A Review of Novel Medical Treatments for Thyroid Eye Disease

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ABSTRACT

Thyroid eye disease (TED) is the most common extrathyroidal manifestation of Graves’ disease. There has been no effective medication to prevent proptosis in thyroid eye disease until 2020 when the anti-IGF-1R receptor antibody, Teprotumumab, was approved by the US Food and Drug Administration (FDA), sparking increased interest in immune-based drug development. This study aims to review the newly developed drug therapy as well as conventional treatment for TED. Treatment of TED has traditionally been high-dose steroids and orbital radiotherapy, but recently there has been a paradigm shift in the treatment of TED in the US with the introduction of the therapeutic agent teprotumumab, which dramatically reduces proptosis. However, concerns remain about the development of hearing impairment as a potentially fatal complication and long-term safety. Recently, several clinical trials are underway to assess the efficacy and safety of novel drugs targeting mTORC1, IL-6, FcRN, and IGF-1R in treating TED. With the explosive increase in interest from academia and pharmaceutical companies in TED, there is anticipation for the development of drugs that are equivalent or superior to teprotumumab while being safer.

Keywords: Thyroid eye disease, Graves' disease, IGF-1R, teprotumumab, IL-6, FcRN
Introduction

Thyroid eye disease (TED), also known as Graves’ orbitopathy or thyroid-associated ophthalmopathy, is a representative extrathyroidal manifestation of Graves’ disease (GD). This condition primarily arises from inflammation and swelling of the orbital and periorbital tissues, leading to symptoms such as eyelid retraction, exophthalmos, diplopia, and dysthyroid optic neuropathy (DON) in severe cases. Consequently, changes in visual function along with cosmetic alterations can lead to a diminished quality of life (QoL) for the patient. TED occurs with various clinical manifestations in 30 to 40% of GD patients (1). While TED is mostly associated with hyperthyroidism due to GD, 10% of TED patients are euthyroid or suffering from hypothyroidism (2).

The annual incidence rate of TED stands at 16 cases per 100,000 in women and 3 cases per 100,000 in men (3). In general, the prevalence of TED is estimated to be between 90 and 305 cases per 100,000 individuals (4). In a cross-sectional study conducted in Korea involving 1632 dysthyroid patients, the prevalence of TED was found to be 17.3%, which is lower than the prevalence rate in Europe (5). Being female, being older, and having a history of smoking or radioactive iodine treatment (RAI) are risk factors for TED (6). Also, it is known that the risk of TED increases with later diagnosis and longer duration of GD (7).

