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Advances in the Management of Thyroid Eye Disease

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Thyroid Eye Disease (TED)

Thyroid eye disease (TED) is a term used to describe a combination of adnexal and orbital findings that occurs most commonly autoimmune thyroid disease. Typical findings in TED include proptosis, upper eyelid retraction with temporal flare, conjunctival injection, chemosis, and periorbital edema (Figure 1). The clinical manifestations of TED often lead to morphologic facial changes that are disfiguring, and may lead to reduced quality of life. Additionally, potential sight-threatening morbidities of TED include exposure keratopathy, optic nerve compression and diplopia. Primary risks factors for TED are environmental influences especially smoking but also prior pathogen exposures, stress and previous use of radioiodine in addition to a complex genetic component [1]. TED more commonly affects women compared to men with a ratio of approximately 5 to 1 [2].

TED is a self-limited condition that manifests in two phases. The initial phase or active phase is characterized by fluctuating inflammatory course over months to years that eventually transitions into a non-progressive phase. Typically, after the resolution of the active phase, there may be mild but incomplete improvement of the associated signs. Unfortunately no treatments are available at this time to prevent disease progression and subsequent permanent facial disfigurement. The mainstay of therapy during the active phase is observation. Systemic corticosteroids may provide symptomatic improvement but seldom halt disease progression. Corticosteroids are also associated with a variety of well-known adverse effects, which may limit treatment. Once the disease reaches a non-progressive phase, the mainstay of treatment remains surgical. Surgical rehabilitation is staged to include orbital decompression, strabismus surgery, and eyelid surgery to improve the disease manifestation.

Pathogenesis

TED is most commonly associated with Graves' disease occurring in 25–50% of patients [3, 4], however it is also associated with Hashimoto's thyroiditis, thyroid carcinoma, primary hyperthyroidism, and primary hypothyroidism. The endocrine manifestations of Graves' Disease are secondary to autoantibody formation to the thyrotropin receptor (TSHR) causing either hyper-stimulation or blockade of the receptor signaling. The role of these thyroid stimulating antibodies (TSI's) is unclear in TED, and the underlying pathogenesis of TED remains poorly understood.

There is broad consensus in the field that orbital fibroblasts are the primary cellular target of the autoimmunity [5–7]. Graves' disease autoantibodies from GD patients have been shown to cause activation of orbital fibroblasts, stimulating release of cytokines and synthesis of extracellular matrix components [8–10]. This in turn may drive a complex, secondary, cell-

based inflammatory response in the orbit. Orbital fibroblasts have a distinct phenotype, and are immunocompetent by virtue of cytokine and chemokine production [11]. These chemoattractants are thought to orchestrate T lymphocyte infiltration [11]. Activated endomysial fibroblasts also produce glycosaminoglycans (e.g. hyaluronan) and collagen, causing edema and fibrosis [12]. Additionally, a subpopulation of orbital fibroblasts appears capable of undergoing adipocyte differentiation [13].

Autoantibodies generated to the Insulin-like growth factor 1 receptor (IGF-1R) also exist in TED patients, and may be responsible, in part, for the pathogenesis of TED [14]. The IGF-1R is highly expressed by orbital fibroblasts from TED patients and appears to be a potential second autoantigen [15]. Antibodies to the IGF-1R are found in the vast majority of patients with GD, and stimulate the production of T cell chemoattractants. IGF-1R is also over-represented on the cell surface of T and B lymphocytes from GD patients, compared to controls (REF). Other potential autoantibodies include those directed against eye muscle proteins (63 kDa and 64 kDa) and retro-orbital fibroblasts (23 kDa). These antibodies are frequently detected in sera of patients with TED, but their role in disease pathogenesis is unclear [16]. The molecular underpinnings of TED are likely multifactorial, and specific therapies have been difficult to develop. Recent research, however, has revealed new potential therapeutic targets.

Multidisciplinary Approach

As the pathogenesis of TED is better characterized, the need for a patient centered, multidisciplinary approach has become more obvious. Careful and coordinated consideration of individual patient needs requires input from various specialists throughout the disease process, with the endocrinologist and ophthalmologist being the primary providers. TED patients require careful endocrine monitoring to maintain euthyroidy, and often require definitive treatment of their underlying thyroid condition by means of radioactive iodine therapy or thyroidectomy. Furthermore, the use of immunosuppressive therapies or biologic agents may require the expertise of a rheumatologist. Smoking cessation is also important, since smoking has been shown to increase both the incidence and severity of TED [17, 18]. Patients must be given all the necessary resources and counseling to achieve smoking cessation as quickly as possible.

