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Thyroid Eye Disease: Towards an Evidence Base for Treatment in the 21st Century

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Abstract

Thyroid eye disease (TED) is the most common extrathyroidal manifestation of Graves' disease. Incomplete understanding of its pathogenesis has hindered development of targeted therapies that might alter the natural course of disease. Smoking cessation and maintenance of euthyroidism appear to reduce the rate of onset and severity of TED. Recent evidence suggests that selenium may lessen the inflammatory symptoms in mild disease. Corticosteroids remain the primary treatment for patients with moderate to severe active TED. Surgical decompression is commonly undertaken in the chronic stable phase, and only rarely in the active phase when vision is threatened by compressive optic neuropathy. Orbital radiotherapy remains an adjunctive strategy during active disease. Targeted immunotherapies have the potential to alter disease progression, but further evidence is needed to establish safety and efficacy. In this article, we review evidence from prospective therapeutic trials of several treatment modalities. We focus on moderate to severe active TED.

Keywords

Thyroid eye disease; Graves' ophthalmopathy; Graves' orbitopathy; Thyroid-associated orbitopathy; Graves' disease; Immunotherapy; Orbital radiotherapy; Rituximab; Treatment; Evidence-based; Review

Introduction

Thyroid eye disease (TED), also referred to as Graves' orbitopathy or ophthalmopathy, is the most common extrathyroidal manifestation of Graves' disease (GD), affecting up to 60% of patients. Despite our detailed understanding of the etiology of hyperthyroidism in GD, the pathogenesis of TED remains uncertain. This has limited development of targeted therapies, particularly those that alter the disease course. Meanwhile, several small randomized controlled trials (RCTs) have examined the efficacy of corticosteroids and orbital radiotherapy in TED. The quality of these studies is variable and some findings are conflicting. This review summarizes the results of recent RCTs and prospective studies that impact management. We place an emphasis on potential preventive strategies, as well as those reserved for patients with moderate to severe disease not responding to corticosteroids.

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Disclosure

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Larger RCTs are needed to evaluate the efficacy of newer therapies, such as those depleting B cells.

TED usually begins with an active, progressive phase, where orbital and periorbital inflammation can last for 6 to 24 months. Expansion of extraocular muscles (EOMs) and orbital fat occurs during this period, and can result in proptosis, compressive optic neuropathy (CON), and compromised EOM motility [1]. TED is sight-threatening in up to 5% of patients [2].

Onset of hyperthyroidism and TED usually occur within 18 months of one another, although a small subset develops ocular manifestations many years before or after the onset of hyperthyroidism. A small minority of patients never develop thyroid dysfunction and are referred to as having euthyroid GD [3]. The majority of patients with TED have mild, self-limiting disease. Up to 20% to 30% of patients with more severe TED benefit from anti-inflammatory treatment [4]. Nonetheless, even patients with mild disease experience a reduced quality of life comparable to patients with life-threatening illness such as breast cancer [5]. Unfortunately, currently available therapies do not appear to alter the natural course of TED even though they provide symptomatic relief [6]. RCTs play an essential role in determining the efficacy of candidate therapies and assessing their potential for altering the natural progression of disease. Such therapies would obviate the need for rehabilitative surgery, which restores anatomy and cosmesis but not eye muscle or eyelid function.

Clinical Classification

A brief review of disease classification and risk factors will now be undertaken. Assessment of disease activity is one of the most challenging facets of managing TED. This results from a lack of biomarkers and the continued reliance on clinical signs and symptoms, many of which wax and wane. Nonetheless, the ability to define disease activity is critical to both RCT design and the evaluation of therapies. The Clinical Activity Score (CAS), a system based on inflammatory symptoms, has been employed since its validation in 1997. It was developed as a tool for identifying active disease and predicting response to corticosteroid therapy [7, 8]. While the advent of CAS has improved patient assessment and provided a metric for response in clinical trials, more precise measures are needed. This is a central goal of the European Group on Graves' Orbitopathy (EUGOGO) and the International Thyroid Eye Disease Society (ITEDS) [9, 10]. Measures of disease severity may aid treatment decisions based upon cost-benefit analyses. The EUGOGO Consensus Statement supports the classification of disease severity as mild, moderate to severe, and sight threatening [9].