Ophthalmic manifestations of TED can range from mild symptoms such as dry eye to sight-threatening symptoms such as DON or corneal breakdown (8). The most typical clinical signs are as follows: eyelid retraction in over 90%, exophthalmos in 60%, restrictive extraocular myopathy in 40%, and ocular pain or discomfort in 30% of TED patients (9). TED is classified based on its activity and severity of symptoms. The Clinical Activity Score (CAS) is most commonly used to assess the activity of TED. TED is considered active CAS 3 or more at first examination and 4 or more at successive examination: spontaneous retrobulbar pain, pain on attempted upward or downward gaze, redness of eyelids, redness of conjunctiva, swelling of caruncle or plica, swelling of eyelids, and swelling of conjunctiva (10). The successive examination includes three additional criteria: increase in proptosis, decrease in unicocular excursion, and decrease of acuity equivalent, and if four or more of these ten criteria are met, the condition is considered as active. According to the European Group of Graves’ Orbitopathy (EUGOGO), TED can be categorized by severity into mild, moderate-to-severe, or sight-threatening, based on various signs and symptoms, impact on daily life and risk to sight (11). Mild TED features minor lid retraction (<2mm), mild soft tissue involvement, and exophthalmos (<3mm), whereas moderate-to-severe TED shows more pronounced symptoms including lid retraction (≥2mm), exophthalmos (≥3mm), and diplopia, and sight-threatening TED involves DON or corneal breakdown. In a recent study among newly diagnosed GD patients, the percentages of mild, moderate-to-severe, and sight-threatening cases were 20%, 5.8%, and 0.3% respectively (12).
TED is a complex autoimmune disease, and while its precise pathological mechanism has yet to be fully explained, recent studies have begun to shed light on more detailed processes. Given the significant association between TED and GD, thyroid-stimulating hormone receptor (TSHR) antibodies (TRAb) are known to play a crucial role in pathophysiology. Recently, it has been discovered that TRAb functionally activates the TSHR in conjunction with the insulin-like growth factor 1 receptor (IGF-1R) on orbital fibrocytes (13). When the autoantibody activates both receptors, it leads to the production of a combination of cytokines that influence subsequent orbital tissue remodeling (14). These pro-inflammatory cytokines recruit inflammatory cells and induce the secretion of glycosaminoglycans such as hyaluronic acid (3). This process creates a large osmotic pressure gradient within the orbit, leading to fluid accumulation between muscle fibers which leads to muscle expansion (8). In addition, activation of the TSHR and IGF-1R can induce the proliferation of orbital fibroblasts and differentiation into adipocytes and myofibroblasts, thereby contributing to an increase in adipose tissue and overall orbital tissue volume (15). Furthermore, both T cells and B cells play integral roles in the pathophysiology of TED. T cells activate B cells via CD40/CD40L binding, promoting the production of autoantibodies and orbital fibroblasts (16). These processes can be repetitive, leading to orbital congestion, and can result in fibrosis of the extraocular muscles (EOM) if sustained over a longer period, potentially causing restrictive strabismus. As these mechanisms underlying TED are gradually being elucidated, many therapeutic approaches targeting these mechanisms are currently being developed.

**Conventional treatments**

**Conservative treatments**

As previously mentioned, the treatment strategy for TED is guided by the level of disease activity and the degree of severity. First, there is a clear evidence-based relationship between smoking and TED, where the odds of TED increase by 2.47 in patients with GD (7, 17). Therefore, cessation of smoking is important for the prevention and inhibition of the progression of TED (18). Moreover, as both hyperthyroidism and hypothyroidism exert a detrimental effect on TED, it is crucial to restore and maintain an euthyroid state through treatments such as antithyroid drugs (19). RAI treatment for hyperthyroidism has been shown to induce or exacerbate TED in 15~20% of patients (20). The occurrence of TED following RAI can be prevented by a short-term course of intravenous (IV) methylprednisolone, beginning at a dosage of 500mg per week, followed by 250mg per week for the next 2 weeks (21).
Selenium
Selenium may be beneficial for patients with mild TED. Recent research findings indicate that irrespective of the presence or absence of TED, selenium levels in patients with GD are significantly lower compared to healthy individuals (22). A randomized controlled trial (RCT) conducted in 2011 showed that patients who received daily administrations of 200μg of sodium selenite (91.2 μg of selenium) for 6 months experienced improvements in QoL and ocular symptoms, along with a reduction in the progression to severe TED by 19% (23). This is thought to be due to the effect of selenium in inhibiting inflammatory cytokines and hyaluronic acid production, as well as suppressing intracellular reactive oxygen species generation in orbital fibroblasts (24). However, this RCT occurred in selenium-deficient areas, and the impact of selenium in non-deficient areas needs to be further investigated.