Several academic centers throughout the country have established multidisciplinary thyroid eye disease teams to facilitate communication and share in treatment decisions on an individual patient level. The goal is to provide all the necessary subspecialty care at a single institution, in a coordinated fashion, and to create a multidisciplinary forum to optimize patient-centered care delivery (Figure 2). These centers also seek to better raise awareness in the community, thus helping to diagnose and treat patients in a more efficient manner.

Management of TED

The management of TED may be subdivided into two categories: management of active TED and management of non-progressive TED.

Traditional Therapies for Active TED

For patients with mild TED, supportive care including ocular surface management offers substantial benefit. Selenium supplementation has also been examined for the treatment of mild, active TED. Selenium is a trace mineral and an essential nutrient for selenocysteine synthesis, which has antioxidant properties. In one study, patients with mild TED were given selenium (100 µg twice daily) and followed for six months. They had a significant improvement in the clinical activity score versus placebo, with no adverse effects reported

[19]. Selenium has been linked to increased risk of Type II Diabetes, but only in doses exceeding 400mcg per day [20]. It is important discuss these data with patients prior to initiating selenium therapy.

During the active phase of TED, corneal exposure can be severe resulting in excruciating pain and loss of vision. Severe exposure must be recognized early, and steps must be taken early to ensure proper ocular surface lubrication and prevent vision-threatening sequelae. Options include artificial tears, ointments, gels and topical cyclosporine [21]. Additionally, the clinician may use punctual plugging or cauterization. Surgical procedures such as tarsorrhaphies may also be necessary in cases of severe or vision threatening corneal exposure.

Management of moderate to severe active TED may require systemic anti-inflammatory medications in order to mitigate the risk of vision loss. TED patients with reduction of visual acuity, visual field deficits, color deficits or afferent pupillary defects are treated promptly with systemic corticosteroids, and some require emergent orbital decompression surgery for compressive optic neuropathy. Systemic corticosteroids may be administered orally or intravenously. Intravenous administration, while potentially less convenient, appears more efficacious and better tolerated. In a study by Macchia et al [22], 25 patients with TED were treated with twice weekly infusions of 1 g of methylprednisolone for 6 weeks, and were compared to a group of 26 patients treated with oral prednisone at a dose of 60–80 mg/day progressively reduced every 2 weeks for a total duration of 4–6 months. Both groups achieved the same level of improvement in signs and symptoms of orbital inflammation, but the intravenous group reported no significant side effects whereas the oral treatment group reported typical side-effects associated with oral steroid therapy. Radiation therapy (RT) has also been used as treatment for active TED. The role of RT for treatment of active TED, however, is controversial. It remains a viable option for patients who cannot tolerate systemic corticosteroid therapy. With a dose of 20 Gy in 10 fractions, one group has reported 96% stabilization of TED with RT, with complete resolution of symptoms in 46% of patients [23]. In this study, most patients received concomitant therapy with corticosteroids. Reports of the effectiveness of orbital radiation in TED are quite variable. Orbital irradiation may provide a small incremental improvement of TED manifestations, but given the paucity of published clinical validity, lack of mechanistic or pathogenic role, and unclear clinical indications, it is difficult to make the case for widespread implementation.

Corticosteroids or observation are the mainstay of therapy in active TED. Corticosteroids are powerful general immunosuppressive agents with well-characterized, but potentially severe adverse effects. Significant research elucidating the pathogenesis of TED will hopefully fuel development of targeted therapies.

