseline CAS = 4.6, RTX induced disease inactivation at 24 weeks (CAS < 3) in 100% compared to 69% patients with IVGC, and no disease relapse was observed with RTX 54 weeks after study entry. About one third of patients had improvement of proptosis > 2 mm from a mean baseline of 23.3 mm, and 60% had improvement of a composite ophthalmic score, compared to 37.5% of patients treated with IVGC. A review of both studies showed that much longer disease duration (mean 30 months) was observed in the US patients as compared to the Italian patients (mean 4.5 months). It was suggested that RTX treatment may be most effective in patients with inflammatory TED of short duration (50).

A recent meta-analysis reviewed 152 TED uncontrolled patients and indicated that patients treated with RTX had a significant reduction of the CAS and relapse rate but not of proptosis or diplopia when compared to baseline (51). A single 500-mg dose of RTX seems as effective as 1000 mg × 2. Recently, responses to lower RTX doses (100 mg) have been reported, with a reduced risk of side effects and better cost-effectiveness (52). Mild infusion-related reactions are common at first infusion (10-30% of patients). In rare cases, a cytokine release syndrome may occur, characterized by marked orbital edema, which is usually responsive to intravenous methylprednisolone (53).

In summary, RTX is effective for inactivating TED and preventing disease recurrences, even in patients resistant to first-line IVGC therapy and in those with significant and short-duration inflammatory disease. The wide use of RTX in hematological and rheumatic disease suggests a good safety profile, although the data on TED remain limited.

**Tocilizumab**

Tocilizumab (TCZ) is a monoclonal antibody that binds to the soluble and membrane-spanning interleukin 6 (IL-6) receptors and is used extensively in the treatment of rheumatoid arthritis (54). Activation of the IL-6/sIL-6 receptor system has been shown in GD and active TED (55, 56). In an open label, noncontrolled study, TCZ appeared promising in inactivating TED, with a mean proptosis reduction of 2.6 mm (57). A randomized clinical trial of TCZ vs placebo in steroid-resistant, active TED was completed. Disease inactivation (CAS reduction ≥ 2) occurred with TCZ in 93% of patients, compared with 59% of placebo patients at week 16. A median decrease in proptosis of 1.5 mm was observed in patients receiving TCZ at 16 and 40 weeks, respectively, vs 0 mm with placebo. Diplopia improved in only about 5% to 6% of patients receiving TCZ. The most frequently reported adverse effects were neutropenia and hypercholesterolemia, while increased risk of bowel perforation, severe infections, and hepatotoxicity have been reported in rheumatic patients receiving the drug but not in TED (58). An ongoing multicenter trial in Italy (NCT04876534) is studying the efficacy of TCZ in comparison with IVGC. Results are expected by the end of 2023.

**Belimumab**

Recently, the B-cell stimulating factor monoclonal antibody belimumab was studied in 27 patients with active, moderate-to-severe TED and detectable TRAb. A preliminary communication suggests an effect on CAS and TRAb levels (59). These results have not undergone peer review yet but may become a promising alternative when IVGCs are contraindicated or ineffective.

**Teprotumumab**

Teprotumumab is a human monoclonal antibody inhibitor of IGF-1R. The drug was originally developed as an antineoplastic agent and was widely tested in humans (60). While teprotumumab was not effective in solid tumors, it was relatively well tolerated. This allowed teprotumumab to be rapidly repurposed for treatment of TED based on the data suggesting an involvement of the IGF-1R.