Glucocorticoids
Systemic glucocorticoids have been used as a treatment for active and moderate-to-severe TED due to their anti-inflammatory and immunosuppressive effects. Specifically, IV glucocorticoids have been proposed as the first-line treatment for moderate-severe and active TED, given their superior efficacy and improved tolerability compared to oral glucocorticoids (25, 26). The most common protocol involves administering 0.5g of methylprednisolone every week for the initial 6 weeks, followed by 0.25g per week for the next 6 weeks, resulting in a cumulative dose of 4.5g (25). In a RCT conducted by Bartalena et al. in 2012, it was observed that higher cumulative doses led to higher overall ophthalmic improvement (28% in 2.25g, 35% in 4.98g, and 52% in 7.47g) (27). A high-dose regimen can be used in severe cases with diplopia, severe inflammatory signs, and exophthalmos (0.75g of IV methylprednisolone weekly for the first 6 weeks, 0.25g weekly for the next 6 weeks, resulting in a total cumulative dose of 7.5g) (11, 27). It is imperative not to exceed a cumulative dose of 8.0g of IV glucocorticoids per cycle, as it could lead to adverse effects such as hepatotoxicity (28). Furthermore, glucocorticoids should not be administered to patients with the following contraindications: recent hepatitis, hepatic dysfunction, uncontrolled hypertension, and serious cardiovascular morbidity (29). While glucocorticoids are primarily used in the treatment of moderate-to-severe and active TED, 20-30% of cases may show poor or no response, and in 20% of cases, there may be a relapse after discontinuation of medication (30).

Orbital radiotherapy
Orbital radiotherapy (ORT) has been used as an adjunctive therapy for active TED for over 60 years due to its
anti-inflammatory effect and the radio-sensitivity of orbital lymphocytes. Typically, a cumulative dose of 20 Gy is administered in 10 fractionated doses for a period of 2 weeks (31). However, there have been studies showing that administering 1 Gy/week for 20 weeks demonstrated similar efficacy and better tolerability (32). Given its long-term use, many prospective and retrospective studies have been conducted, but the efficacy for TED is still a matter of debate. There have been two RCT studies which found that ORT showed effects on diplopia and ocular motility when compared to sham irradiation, but it did not have significant effects on proptosis, CAS, or eyelid swelling (33, 34). Moreover, there is level 1 evidence suggesting that proptosis, eyelid retraction, and soft tissue changes do not improve through ORT (35). Nevertheless, it has been found that the combined use of ORT and glucocorticoids is more effective and safer than using each individually (36, 37). In a retrospective study conducted in 2016, it was observed that the combined use of ORT and IV glucocorticoids resulted in a reduction in the volume of the EOM and an improvement in ocular motility, compared to the use of glucocorticoids alone (38). While ORT is generally safe, there is a potential risk of side effects such as cataracts or radiation retinopathy.

**Mycophenolate**

Mycophenolate (MMF) acts to inhibit the proliferation of T cells and B cells and the production of antibodies by suppressing inosine monophosphate dehydrogenase. Additionally, MMF is known to inhibit the proliferation of fibroblasts (39). In a multicenter, randomized, observer-masked trial (MINGO study) involving 164 patients with active and moderate-to-severe TED, the combination of MMF 360 mg every other day for 24 weeks with IV methylprednisolone showed improvement in the composite ophthalmic index (eyelid swelling, CAS, exophthalmos, lid width, diplopia, and eye muscle motility) compared to steroid monotherapy (40). In a meta-analysis conducted in 2022, the use of MMF alone or in combination with glucocorticoids showed higher response rates, efficacy, and fewer adverse events compared to the use of glucocorticoids alone (41). The EUGOGO also suggests a regimen of 0.72g of MMF sodium daily for 24 weeks in combination with IV glucocorticoids (cumulative dose of 4.5 g over 12 weeks), as a first-line treatment for moderate-to-severe and active TED (11).

**Cyclosporine**

Cyclosporine is an immunosuppressant that inhibits calcineurin, a protein that activates T-cells, thereby suppressing the proliferation of T-cells and the production of interleukin-2. In one RCT, the combined use of cyclosporine and oral prednisolone showed better ophthalmic outcomes than the use of oral prednisolone alone (42). In another RCT, improvements in exophthalmos and visual activity were observed when cyclosporine and
prednisolone were administered together in patients who did not respond to glucocorticoids (43). As a result of these findings, the concurrent use of cyclosporine and oral glucocorticoids is considered a second-line treatment for moderate-to-severe and active TED (11). However, there are yet to be significant results regarding the use of cyclosporine alone, and further research is needed.

