Current Understanding of the Progression and Management of Thyroid Associated Orbitopathy: A Systematic Review

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ABSTRACT

Thyroid associated orbitopathy (TAO) is a common diagnosis encountered by ophthalmologists and oculoplastic surgeons. TAO has a varying clinical presentation that can include upper eyelid retraction, restrictive strabismus, proptosis, exposure keratopathy, and optic neuropathy. In this review, we discuss the most recent literature on and the current understanding of the pathophysiology of TAO. We also review available and potential future treatment options for the management of TAO.

Key Summary Points

- Thyroid associated orbitopathy (TAO) is an inflammatory condition affecting the orbit and adnexa.
- Patients with thyroid abnormalities should be screened for TAO and referred to a multidisciplinary TAO group early in the disease course.
- Corticosteroids have been the standard of care for severe active disease since the 1960s.
- Rituximab has shown mixed results in the control of active disease.
- Tocilizumab has demonstrated efficacy in reducing the clinical activity score and proptosis in a small RCT.
- Teprotumumab, an IGF-1R antibody in clinical trials, has shown efficacy in treating active disease and reducing proptosis in a phase III trial.

INTRODUCTION

Thyroid associated orbitopathy (TAO), also known as Graves’ orbitopathy (GO) and thyroid eye disease (TED), is a disabling and disfiguring...
inflammatory condition affecting the orbit and ocular adnexa. TAO is associated with distinct clinical features, including upper eyelid retraction, restrictive strabismus, and proptosis. In certain cases, TAO can be vision threatening due to compressive optic neuropathy or corneal decompensation from exposure keratopathy.

A 2017 prospective study by the European Group on Graves’ Orbitopathy (EUGOGO) determined the overall prevalence of TAO in a European population to be 10 per 10,000 persons [1]. The prevalence of moderate to severe disease was 2.96–4.45 per 10,000 persons, while the prevalence of vision-threatening disease was lower at 0.18 per 10,000 persons. Previous cross-sectional studies have found that 2% of TAO cases are vision threatening [2, 4]. The incidence is higher in females than males in all age groups, with the 40–60 year-old age group exhibiting the highest incidence in both men and women [3, 5]. Among patients with TAO in the Olmstead County, Minnesota population, Bartley found that 90% had Graves’ hyperthyroidism, 3% had Hashimoto’s thyroiditis, and 5% were euthyroid [5].

In addition to the morbidity associated with TAO, there is a significant impact on quality of life. Patients have difficulty with important activities of daily living, including reading and driving [6]. Further, the impact on quality of life score increases with the severity of the disease [6]. TAO has been associated with increased rates of anxiety and depression, which is partially attributable to altered cosmetic appearance [7]. Patients, particularly younger patients and women, report decreased confidence and increased social isolation, which affects mood and increases anxiety and depression [7, 8]. It is important to recognize the psychosocial component of TAO to improve clinical care.

In this review, we discuss the natural history and course of TAO. The current understanding of the pathophysiology and mechanism of disease progression is reviewed. Additionally, we review the most recent advances in medical treatment and discuss potential future therapeutic options.

**METHODS**

We performed a systematic review of the PubMed database, focusing on the most recent studies and clinical trials on the medical management of TAO. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

**NATURAL HISTORY OF TAO**

TAO manifests initially as an acute active phase. The active phase is mediated by the innate immune system. Though the pathophysiology of TAO is not yet completely understood, orbital fibroblasts are believed to be the key cells that are responsible for the soft tissue inflammation and muscle enlargement associated with the disease (Fig. 1). Activation of orbital fibroblasts that express insulin-like growth factor-1 receptor (IGF-1R) and thyrotropin receptor leads to the production of proinflammatory cytokines, including IL-6, IL-12, IL-17, IFN-γ, and TNF-α [9, 10] (Fig. 2).