**Teprotumumab in active TED**

Teprotumumab has been the object of 2 randomized, placebo-controlled, double-blinded studies, both conducted in active, recent-onset, moderate-to-severe TED. In a Phase 2 study published in 2017, teprotumumab was infused at 10 mg per kg of body weight on the first dose, followed by 20 mg per kg of body weight every 3 weeks for 7 additional doses. The drug demonstrated remarkable efficacy (8). Sixty-nine percent of patients in the treatment group experienced a response as compared to 20% in the placebo group. In the teprotumumab group, the mean decrease in CAS was 4 points at the end of the 24-week therapeutic period, from a mean baseline of 5.1. The mean decrease in study-eye proptosis was 3 mm in the treatment group and 40% of treated patients experienced a decrease of ≥ 4 mm. Subjective diplopia responded in 68% of treated patients vs 26% in controls. There were large improvements in TED-specific QoL measures as well. Improvement was rapid, with 50% of the responses occurring within 10 weeks of study initiation. A Phase 3 study (OPTIC) with very similar design and protocol was recently published (7). This study almost completely reproduced results of the previous study, with proptosis decreasing by at least 2 mm in 83% of treated cases (mean decrease 2.8 mm), 60% of treated cases achieving a CAS of 0 or 1, and 68% experiencing a reduction in diplopia of ≥ 1 Gorman grade. The results of these studies led to the US Food and Drug Administration approval of teprotumumab for TED in January 2020, the only drug to earn such approval to date. The findings of the OPTIC study were solidified by its extension trial, the OPTIC-X study. In this study, 37 patients previously treated with placebo received teprotumumab. The proptosis response was 89% in this group, with a mean decrease in proptosis of 3.5 mm. The effect on CAS was similar to that in the OPTIC study. In those patients previously treated with teprotumumab without a favorable response, retreatment resulted in a response in 2 of 5 patients. In patients who had responded but had experienced a relapse, 5 of 8 experienced a retreatment response (10). These data suggest that duration of TED may not be as important in predicting response to teprotumumab as it appears to be with classically anti-inflammatory therapies. However, the findings also show that relapses after teprotumumab do occur. In the 48 weeks follow-up phase of the OPTIC study, described in the OPTIC-X study, the relapse rate was nonnegligible (29.4%) (10). In addition, a comprehensive review of the data from the 2 randomized studies, 7 out of 88 patients in the teprotumumab arms required additional medical or surgical treatment, including 3 undergoing orbital decompression (61). This suggests that retreatment may be necessary in some patients, with schedules that need to be explored in additional formal clinical studies.
Teprotumumab in chronic TED

The data from the OPTIC-X study (10) and the wide indication for TED granted by the Food and Drug Administration have paved the way for its use in populations other than those represented in the 2 formal trials (7, 8). Teprotumumab has been shown in several postmarketing reports to have efficacy in patients with chronic TED (11, 62, 63). The largest (retrospective) series to date reported 31 patients with chronic, stable TED (>2 years, mean duration 81 months) and with CAS ≤ 3. The mean proptosis reduction was 3.5 mm, which is similar to that reported in patients receiving teprotumumab with active disease in the former trials. Of 15 patients with diplopia, 7 had complete resolution and 3 others experienced an improvement ≥1 grade on the Gorman scale. There was also a reported decrease in orbital fat volume and extraocular muscle volume on radiographic imaging, similar to that reported in patients with active TED (11). These results are to be considered limited by their observational nature but are certainly promising.

In most studies, teprotumumab was well tolerated; however, certain side effects occurred with enough consistency to be considered associated with the drug. Muscle spasms have been reported in 20 of 128 treatment courses from the 3 studies previously listed (37 patients in the OPTIC-X study were treated twice). Hyperglycemia, mostly in patients with preexisting diabetes mellitus, was observed in 10 of 91 patients for 128 individual treatment courses. Hyperglycemia was easily controlled with medical management. Hearing loss of variable degree has been reported in 14 of 128 treated patients. The hearing changes appear to be mostly mild and transient, but there were some persistent cases. The exact etiology of the hearing changes remains unclear, but IGF-1 appears to have an important role in mammalian auditory function (64). Ongoing monitoring of audiology testing prior, during, and after teprotumumab treatment is recommended while the extent of this effect is clarified (65). Given the importance of IGF-1 signaling during embryogenesis, the drug is extremely teratogenic in animals. Care should be taken to avoid administration during pregnancy, and pregnancy should be avoided for 6 months following the last infusion.