**Novel treatments**

**IGF-1R targeting agents**

The IGF-1R plays an important role in the pathogenesis of TED, leading to the development of new drugs targeting the IGF-1R. Teprotumumab is a human monoclonal antibody that binds to the extracellular portion of IGF-1R, blocking activation. It was approved by the US Food and Drug Administration (FDA) in 2020, making it the first drug approved for the treatment of TED. The safety and efficacy of teprotumumab for moderate-to-severe and active TED have been well established through two RCTs. In a phase 2 study conducted in 2017 (44), teprotumumab was administered every 3 weeks for 8 cycles, initially at a dose of 10 mg/kg and subsequently at 20 mg/kg. The results showed that 69% of patients in the teprotumumab group had an improvement of at least 2 points in CAS or a decrease of at least 2mm in proptosis, which was more effective compared to a 20% improvement in the placebo group. A phase 3 study (OPTIC) conducted in 2020 (45) showed that the proportion of patients who demonstrated a decrease of at least 2mm of proptosis after 24 weeks was higher in the teprotumumab group than in the placebo group (83% vs 10%). Significant differences were observed in mean change in proptosis (-2.82 mm vs -0.54mm), CAS (59% vs 21%), diplopia (68% vs 29%), and QoL (13.79 points vs 4.43 points), with the teprotumumab group having consistently better results. Furthermore, the OPTIC study was able to confirm a decrease in EOM and orbital fat volume, as well as in EOM inflammation measured by MRI, after treatment with teprotumumab (46). Combining the two studies, adverse events occurred in 80% of the 84 patients who received teprotumumab, and in 71% of the placebo group, with 94% of these being mild to moderate (grade 1 or 2) adverse events (47). The most common adverse events included muscle spasms, nausea, alopecia, diarrhea, fatigue, hyperglycemia, and hearing impairment (47). Among these, hearing impairment is a concerning adverse event that requires further research. In a prospective observational study involving 27 patients, new-onset otologic symptoms were observed in 22 individuals (81.5%) after a mean of 3.8 infusions of teprotumumab (48). From these symptoms, conditions like tinnitus (100%), ear plugging (100%), and autophony (83.3%) mostly resolved, however, only 45.5% of patients with hearing loss returned to baseline.

In 2022, an extension study of the OPTIC study (OPTIC-X) was conducted, targeting patients from the OPTIC
study for which proptosis did not respond to treatment and those who experienced disease flare (49). In patients who had initially been treated with a placebo (OPTIC) and later administered teprotumumab in the OPTIC-X study, a proptosis reduction of at least 2mm was observed in 89% of placebo-treated patients, with a mean change of -3.5mm, mirroring the outcomes of the OPTIC study. The median TED duration in this study was 12.9 months. Compared to the OPTIC study, which had a duration of 6.3 months, this showed that patients with a longer disease duration could have similar results to those treated early. There have also been studies indicating that teprotumumab is effective in treating stable and chronic TED. In a retrospective study involving 31 patients suffering from TED for over two years, the administration of teprotumumab resulted in improvements in inflammation, diplopia, strabismus, and orbital soft tissue volume, including a mean reduction of 3.5mm in proptosis (50). Moreover, in a study of 21 patients with various grades (mild, moderate, severe, DON) and stages (active or stable) of TED, improvements were observed in CAS, proptosis, and duction, regardless of the clinical subgroup (51). However, additional placebo-controlled RCTs are necessary to elucidate the effect of teprotumumab in chronic TED.

Due to the drawback of teprotumumab requiring a total of 8 IV infusions for administration, the development of an IGF-1R inhibitor that can be administered through subcutaneous injection or oral administration for improved convenience is currently underway. Recently, research on linsitinib, an oral inhibitor of IGF-1R, has been progressing. Linsitinib is a highly selective small-molecule dual inhibitor for IGF-1R and the insulin receptor. It binds to the cytoplasmic tyrosine kinase domain, thereby suppressing the intrinsic tyrosine kinase activity of IGF-1R (52). Recent research using an experimental mouse model demonstrated that linsitinib effectively prevented autoimmune hyperthyroidism in early-therapy group and reduced immune infiltration in orbit in late-therapy group, suggesting its potential as a novel treatment for TED (53). At present, a phase 2b RCT is underway to investigate the efficacy and safety of linsitinib in active TED (ClinicalTrials.gov identifier: NCT05276063).