The upregulation of proinflammatory cytokines leads to increased production of hyaluronan by orbital fibroblasts. Deposition of hyaluronan and increased adipogenesis results in enlargement of orbital soft tissues. Hyper trophy of the extraocular muscles and expansion of the orbital fat component lead to the characteristic clinical findings of strabismus, eyelid retraction, and proptosis in TAO [11–15]. The active phase of TAO occurs when inflammatory clinical characteristics are changing and

**Fig. 1** Coronal CT image demonstrating enlargement of extraocular muscles in thyroid eye disease

![Coronal CT image demonstrating enlargement of extraocular muscles in thyroid eye disease](image)
Fig. 2 Representative figure demonstrating the complex interaction of the immune system, proinflammatory cytokines, and autoantibodies on orbital fibroblasts leading to the clinical characteristics of thyroid associated orbitopathy. Sites of action of targeted therapies are displayed. Reproduced with permission from the Department of Art as Applied to Medicine, The Johns Hopkins University School of Medicine
progressive. The active phase can last up to 24 months (as described by Rundle) and is then followed by an inactive phase [16]. The active phase can be prolonged or the disease can be reactivated by certain risk factors, including smoking [17].

The clinical features that develop in TAO vary between patients depending on the severity of their disease. The severity of TAO is determined by the presence or absence of specific clinical features, and there are many clinical severity and activity scores available to monitor disease course for clinical and research purposes, including the European Group on Graves’ Orbitopathy (EUGOGO) [18, 19], VISA (Vision, Inflammation, Strabismus, Appearance) [20], NOSPECS [21, 22], and CAS (Clinical Activity Score) [23] scores. The EUGOGO classification identifies mild disease as the presence of mild lid retraction (< 2 mm), mild exophthalmos (< 3 mm), mild soft tissue involvement, and corneal exposure that is responsive to topical lubrication. Moderate to severe TAO is defined as lid retraction > 2 mm, exophthalmos > 3 mm, moderate to severe soft tissue involvement, and presence of diplopia. Sight-threatening TAO is defined as presence of direct optic neuropathy or corneal breakdown (Table 1).

**Drivers of Disease Progression**

Progression of TAO varies among individual patients. Males and smokers are more likely to have severe disease [24]. In a study of 59 untreated patients with mild disease observed over the course of a year, 13.5% of patients had a progressively worsening clinical course [25]. Additionally, it is known that younger patients are more likely to have orbital fat expansion while older patients are more likely to develop extraocular muscle enlargement [24, 26, 27].

Smoking is a well-known risk factor for both the progression of TAO and for more severe disease [28–30]. It has been shown that hypoxic cell culture conditions induce increased adipogenesis in orbital fibroblasts, suggesting a possible mechanism by which smoking may lead to disease progression and more severe disease states [31]. Furthermore, passive or second-hand smoke exposure has been shown to worsen Graves’ disease and may worsen ophthalmopathy, as shown in childhood TAO [32, 33]. All smokers should be counseled on the association of smoking with worse clinical outcomes including risk of blindness, and the importance of smoking cessation should be emphasized at clinic visits.

Radioactive iodine (RAI) treatment has been associated with increased risk of active disease compared with thyroid medication [34, 35]. Interestingly, there was no significant difference in the rate of ophthalmopathy between RAI and thyroidectomy. Steroid prophylaxis is recommended in patients with preexisting TAO while undergoing RAI treatment.

Smoking and RAI are known risk factors for a more severe disease course; however, it is difficult to predict which patients will have more severe disease in the absence of these specific risk factors. It is important to follow patients closely after initial presentation to establish an understanding of their disease progression and

| Disease Severity          | Clinical Features                                      |
|---------------------------|--------------------------------------------------------|
| Mild Graves’ ophthalmopathy | Lid retraction < 2 mm                                  |
|                           | Mild soft tissue involvement                           |
|                           | Exophthalmos < 3 mm                                   |
|                           | No diplopia or transient diplopia                     |
|                           | Exposure keratopathy responsive to lubrication        |
| Moderate-to-severe Graves’ ophthalmopathy | Lid retraction > 2 mm                                   |
|                           | Moderate to severe soft tissue involvement            |
|                           | Constant or inconstant diplopia                       |
|                           | Exophthalmos > 3 mm                                   |
| Sight-threatening Graves’ ophthalmopathy | Presence of optic neuropathy                         |
|                           | Presence of corneal decompensation                    |

Table 1 Adapted from the European Group on Graves’ Orbitopathy severity classification [18, 19]
to encourage them to notify the clinician of any significant clinical changes.