Modifiable Risk Factors

Smoking

Studies conducted in monozygotic twins reveal concordance rates of 30% to 60%, suggesting that both genetic and environmental factors contribute to the pathogenesis of GD [11]. Smoking has been identified as an important contributing environmental factor in the development of GD. In a matched case-control study of same-sex twin pairs, of which 34% were monozygotic, Brix et al. [12] found that among those concordant for smoking, the twin with GD had a history of smoking more often than did their healthy sibling. This difference was not observed in patients with non-autoimmune thyroid disease. Ample evidence from nonrandomized trials implicates smoking in the pathogenesis of TED as well. A meta-analysis of six studies demonstrated a greater than fourfold increased incidence of TED among smokers with GD [13]. A subsequent systematic review of 15 studies by Thornton et al. [14] also identified a strong correlation between smoking and disease progression with a reduced response to therapy (relative risk [RR] 0.73; 95% CI, 0.62–0.85; $P < 0.001$).

Currently, no prospective evidence supports the efficacy of smoking cessation in reducing risk of TED. Nonetheless, retrospective studies suggest that stopping tobacco use is associated with less severe TED, especially with regard to the development of diplopia and proptosis [15]. In a prospective study of 253 patients with new-onset GD, the greatest dose-dependent correlation between cigarette smoking and TED concerned diplopia [16]. Heavy smokers carried an RR that was sevenfold greater than that in nonsmokers (95% CI, 3.0–16.5; $P < 0.0001$), while former smokers were not at significantly increased risk (RR 1.8; 95% CI, 0.5–7.7; $P = 0.38$). Additionally, heavy smokers had an RR for proptosis of 3.37 (95% CI, 1.5–7.6; $P = 0.003$), while that of former smokers was similar to nonsmokers (RR 0.9; 95% CI, 0.2–3.3; $P = 0.87$) [16]. Smoking may either delay or reduce the efficacy of treatment. A retrospective study of 150 patients with severe TED who were treated with orbital radiotherapy combined with oral corticosteroids responded at a rate of 94% in nonsmokers compared to 68% in smokers [17]. A subsequent prospective trial of 60 patients with moderate TED treated similarly also revealed that nonsmokers had better initial responses to therapy [18]. In aggregate, evidence supports smoking cessation as a strategy for minimizing progression of TED and improving response to treatment.

Thyroid Dysfunction

Thyroid dysfunction is associated with more severe TED. In a retrospective study, patients with dysthyroidism were nearly threefold more likely to develop severe TED compared to their euthyroid counterparts [19]. Thyroid functional status and TED severity were assessed 12 months after diagnosis of TED, and 18 months following the detection of hyperthyroidism. In another study, the rate of TED progression after radioiodine (RAI) therapy was reduced by promptly initiating thyroid hormone replacement and thus maintaining euthyroidy [20]. Both studies were retrospective, but a third prospective trial of 443 patients found that patients with elevated TSH following RAI were at increased risk of development or progression of TED during 12 months following thyroid ablation [21]. Overall, these findings suggest that control of thyroid function could mitigate the severity of TED, and suggest monitoring thyroid function every 4 to 6 weeks during the initial phase of TED [9].

Treatment: Mild TED

Of patients with TED, the majority have mild disease. Symptoms include dry eye and mild diplopia, which are easily treated with artificial tears, ointments, and prisms. The symptoms and signs of mild TED typically improve spontaneously. Conservative therapy is recommended should moderate to severe disease develop. However, many patients with mild TED experience reduced quality of life, as assessed by a Graves' orbitopathy specific quality-of-life questionnaire (GO-QOL) [22]. Effective treatments for mild disease with acceptable side-effect profiles have been limited until recently. Very recently, an RCT compared the efficacy of selenium or pentoxifylline to placebo in 159 patients with mild TED [23•]. Selenium is an essential trace element possessing antioxidative and anti-inflammatory properties. Patients in each arm were treated for 6 months, at which time treatment with selenium, but not pentoxifylline, was associated with improved QOL, decreased eyelid aperture and soft tissue signs, and slowed progression of TED compared to placebo. CAS decreased in all groups, but the change was significantly greater in the selenium-treated patients and was durable after 12 months (1.3 and 1.2 CAS points at 6 and 12 months, respectively). This study has been criticized for failing to assess serum selenium levels [24, 25]. Additionally, the potential impact of normalized eyelid aperture on QOL and CAS may have resulted in an overestimate of selenium's beneficial effects. Soft tissue signs and eyelid aperture are difficult to quantify with current techniques, making small changes in either difficult to interpret. Further studies aimed at verifying the efficacy of selenium in

mild TED are warranted. Nonetheless, this study provides evidence that selenium may represent a well-tolerated and effective therapeutic strategy in mild TED.