Research on subcutaneously administered IGF-1R antibodies is actively being conducted, and among them, a phase 1,2 RCT comparing lonigutamab with a placebo is in progress (ClinicalTrials.gov identifier: NCT05683496). Clinical trials are also underway for VRDN-001, a full antagonist antibody of IGF-1R, with two phase 3 RCTs investigating safety and efficacy in active (ClinicalTrials.gov identifier: NCT05176639) and chronic TED patients respectively (ClinicalTrials.gov identifier: NCT06021054). Additionally, the modified form of this drug, VRDN-002, preliminarily showed a desirable pharmacokinetic profile when administered subcutaneously in monkeys (54).
Rituximab

Rituximab is a chimeric monoclonal antibody of human and mouse origin that targets the antigen CD20 on B cells, leading to B cell depletion. Various studies have been carried out to assess the effects of rituximab on TED, yielding conflicting results. A RCT conducted in Italy in 2015 compared the effects of rituximab and IV methylprednisolone in 31 patients (55). 24 weeks later, the rituximab group demonstrated a 100% reduction in the CAS, proving to be more effective than the methylprednisolone group, which showed a 69% reduction. Moreover, five instances of disease reactivation were observed in the methylprednisolone group, whereas none were observed in the rituximab group. However, improvements in proptosis or diplopia were not observed. A meta-analysis of 152 TED patients revealed that while rituximab decreased the CAS and TRAb levels compared to the baseline, it did not affect proptosis (56). On the contrary, a RCT conducted in the US at Mayo Clinic found that rituximab showed no effect on improving the CAS, including proptosis and diplopia, compared to a placebo (57). Comparing these two RCTs, the one conducted in Italy had an average TED duration of 4.5 months, while the one conducted in the US had an average duration of 12 months. Hence, rituximab could be a more effective treatment method for TED patients with a shorter disease duration (58). Adverse events occur relatively commonly, with mild infusion reactions (10-30%) which is generally well tolerated and mild (59).

IL-6 targeting agents

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that activates T cells and B cells, and promotes the expression of TSHR in orbital fibroblasts. In a RCT conducted on 32 patients with moderate-to-severe corticosteroid-resistant TED, it was observed that the CAS decreased more effectively in the tocilizumab, a monoclonal antibody targeting IL-6 which is indicated in various autoimmune disease such as rheumatoid arthritis compared to the placebo group (93.3% vs 58.8%, results at 16 weeks post-administration) (60). Additionally, a reduction of 1.5mm in exophthalmos was observed in the tocilizumab group at both 16 and 40 weeks, while no change was noted in the placebo group. However, no significant differences in the CAS were observed in the results at 40 weeks between groups. Infections and headaches constituted a high proportion of adverse effects, and neutropenia and hypercholesterolemia were also observed. In a case series study involving 9 patients with TED, subcutaneous tocilizumab was found to be effective in improving the CAS and decreasing thyroid-stimulating immunoglobulins (61). A phase 2 RCT comparing tocilizumab and IV methylprednisolone is currently underway (ClinicalTrials.gov identifier: NCT04876534). A phase 3 multinational RCT is also in progress to evaluate the efficacy and safety of satralizumab, another monoclonal antibody against IL-6 which is approved to treat neuromyelitis optica spectrum
disorder (NMOSD) (ClinicalTrials.gov identifier: NCT05987423). The recently developed long-acting anti-IL-6 antibody, TOUR006, is currently undergoing a phase 2 RCT comparing TOUR006 20mg, 50mg, and placebo in active TED patients (ClinicalTrials.gov identifier: NCT06088979).