In summary, teprotumumab represents a major advance in the treatment of TED. Its mode of action, not through classic anti-inflammatory effects but rather by interfering with one of the primary mechanisms responsible for orbital tissue expansion, has shown excellent efficacy in reduction of proptosis and diplopia and the enhancement of QoL. Indeed, a subset of patients from the OPTIC study who underwent orbital imaging before and after teprotumumab treatment displayed marked decreases in orbital fat and extraocular muscles volumes (66). These anatomical changes are largely unaffected by classically immunosuppressive treatments available previously. These early data suggest that the teprotumumab can at least partially reverse the remodeling of orbital tissues caused by TED, independently of whether inflammation as measured by CAS is still active. It is also remarkable that this drug, not generally known to have any direct anti-inflammatory activity, was able to improve CAS, a parameter of active inflammation. Given its efficacy, the drug is rapidly becoming first-line treatment for TED in the United States, despite its very high cost. Nevertheless, cost-effectiveness studies, especially with regard to the potential for this treatment to avoid eye surgery, are needed. Teprotumumab has not been approved for use in other countries and the European Group on Graves’ Orbitopathy lists IVGC as the first-line treatment for moderate-to-severe TED in combination with MMF (36). This divide between the United States and the rest of the world is clearly likely to affect future studies, as regulatory agencies may require additional studies not yet performed. In addition to well-designed postmarketing safety studies, several other aspects need to be further studied—for example, the long-term durability of teprotumumab effects, its impact on the need for eye surgery, and its efficacy in IVGC-unresponsive TED.

Local Treatments

External Beam Radiation Therapy

The utility of external beam radiation therapy (EBRT) to treat active TED has long been debated. There is a body of largely retrospective literature evaluating EBRT either alone or in combination with GC. The typical radiation dose reported is 20 Gy in 10 fractions. These studies suggest that EBRT can be effective in reducing the signs/symptoms of acute inflammation associated with TED including pain and tearing, reducing the CAS (67). EBRT was variably shown to improve extraocular motility and diplopia in some series (68-70). Other studies have shown its utility in improving or preventing compressive optic neuropathy compared with steroid alone, as well as avoiding surgical orbital decompression (Gold, 2018 #441) (71). These studies should be taken with caution, as they are retrospective or uncontrolled. Proptosis and eyelid retraction are less often improved with EBRT. There are few reported complications, with rare reports of radiation induced retinopathy. Care should be taken in patients with diabetes or other significant microvascular compromise, as this is thought to increase this risk of complications.

Local and Intraorbital Agents

The application of topical lubricating drops, gels, and ointments is essential for TED patients suffering from keratopathy. Preservative-free products are recommended, as preservatives themselves may worsen the keratopathy. Additional protection of the eyes with moisture chambers, goggles, or taping of the eyelids may be utilized at night during sleep and, in severe cases, during the day. Punctal plugs help retaining ocular surface lubrication by preventing the escape of liquid through the lacrimal outflow system.

Local injection of corticosteroid into the orbit has been used with variable reports of success (72, 73). Overall, however, there are limited data on the topic, and larger studies are needed to confirm efficacy. There are risks of orbital injection, the most serious of which include retrobulbar hemorrhage and elevation of intraocular pressure. In addition, the procedure is limited by the need for specific expertise in orbital anatomy.

Ongoing/Upcoming Clinical Trials in TED

Other Immunosuppressants

RVT-1401 is a fully human anti-neonatal Fc receptor (FcRn) monoclonal antibody that has been studied in a Phase 2a multicenter, open trial in 7 patients with moderate-to-severe TED (NCT03922321). RVT-1401 interferes with the intracellular recycling of immunoglobulins, decreasing their half-life.
The antibody decreased total serum immunoglobulin G by 56% to 70%, mean serum TRAb by about 60%, mean proptosis by 1.3 mm, and achieved overall proptosis response in 42% of patients (unpublished data). A subsequent Phase 2b study (NCT03938545) was terminated by premature unmasking of treatment assignments necessitated by a program-wide review. Its results have not been published.

A Phase 2b multicenter, randomized clinical trial of TCZ vs IVGC (NCT04876534) is underway and estimates to recruit 64 patients by the end of 2022. Parameters of both disease inactivation and improvement will be measured as end points.