**TREATMENT MODALITIES**

**Selenium**

Selenium plays a role in the cellular redox maintenance and may reduce reactive oxygen species [36–38]. A large multicenter, randomized, double-blinded, placebo-controlled trial was performed comparing selenium 100 µg twice daily versus placebo in patients with mild TAO. The primary outcome was overall ocular improvement and quality of life measured at 6 months of treatment. There was a significant improvement in both overall ocular improvement and quality of life at 6 months which continued at 12 months with discontinuation of selenium [39]. While there was an observed benefit and no adverse events associated with selenium treatment, one controversy regarding this data is that the study was performed in areas of Europe that are known to be selenium deficient [39]. Additional studies in areas that are not selenium deficient are warranted to determine its role in the treatment of mild disease. Given its low side-effect profile, many clinicians will recommend selenium supplementation in patients with mild TAO [39].

**Corticosteroids**

Corticosteroids have been the mainstay first-line treatment in TED since the 1960s [40]. Corticosteroids are steroid hormones that are used to modulate the immune system and reduce inflammation in a myriad of medical conditions. In vitro studies have shown that corticosteroids reduce activation of proinflammatory cytokines in orbital fibroblasts [41, 42].

The EUGOGO classification is used to determine the need for treatment (Table 1). According to EUGOGO guidelines, intravenous glucocorticoids are advised in moderate to severe active disease, while surgical rehabilitation is recommended in moderate to severe inactive disease [18, 19]. Sight-threatening TED demands immediate intervention, while mild disease can be monitored without intervention. The clinical activity score can be used to determine if the disease is active or inactive (Table 2) [23]. Cases of moderate to severe active disease should proceed with intravenous glucocorticoid therapy followed by rehabilitative surgery once the disease becomes inactive. In cases of sight-threatening disease, an initial trial of two weeks of intravenous glucocorticoid therapy is recommended, and urgent decompression should be performed if there is no improvement.

The recommended dosing for orbital inflammation without diplopia is 500 mg weekly for 6 weeks followed by 250 mg weekly for 6 weeks. If diplopia is present, the recommended dosing schedule is 750 mg weekly for 6 weeks followed by 500 mg weekly for 6 weeks total [43]. The total cumulative dose of corticosteroids should not exceed 8 g. Comparative studies of intravenous versus oral corticosteroids have demonstrated a significant benefit from intravenous administration. Intravenous administration was found to be more effective and required fewer surgeries than oral therapy [43, 44]. When the clinical course has stabilized, rehabilitative surgery should be considered to

| Table 2 | Adapted from the Clinical Activity Score (CAS). A score of 3 or greater is indicative of active disease that would be responsive to immunosuppressive therapy [23] |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Spontaneous orbital pain | 1 |
| Pain on up or down gaze | 1 |
| Eyelid erythema | 1 |
| Conjunctival erythema | 1 |
| Eyelid edema | 1 |
| Chemosis | 1 |
| Caruncular inflammation | 1 |
| Increase in proptosis of 2 mm or more between 1 and 3 months | 1 |
| Decrease in visual acuity of 1 or more lines between 1 and 3 months | 1 |
| Decrease in motility of 5 or more degrees between 1 and 3 months | 1 |
address clinical symptoms including proptosis, diplopia, and lid retraction.

Contraindications to glucocorticoid therapy include hepatitis or liver disease, uncontrolled diabetes, hypertension, and severe cardiovascular disease. Patients are often comanaged with a primary care physician or endocrinologist to monitor glucose levels and blood pressure while on treatment.