**Sirolimus**

Sirolimus is a macrolide immunosuppressant used to prevent organ rejection after transplantation. It targets the mammalian target of rapamycin (mTOR), which regulates cell growth and proliferation, and possesses anti-fibrotic characteristics by acting on myofibroblasts (62). Sirolimus, by inhibiting the mTOR complex 1 (mTORC1) involved in adipogenesis, also has the effect of reducing adipogenesis (63). Since adipogenesis and fibrosis play a significant role in the pathogenesis of TED, sirolimus can be a potential treatment for TED. Moreover, as sirolimus blocks the downstream signaling of IGF-1R (64), it may hold further significance in the treatment of TED. Another advantage is that sirolimus, due to its relatively small dosage, rarely results in side effects (65). In a case study, administration of sirolimus to a TED patient unresponsive to corticosteroids and conventional immunosuppression resulted in improvements in diplopia and fields of binocular single vision after 15 months (66). In a recent observational, single-center clinical study, the effects of oral sirolimus and IV methylprednisolone were compared among 30 patients with moderate-to-severe and active TED (67). The study found that, after 24 weeks, the proportion of patients who showed improvement in two or more measures (CAS, exophthalmos, lid aperture, eye muscle ductions, and visual acuity) was significantly higher in the sirolimus group than in the methylprednisolone group (86.6% vs 26.6%). There was also greater improvement in QoL in the sirolimus group, and no serious adverse events were observed. However, as there are currently no results from RCTs on the effects of sirolimus, the efficacy needs to be substantiated. Currently, two phase 2 RCTs are in progress to compare the effects of sirolimus and methylprednisolone (ClinicalTrials.gov identifier: NCT04598815, NCT04936854).

**Statins**

Statins competitively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the key-limiting enzyme in cholesterol synthesis, and have the effect of reducing low-density lipoprotein (LDL) cholesterol and decreasing cardiovascular risk. Additionally, statin possesses anti-fibrotic and anti-inflammatory properties (68, 69). More specifically, statins are known to decrease TNF-α and IL-6, which are involved in the pathogenesis of TED (16, 70, 71). Recent studies have focused on the role of cholesterol in TED and medications that reduce cholesterol. A retrospective study published in 2018 revealed a positive relationship between LDL cholesterol and
TED in patients with recent onset GD (72). Two cross-sectional studies have found that statins can reduce the risk of progression to TED in patients with GD (73, 74). There are also emerging studies suggesting that statin therapy can be effective not only in preventing but also in treating TED. Reynolds et al. conducted a study on 30 patients with both TED and restrictive strabismus; those who used statins underwent fewer decompressions and surgeries, and exhibited less restriction and muscle involvement compared to nonusers (75). Lanzolla et al. conducted a phase 2 RCT comparing the administration of both atorvastatin and IV methylprednisolone versus IV methylprednisolone alone in patients with moderate-to-severe and active TED (76). The study found improvements in the overall combined response (exophthalmos, CAS, eyelid, and diplopia) and QoL in the group that received statins. The statin group also showed fewer TED relapses (0% vs 15%), and no serious adverse events. In addition, a phase 3 RCT is planned as an extension of this study (ClinicalTrials.gov identifier: NCT05049603). Another phase 3 RCT comparing the group receiving simvastatin with the non-treatment group is also underway (ClinicalTrials.gov identifier: NCT03131726). A recent systematic review also confirmed that statin therapy can contribute to the prevention and treatment of TED with fewer adverse events (77).