Treatment: Moderate to Severe TED

Corticosteroids

Corticosteroids are the most commonly used medical therapy for active, moderate to severe TED. These agents alleviate the symptoms associated with inflammation [6]. However, whether they alter disease outcome remains uncertain. Results from three RCTs suggest that intravenous (IV) corticosteroids are more effective at reducing inflammation and cause fewer adverse events than orally administered agents [26–28]. Efficacy was evaluated as a reduction in CAS. Corticosteroids failed to decrease proptosis, diplopia, lid aperture, or improve visual acuity. These studies involved total doses of 4.0 to 4.5g, administered over 12 to 14 weeks. A prospective, nonrandomized trial of 82 patients compared oral prednisone and IV methylprednisolone. Subjects in both arms were also treated with a standardized radiotherapy dose [29]. While this study was limited because substantially different corticosteroid doses were administered to the two groups (9–12 g IV vs 6 g oral), patients receiving IV corticosteroids achieved greater reduction in CAS. In aggregate, data from RCTs and prospective trials suggest that IV corticosteroids are more effective than oral corticosteroids in the treatment of TED.

Corticosteroid therapy is complicated by side effects, including decreased bone density, weight gain, liver failure, hypertension, infections, gastric ulcers, glucose intolerance, and death in aggregate doses exceeding 8 g [30]. Administration of less than 8 g of IV methylprednisolone minimizes risk of hepatotoxicity, but close monitoring of liver function, blood sugar, and blood pressure remains necessary.

Periocular and orbital corticosteroid administration has been proposed as a strategy for minimizing systemic side effects [31, 32], but studies have demonstrated limited efficacy. The first RCT by Marcocci et al. [33] showed that retrobulbar corticosteroids were less effective in reducing the ophthalmopathy index than those administered systemically when combined with radiotherapy. Subsequently, a prospective nonrandomized study found that patients treated with periorbital corticosteroids experienced improved ocular motility compared to untreated controls. However, significant differences in baseline ocular motility between the two treatment groups may limit the validity of this study [34]. Patients with active TED (CAS = 4) treated with peribulbar triamcinolone demonstrated similar improvement of CAS but manifested fewer side effects than those treated with oral corticosteroids in another study [35]. These findings support the contention that locally administered corticosteroids appear relatively safe, but larger trials are needed to establish their efficacy.

Radiotherapy

Orbital radiotherapy was initially used to treat TED patients during the 1970s [36]. Conflicting results from several studies have called its efficacy into question. Design deficiencies and poor standardization limit the impact of those studies. In a recent review and meta-analysis of three RCTs, Steibel-Kalish et al. found only modest improvement of EOM motility [37, 38] and diplopia [37] in patients treated with orbital radiotherapy compared to sham-irradiated controls [37–39, 40]. The benefit was not clinically important since patients in the two groups ultimately required strabismus surgery at similar rates. Moreover, they demonstrated similar GO-QOL and subjective eye scores [37].

Bradley et al. [41] reviewed published studies of orbital radiotherapy in TED, including nine randomized trials and five observational studies. While findings from observational studies

suggest that orbital radiotherapy lessens eyelid swelling and proptosis, retrospective analysis and selection bias confound this conclusion [42, 43]. Furthermore, several studies have identified an increased risk of radiation-induced retinopathy in diabetic patients [43–45]. In conclusion, radiotherapy should play a minor role in the treatment of non sight-threatening TED.

Cyclosporine

Cyclosporine has been evaluated in active TED in two RCTs [46, 47]. These studies showed that this agent is not as effective as oral corticosteroids in reducing inflammation. However, the combination of oral corticosteroid and cyclosporine may be superior to oral steroids administered as a single agent, suggesting that it might be steroid-sparing. Whether cyclosporine adds benefit to IV corticosteroids has not been examined.

Somatostatin Analogues

The therapeutic potential of somatostatin analogues for patients with TED was based on identification of somatostatin receptors in diseased orbital tissue and on orbital fibroblasts [48]. Results of pilot studies utilizing long-acting agents such as octreotide and lanreotide appeared promising, but efficacy has not been sustained in four RCTs [49–52]. Thus, somatostatin analogues cannot be recommended for the treatment of TED.