Rituximab

Rituximab is a humanized chimeric monoclonal anti-CD20 antibody. Extraocular muscles and orbital fat have been shown to have lymphocytic infiltration during the active phase of TED. Additionally, TSH receptor antibodies (TRAb) have been shown to be elevated in the onset of active disease [45]. Rituximab targets B cells, which leads to B cell depletion and therefore may affect autoantibodies to the TSH receptor.

Stan et al. conducted a prospective randomized controlled study with 21 patients randomized to two 1000 mg rituximab infusions or two saline infusions two weeks apart. The primary outcome was a reduction in CAS score at 24 weeks. This study did not meet its targeted sample size, and demonstrated no significant benefit of rituximab compared to placebo [46]. Another double-blinded, randomized trial by Salvi et al. demonstrated improved outcomes with rituximab compared to IV methylprednisolone. In this study, 32 patients were randomized to receive rituximab (1000 mg twice or 500 mg once) or IV methylprednisolone (7.5 g). At 24 weeks, all rituximab patients had improved, compared with 69% of the methylprednisolone patients [47].

Rituximab is typically well tolerated. The most common side effects are hypotension, transient fevers, and pruritus. Serious adverse events including dysthyroid optic neuropathy, vasculitis, and sudden death have been reported [46, 48]. Results of these trials are contradictory, and no other randomized controlled studies have been performed to further elucidate the utility of anti-CD20 therapy in thyroid eye disease.

Tocilizumab

Tocilizumab is a humanized monoclonal anti-IL-6 antibody. It has been shown that fibroblasts increase the secretion of IL-6, leading to increased adipogenesis. Small case series have also demonstrated a reduction in inflammation on biopsy of orbital fat [49] and a reduction in TSI [50] following tocilizumab therapy.

Perez-Moreiras performed an interventional, nonrandomized study of 18 patients with active thyroid eye disease refractory to intravenous corticosteroids. Patients were administered tocilizumab therapy and were found to have reductions in CAS score, TSI levels, proptosis (72%), and extraocular motility (83%). These results are limited by the small and nonrandomized design of this study [51].

The Tocilizumab for Graves’ Orbitopathy study group conducted a masked randomized control trial of 32 patients randomized to intravenous tocilizumab 8 mg/kg at 0, 4, 8, and 12 weeks versus placebo. All patients had moderate to severe disease that did not respond to corticosteroids. There was a significant difference in the number of patients who achieved the primary outcome, a change in CAS score of at least 2, with 93.3% of patients in the tocilizumab group achieving this endpoint compared to only 58.8% of controls. In addition, there was a 1.5 mm reduction in proptosis in tocilizumab patients compared to no change in proptosis in controls. Thus, there are promising data supporting the use of tocilizumab to treat TAO [52].

Teprotumumab

Teprotumumab is a human monoclonal IGF-1R antibody. Though IGF-1R is a widely expressed receptor, IGF-1R expression is increased on fibroblasts from the orbit, skin, and thyroid of patients with Graves’ disease. The upregulation of IGF-1R and the TSHR in orbital fibroblasts has been proposed to lead to the accumulation of hyaluronan within orbital fat and muscle [10, 53, 54].

Teprotumumab has been evaluated in clinical trials. Smith et al. conducted a phase 2
placebo-controlled, double-blinded study enrolling patients with moderate to severe active TED [55]. 88 patients were enrolled in this study and were administered infusions of teprotumumab or placebo every 3 weeks for 24 weeks. The patients were stratified by smoking status, though there were more smokers in the placebo group than the active drug group. This study demonstrated a reduction in both clinical activity score and proptosis at 24 weeks. Infusions were associated with few severe adverse events, including diarrhea and Hashimoto’s encephalopathy, which were thought to be associated with the study drug. Additional side effects included nausea and muscle spasms, and diabetic patients were noted to have developed hyperglycemia.