Biologic Therapies for Active TED

Immunomodulatory therapies, which target the underlying molecular basis of disease, are being considered as alternatives for TED patients unable to tolerate corticosteroids. Individual cellular constituents of the immune system may be targeted as demonstrated by the anti-B cell drug, Rituximab. Alternatively targeted disruption of cytokines instrumental in the pathogenesis can be considered. Rituximab is a monoclonal chimeric antibody to CD20, a transmembrane protein present on immature and mature B cells but not plasma cells. Currently it is approved for treatment of non-Hodgkin lymphomas, chronic lymphocytic leukemia and rheumatoid arthritis. Rituximab effectively depletes the CD20 B cell population for 6 to 9 months. Rituximab treatment for TED has shown preliminary promise with the vast majority of patients demonstrating improvement in the clinical activity

score and sustained efficacy for greater than 18 months [24]. Optimal dosing is yet unclear and published doses have ranged from 1000mg per infusion for 3–4 infusions, to as low as 100mg in a single infusion. Salvi et al. noted improvement in visual acuity as short as 3 hours after infusion, and no relapse in disease activity in 32–86 weeks, after a single dose of 100mg of Rituximab. Two patients in this study had infusion site reactions requiring treatment with IV corticosteroids, but no other significant adverse effects were noted [24].

A prospective study was published in 2010 where 12 TED patients with active disease were treated with 1000mg of Rituximab on days 1 and 15[25]. Clinical activity scores demonstrated a statistically significant decrease from baseline at each of the follow-up visits. Thyroid-stimulating immunoglobulin and thyroid-stimulating hormone levels demonstrated no statistically significant change from baseline. B-cell depletion was observed within 1 month after rituximab treatment, and peripheral B-lymphocyte counts started to increase 36 weeks after the infusion. B-cell depletion was well tolerated, and there were no adverse effects of the rituximab infusions [25]. TSI levels remained unchanged, suggesting effect at the antigen-presenting level.

While Rituximab is not considered standard of care, it represents a potential alternative for treatment of severe, active TED in patients who demonstrate contraindication or inadequate response to corticosteroids. Rituximab has been associated with numerous adverse effects such as myelosuppression, severe mucocutaneous reactions and progressive multifocal leukoencephalopathy, but these have not been reported in any TED patients thus farREF. Rituximab must be prescribed by or in conjunction with a rheumatologist, with close follow-up and monitoring for adverse effects.

Several molecules have been studied for their role in TED but recently a growing body of evidence from ex vivo assays using orbital tissue from TED patients suggest that insulin-like growth factor 1 receptor (IGF-1R) plays important roles in regulating the autoimmune response that underlies TED. Data supporting inhibition of IGF-1R as a therapeutic strategy for TED has been published by six independent laboratories employing a range of experimental techniques including radioligand binding, immunohistochemistry, FACS fluorescence cytometry, cytokine ELISA assays, immunoprecipitation, signal transduction kinase assays, gene chips and quantitative PCR. Key evidence linking IGF-1R with the autoimmune mechanism of TED are summarized below

- Graves' autoantibodies interact directly with IGF-1R expressed on orbital fibroblasts. [26]
- IGF-1R, and proteins involved in IGF-1R signaling, are upregulated/dysregulated in orbital fibroblasts from TED patients. [7, 27]
- Graves' autoantibodies reproduce key pathophysiological responses specifically in orbital fibroblasts from TED/GD patients and these responses are mimicked by IGF-1. [10, 28]
- IGF-1R & TSHR, the two main autoantigens implicated in TED, are physically and functionally coupled in orbital fibroblasts. [7]
- Inhibiting IGF-1R completely blocks pathophysiological responses elicited by autoantibodies in orbital fibroblasts from TED patients, irrespective of the relative role of any particular autoantigen. [10]

A specific monoclonal antibody antagonist of human IGF-1R which is well-tolerated at pharmacologically active exposures is being considered for trial in TED patients.

Future Directions

The future of TED therapy will likely yield more targeted therapies, based on the biochemical mechanisms underlying the condition. The ultimate goal is early identification of TED, with effective halting and reversal of the active inflammatory process. This is will likely require individual tailoring of therapy, based on diagnostic studies that reveal which autoimmune pathways are most active in a particular patient. Biologic therapies appear to hold the key to achieving this goal.

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Figure 1.

a. Typical clinical appearance of a patient with TED, demonstrating lid retraction, proptosis, conjunctival injection and chemosis b. Detail demonstrating marked conjunctival injection over the insertion of the medial rectus and caruncular edema in the same patient.

Old Referral Paradigm

Figure 2A

Thyroid Eye Disease Center

Figure 2B

Figure 2.

a. Old Referral Paradigm: Patients were referred from service to service with little communication between physicians b. Thyroid Eye Disease Center Paradigm. Patient-centered approach with simultaneous, coordinated care from various specialties.