A variety of other agents addressing proposed pathogenic mechanisms are also under study, with very little data currently. A number of these agents are listed in Table 2.

**Anti-vascular Endothelial Growth Factor Injections**

Increased blood vessel density in orbital fat has been demonstrated histopathologically in patients with active TED, compared with that in healthy controls and chronic TED. In addition, histological staining of orbital fat specimens with podoplanin demonstrated rare, small lymphatic channels (74). These vascular formations suggest that angiogenesis and lymphangiogenesis may be occurring in the setting of active TED. This is of potential importance since the orbit has been considered to be devoid of lymphatic channels and, hence, at risk of orbital fluid deposition with limited means of egress. This unique characteristic of the orbital tissue may play a role in the reasons why the inflammation and edema associated with TED cause damage in the orbit but not in most other parts of the body. This study also quantitatively demonstrated an increased expression of vascular endothelial growth factor (VEGF) receptor 2 and VEGF signaling molecules VEGF-A, VEGF-C, and VEGF-D in orbital fat of patients with acute TED. Hence, anti-VEGF treatments may be beneficial to patients by reducing angiogenesis and resultant vessel leakage in the active phase of TED. Given the risks of systemic administration of these drugs, drug delivery directly to the orbit is being considered, with a clinical trial currently in planning stages.

**Subcutaneous and Oral IGF-1R Inhibitors**

More convenient drug delivery modalities are likely to evolve from the present landscape, where teprotumumab is currently infused over 1 hour every 3 weeks for 8 doses. Alternatives such as subcutaneous injection of teprotumumab or of IGF-1R inhibitors amenable to oral administration would allow for more efficient and economical drug delivery. VRDN-001 is a monoclonal antibody very similar to teprotumumab and able to inhibit the IGF-1R (75). A modified version of this antibody, termed VRDN-002, has preliminarily shown excellent pharmacokinetics when administered subcutaneously to monkeys (76). A clinical trial is in the planning stages for an existing oral IGF-1R inhibitor, linsitinib, to study whether a response similar to those seen with teprotumumab can be achieved.

**Targeting the TSHR**

Given the new model for the pathogenesis of TED as previously described, inhibition of the TSHR is an attractive strategy. In addition to interfering with the mechanism responsible for TED, such a treatment could also treat hyperthyroidism as an added benefit. A human monoclonal TSHR-blocking antibody named K1-70 can completely inhibit the effect of a potent TSHR-stimulating antibody in rat thyroid glands in vivo (77). Preclinical studies in rats and monkeys showed no off-target effects of K1-70 (78). K1-70 has been administered to a patient with long-standing TED and thyroid cancer. The patient experienced complete resolution of CAS and significant reduction of proptosis (79). No significant side effects were described. While this report is limited by the potential confounding effect of concurrent antineoplastic therapy, it supports the concept of the direct involvement of TSHR activation in TED but clearly paves the way to potential future clinical applications. A Phase I clinical trial with K1-70 in GD patients is currently under way (NCT02904330).

Small molecule TSHR inhibitors are also being actively developed and studied. Such agents would offer the advantage of oral use, more favorable pharmacokinetics, and lower production costs (80). In recent years, several molecules have been described and reported, with variable activity (81). These allosteric antagonists do not interfere with TSHR-TSH binding, but rather interfere with TSHR signal transduction at the transmembrane domain. The expectation is therefore for these drugs to be effective toward any TRAb mixture. Several molecules have been described that are able to inhibit TSH in vitro. A human monoclonal TSHR-blocking antibody named S37a, has been described, capable of potent TSHR inhibition, without effect on the luteinizing hormone and follicle-stimulating hormone receptors. The drug was well tolerated in mice, but more detailed toxicity studies would be needed (82). To date, no such agent has been used in humans.