This study was particularly significant, as this is the first medical therapy that has demonstrated a reduction in proptosis. Douglas determined that patients with higher baseline proptosis had a greater response to teprotumumab than patients with lower baseline proptosis (mean reduction 3.7 vs. 2.6 mm) [53]. Further, there was improvement in proptosis in all gender- and smoking-stratified groups. The results of the phase II trial are somewhat limited by the higher number of smokers in the placebo group.

More recently, data from the phase III trial have been presented. The phase III trial confirmed the results of the phase II trial. There was a significant difference in proptosis reduction between the teprotumumab group and the placebo group at weeks 6, 12, 18, and 24. Data from secondary endpoints are yet to be presented at the time of this review [56, 57].

Teprotumumab is a promising medical therapy for the treatment of TAO. Further studies will be needed to evaluate the results of this therapy in patients with inactive disease and to compare its efficacy to those of tocilizumab, rituximab, and other immunomodulators.

Orbital Radiotherapy

Orbital radiotherapy is a well-established treatment for TAO. Orbital lymphocytes and fibroblasts are sensitive to radiation treatment. Standard dosing is a total of 20 Gy bilaterally over two weeks, though some studies indicate a lower dose may be effective in appropriate patients [58]. Older studies have shown that orbital radiotherapy is as effective as corticosteroid treatment and that a combination of steroid and radiation is more effective than either modality alone [59, 60].

A recent study was conducted with 40 patients with moderate to severe disease resistant to high-dose corticosteroid therapy. Patients were given 20 Gy in 10 fractions with concurrent 500 mg methylprednisolone weekly. 32.5% of patients had a regression in diplopia and there was a median reduction in CAS score of 2. Treatment was well tolerated, with 7.5% of patients developing cataract and 12.5% of patients developing dry eye [61]. Additionally, Bartalena et al. conducted a randomized trial of 48 patients which confirmed that combined therapy is superior to steroids alone in patients with moderate to severe disease [62].

Additionally, low-dose radiotherapy has been shown to be effective. Cardoso et al. conducted a study where 18 patients received 10 Gy over 10 weeks. All patients in the study showed improvements in ocular pain, motility, and edema [63]. Additionally, Kahaly performed a randomized blinded trial comparing radiation doses. The study showed that low dose (1 Gy/day) and high dose (2 Gy/day) were equally effective. Low-dose radiation therapy may reduce side effects, including retinopathy, cataract formation, and secondary tumors [58].

Orbital radiotherapy is an important adjuvant to steroid therapy in the appropriate patient with active moderate or severe TAO. The side effects are limited, and multiple studies have consistently demonstrated the treatment’s efficacy.

Surgical Management

Despite appropriate medical therapy, nearly 20% of patients with TAO will require some form of surgical therapy. The EUGOGO consensus guidelines propose urgent orbital decompression in vision-threatening disease if there is a poor response to corticosteroids. There
are multiple treatment algorithms for surgical decompression, including balanced decompression, medial and floor decompression, lateral wall decompression, and orbital fat decompression. Surgical management often varies based on surgeon preference and training, though results from balanced decompressions appear to be greater. A recent retrospective multivariate analysis determined that greater preoperative proptosis, balanced decompression, and history of orbital radiation were predictors of a greater reduction in proptosis after decompression [64]. In cases of compressive optic neuropathy, posteromedial decompression is recommended [65, 66]. Comparative studies of orbital decompression techniques would help define an optimal surgical management algorithm.

Rehabilitative surgery is postponed until the disease is inactive and clinical measurements are stable. The goal of rehabilitative surgery is to restore the patient to as close to the predisease state as possible. Rehabilitative surgical options include orbital decompression for severe proptosis or aesthetic concerns, strabismus surgery, followed by upper and lower lid retraction repair. Again, surgical techniques can differ based on surgeon preference and have varying degrees of success. A recent survey of members of the American Society of Ophthalmic Plastic and Reconstructive Surgeons demonstrated that the majority of survey respondents prefer a balanced medial and lateral decompression as their first approach [67]. More research is needed to compare the outcomes of different surgical approaches and determine an optimal decompression protocol.