**FcRN targeting agents**

The neonatal Fragment Crystallizable Receptor (FcRN) plays a role in protecting IgG from intracellular degradation and increasing its half-life. Recently, monoclonal antibodies that target FcRN are emerging as treatments for autoimmune diseases such as myasthenia gravis and immune thrombocytopenia, including TED (78). Batoclimab (IMVT-1401), a fully human monoclonal antibody to FcRN, can block this IgG recycling process, thereby reducing the levels of IgG and consequently decreasing the pathogenic TRAb (79). In an open-label, multicenter, phase 2a study (ASCEND-GO 1, ClinicalTrials.gov identifier: NCT03922321), the effects of batoclimab were evaluated following six weeks of subcutaneous injections in seven patients with moderate-to-severe TED. Serum IgG and TRAb decreased by 64.8% and 56.7% respectively compared to the baseline, with four out of seven patients showing an improvement of 2 points or more in CAS and three patients experiencing a reduction in proptosis (79). However, a subsequent double-blinded, phase 2b study (ASCEND-GO 2, ClinicalTrials.gov identifier: NCT03938545) was terminated due to an increase in total cholesterol and LDL levels in patients administered with batoclimab. Currently, a multi-center, quadruple-masked, phase 3 study is underway to observe the effect of batoclimab on proptosis (ClinicalTrials.gov identifier: NCT05517421, NCT05524571). Furthermore, efgartigimod (Vyvgart), an FDA-approved FcRN antagonist for myasthenia gravis treatment, has recently initiated a phase 3 RCT to evaluate its efficacy and safety compared to placebo in active and moderate-
to-severe TED patients (ClinicalTrials.gov identifier: NCT06307626, NCT06307613). The ongoing clinical trials referenced in this paper are summarized in Table 1.

**TSHR targeting agents**

Various studies have been conducted targeting TSHR, which plays a crucial role in the pathophysiology of TED. The TSHR-blocking antibody, K1-70, has demonstrated a dose-dependent reduction in total T4 and free T4 levels as well as TRAb in rat thyroid glands in vivo (80). In a case report where K1-70 was administered to a patient with follicular thyroid cancer, GD, and TED, there was a decrease in serum thyroid-stimulating antibody level, and amelioration of proptosis and inflammation was observed (81). In a phase 1 clinical trial conducted on 18 patients with TED, K1-70 was found to be safe and well-tolerated, with no significant immunogenic response observed (82). Due to the inability to fully control the progression of TED by blocking IGF-1R alone, combining an IGF-1R inhibitor and a TSHR inhibitor could yield greater benefits. In vitro study where linsitinib and a small molecule TSHR inhibitor, ANTAG3, were used in combination, a synergistic effect was observed in inhibiting the production of hyaluronic acid in orbital fibroblasts (83).

**Conclusion**

TED severely impacts patients' QoL due to its significant aesthetic deformities such as proptosis and lid retraction, as well as functional impairments like diplopia and visual acuity decline. Despite this, effective drugs for improving proptosis have been lacking, making treatment more challenging. However, recent developments in antibodies blocking the IGF-1R, such as teprotumumab, have sparked increased interest and development in new medications. While teprotumumab has been approved in the US, recent RCTs of teprotumumab in active TED have been conducted in Japan; however, hearing impairment remains a major side effect to address. Teprotumumab as well as high-dose steroids, as disease modulators, are expected to reduce inflammation during the active inflammatory phase, thereby reducing sequelae of the condition. Drugs like rituximab and orbital radiotherapy, on the other hand, are anticipated to reduce the duration of active inflammation as disease modifiers. Teprotumumab has shown great effectiveness in reducing proptosis, making it challenging for other drugs to compete in this aspect. However, like steroids, proptosis may recur after discontinuing teprotumumab. There is hope for the development of drugs that address these drawbacks and effectively cover both the modulating and modifying roles, leading to further advancements in TED treatment. Active research is underway on novel IGF-1R inhibitors like linsitinib, as well as medications targeting IL-6 and FcRN, with the aim of potentially treating
TED. If long-term data on these novel drugs continues to accumulate, the treatment paradigm for TED could undergo continuous transformation. Therefore, there is a constant need for more in-depth research into the mechanisms and new, safe drug development through research and development.
REFERENCES


Table 1. Ongoing clinical trials for novel drugs targeting thyroid eye disease

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IV = intravenous; SC = subcutaneous