Rituximab

Rituximab is an anti-CD20 chimeric, humanized, monoclonal antibody that targets mature B cells [53]. B cells are involved in the pathogenesis of autoimmune disease by virtue of their ability to generate pathogenic antibodies, present antigen, and produce cytokines. While a randomized, prospective clinical trial has yet to be completed, these agents have garnered significant interest. Four studies examining their efficacy in TED have been published, including 28 patients with moderate to severe TED, several of whom were steroid-resistant. These patients were treated with a dose of rituximab routinely used in rheumatoid arthritis (two doses of 1 g administered 2 weeks apart). These studies suggest that this regimen reduces the CAS within 1 month of treatment, and is sustained for at least 1 year [54, 55•, 56, 57]. Salvi et al. [55•] found a greater CAS reduction in nine patients treated with rituximab compared to 20 others treated with IV methylprednisolone (8 g over 16 weeks). The short- and long-term side-effect profiles of rituximab were examined recently in 20 patients with GD [58]. Most commonly, infusion reactions and serum sickness-like reactions were described. Notably, patients receiving IV corticosteroids experienced significantly more adverse events than those treated with rituximab [55•]. Because robust RCTs have yet to establish the efficacy of rituximab in TED, this agent is currently reserved for patients with moderate to severe, active disease who respond poorly to corticosteroids.

Other

Evidence for efficacy of several other therapeutic strategies has been derived from uncontrolled prospective trials or small RCTs. These will require larger studies with comparisons to current therapies such as corticosteroids before they can be considered further.

Anti-Tumor Necrosis Factor- α (TNF- α) Antibodies—Cytokines such as TNF- α are suspected of being involved in the pathogenesis of autoimmune diseases such as GD and TED. An uncontrolled prospective pilot study of etanercept in 10 patients with mild to moderate TED showed a reduction in CAS of 2.4, and subjective improvement in 60% of patients at 12 weeks [59].

Intravenous Immunoglobulin (IVIG)—Two studies, including one RCT and another nonrandomized prospective trial, have evaluated the efficacy of IVIG compared to oral prednisone in severe, active TED [60, 61]. These showed similar efficacy between the two groups, but significantly fewer side effects with IVIG.

Plasma Filtration—A recent RCT compared plasma filtration with or without IV corticosteroids in 20 patients with severe, active TED [62]. Plasma filtration seemed to lower CAS at 1 month compared to patients treated with IV corticosteroid alone, but differences were not maintained at 3 months.

Colchicine—Colchicine is approved for the treatment of gout and familial Mediterranean fever, but is used widely in the treatment of pericarditis and Behçet's disease as well [63, 64]. The drug has been shown to modulate prostanoid production and inhibit neutrophil activity, resulting in anti-inflammatory effects [65]. An RCT comparing 22 patients treated with oral colchicine or oral prednisone demonstrated similar reductions in CAS, but patients treated with colchicine experienced fewer side effects [66].

Treatment: Sight-Threatening TED

Sight can be threatened in up to 5% of patients with TED [67]. Crowding at the orbital apex, which results from EOM enlargement, can result in CON. To determine optimal treatment for CON, Wakelkamp et al. [68] conducted an RCT in Europe comparing the efficacy of urgent orbital decompression surgery versus IV methylprednisolone as first-line treatment. Patients found unresponsive to the initial therapy were switched to the second treatment arm. Improvement was observed in nearly all cases. It was notable that patients first treated with surgery more often required switching than patients initially receiving corticosteroids (85% vs 45%, respectively). However, only 4 of 10 patients undergoing surgical decompression experienced side effects, primarily transient numbness of facial skin. In contrast, 12 of 14 patients treated with IV corticosteroids gained weight and became cushingoid. It must be noted that this study has not been replicated in North America, where early decompression surgery is performed more routinely. While additional randomized trials are needed, both strategies appear effective in treating CON.

Conclusions

Improving therapeutic options in TED has proven to be an arduous process. This has resulted in large part from the uncertainty surrounding its pathogenesis [69]. Recruiting patients to large RCTs has proven challenging [70] but completion of these studies is critical to therapy development. Marcocci et al. [23••] recently reported results of a well-designed RCT in mild TED that should provide a framework for future studies in this patient group. Use of IV corticosteroid therapy in the active phase of TED is supported by substantial evidence of its benefits. Surgical rehabilitation is ultimately required in as many as 80% of patients with moderate to severe disease. Orbital radiotherapy appears to improve EOM motility abnormalities and diplopia in the active phase, although results remain conflicting. Enthusiasm for biological agents that target specific aspects of disease pathogenesis appears justified [71]. Currently, rituximab represents the most promising immunomodulatory therapy in moderate to severe TED. RCTs are needed to confirm its efficacy.

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