FUTURE MEDICAL THERAPIES

Additional therapies have been proposed and are in varying stages of study for efficacy in TAO. Methotrexate has been used to effectively treat autoimmune diseases such as rheumatoid arthritis. Its mechanism of action is the inhibition of the enzyme dihydrofolate reductase, which interferes with DNA and protein synthesis and in lower doses has anti-inflammatory properties. A retrospective review demonstrated an improvement in both CAS score and motility restriction with methotrexate therapy [68]. Prospective data have not been presented.

TNF-α is known to be upregulated in TAO. Several studies have evaluated the use of TNF-α antagonists. In a retrospective review of adalimumab in TAO, six of 10 patients showed a reduction in inflammation; however, three patients had an increase in inflammation [69]. Infliximab has been shown to be beneficial in single case reports [70]. It is difficult to interpret the utility of anti-TNF therapy with limited small-scale studies.

Cyclic peptides may be another promising avenue for future therapy. Holthoff et al. established a mouse model that was immunized with a recombinant adenovirus expressing the human TSH receptor (TSHR) [71]. Cyclic peptides were created that replicated the tertiary structure of the TSHR leucine-rich repeat domain. The cyclic peptides were able to stabilize TSH receptor-binding antibodies, reducing thyroid hyperplasia and improving retro-orbital fibrosis [71]. This is an encouraging result in an animal model, and future confirmatory animal studies may lead to translation to clinical therapy for TAO.

Other potential targets on the inflammatory cascade include the interleukin pathway. IL-17 is known to be upregulated in many autoimmune diseases [72], and targeted therapies against IL-17 have shown promise in psoriasis and ankylosing spondylitis [73, 74]. Further, IL-15 and IL-17 are upregulated in patients’ tears in active disease compared with inactive disease. A targeted therapy to IL-15 or IL-17 may have a role in the management of TAO [75]. Other avenues of potential study should include targeting hyaluronan synthesis, adipogenesis, and fibroblast differentiation.

CONCLUSIONS

Thyroid associated orbitopathy is a debilitating and vision-threatening disease. The pathophysiology is yet to be completely elucidated; however, TAO is understood to be an inflammatory disease. Activation of proinflammatory cytokines results in increased hyaluronan
production by orbital fibroblasts, leading to the classic clinical manifestations of TAO.

Patients with thyroid abnormalities should be screened and educated about the signs and symptoms of TAO. Upon diagnosing TAO, a referral to a TAO specialist multidisciplinary group should be made early in the course of the disease per the Thyroid Eye Disease Amsterdam Declaration Implementation Group UK (TEAMeD) guidelines [76]. A multidisciplinary group including oculoplastic surgery, strabismus surgery, and neuro-ophthalmology can closely monitor patients for disease progression and implement appropriate medical and surgical therapy.

Oral selenium supplementation is recommended in mild disease, given the low risk and potential benefit. Corticosteroids remain the mainstay first-line treatment in active moderate-to-severe and vision-threatening disease. Intravenous corticosteroids have been shown to be superior to oral administration. Orbital radiotherapy is an important adjuvant to corticosteroid treatment, and low-dose radiation may be adequate in the treatment of TAO.

Biologic agents have demonstrated potential as therapeutic alternatives or adjuncts in the treatment of TAO. The data on rituximab is contradictory and thus will require future analyses to determine its efficacy. Tocilizumab studies did demonstrate an improvement in disease state; however, the trials were limited by size.

The results of the teprotumumab clinical trials are of great interest. Teprotumumab is the first therapy to demonstrate an improvement in proptosis and therefore may reduce the need for orbital decompression. We anticipate that teprotumumab will play an important role in the medical management of TAO.

Surgical management is still required in cases of severe vision-threatening disease that is refractory to medical management, and as restorative treatment when the disease is quiescent. The management of TAO has evolved significantly and will continue to do so. We anticipate significant improvements in the management of TAO patients with the use of upcoming biologic agents and targeted therapies.

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