**Table 2.** Additional upcoming studies listed at clinicaltrials.gov, not discussed in the text

| Drug         | Mechanism                        | Design       | Controls | Status        | Trial no.  |
|--------------|----------------------------------|--------------|----------|---------------|-----------|
| Secukinumab  | Anti-IL-17a                      | Randomized   | Placebo  | Recruiting    | NCT04737330 |
| Hydroxychloroquine | Anti-inflammatory         | Randomized   | N/A      | Not yet recruiting | NCT05126147 |
| Sirolimus    | mTOR inhibition                  | Randomized   | IVGC     | Not yet recruiting | NCT04936854 |
| Sirolimus    | mTOR inhibition                  | Randomized   | IVGC     | Not yet recruiting | NCT04598815 |
| Tamsulosin   | Catecholamine alpha receptors inhibition | Single group assignment | N/A      | Not yet recruiting | NCT04359979 |
| Bimatoprost  | Anti-prostaglandin               | Single group assignment | N/A      | Not yet recruiting | NCT03708627 |
| Doxycycline  | Inhibition of multiple cytokines | Randomized   | Placebo  | Not yet recruiting | NCT02203682 |

Abbreviations: IVGC, intravenous glucocorticoids.
Since blockade of the IGF-1R may not completely block the effect of TSHR stimulation responsible for TED symptoms, it is possible that combined TSHR and IGF-1R blockade could provide greater benefits (80). In vitro studies with a small molecule IGF-1R inhibitor, linsitinib, in combination with a small molecule TSHR inhibitor, ANTAG3, indicated a synergistic effect in inhibiting the production of hyaluronic acid by cultured orbital fibroblasts (81).

Biomarkers in TED

Given the difficulties in objectively and quantitatively assessing the various manifestations of TED, biomarkers of severity and activity have been sought. TRAb are natural candidates, and their level roughly correlates with the risk of developing TED in patients with GD and with the severity for those who already have it (83). In addition, TRAb were found to significantly but loosely correlate with CAS (R² = 0.278) (84). IGF-1R antibodies can be found in patients with TED and in controls (85), but they do not seem to correlate with the disease or its severity (86). As previously mentioned, cholesterol levels are higher in patients with TED, but there is no correlation with TED severity or activity. While these markers, together with other epidemiological risk factors, are of interest in offering some prediction for the occurrence or severity of TED, they are for the most part proximal to the pathogenic events and are therefore not likely to reflect responses to treatment. For example, if blockade of the TSHR resulted in improvement of TED, one would not expect a drop in TRAb following treatment. There is a need for biomarkers that are distal to the pathogenic events being treated to provide measurable correlates of response to treatment. One such example is the measurement of serum and urine glycosaminoglycans, which have provided encouraging correlations in early studies (87), but have not been revisited in recent years.

Conclusions

Until recently, immune suppression and surgery have been the mainstays of treatment for TED patients, often yielding imperfect results. In the past few years, it has become clear that the interaction between stimulating TRAb and the TSHR/IGF-1R complex on the orbital fibroblast is one of the primary events leading to many of the manifestations of TED. This has stimulated many translational and clinical studies targeting this phenomenon. These studies have allowed the clinical development of teprotumumab, an IGF-1R targeted therapy, demonstrating novel benefits on TED. This drug clearly represents a major advance in the field, especially given its effect on proptosis and diplopia, which have been largely unaffected with medical therapies developed earlier. Further studies are needed with regard to its adverse effects on the auditory system and on its long-term efficacy. Inhibition of the TSHR either alone or in combination with IGF-1R inhibition is another attractive potential therapeutic path, possibly with even greater target specificity. Finally, the role of immunosuppression with biologics in the treatment of TED will likely be redefined, as the available drugs may be used with the aim of targeting specific disease features (i.e., inflammation, diplopia, relapses) based on data derived from ongoing and planned randomized clinical trials.

Disclosures

G.B. received consulting and advisory board fees from Horizon Therapeutics, and consulting fees from Momenta Inc. M.S. received consulting fees from Valenza Bio Inc., speaker’s fees from IBSA, and institutional research funding from Roche and Glaxo-Smith Klein. S.K.F. received consulting and advisory board fees from Horizon Therapeutics, advisory broad fees from Viridian Therapeutics, and product development fees from Poriferous and WL Gore, and consulting fees from Medtronic. She also reports textbook royalties from Springer and Thieme.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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