Medical management of thyroid eye disease

Dawn D. Yang, MD, Mithra O. Gonzalez, MD, Vikram D. Durairaj, MD, FACS *

University of Colorado Denver School of Medicine, Department of Ophthalmology, Division of Oculofacial Plastic and Reconstructive Surgery, United States

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Abstract Thyroid eye disease (TED) is the most common cause of orbital disease in adults. The immunologic pathogenesis of TED has been an area of active research and considerable progress has resulted in an expansion of therapeutic options. Although surgical intervention may be required, a majority of TED patients can be managed with medical therapies. Of medical therapies, glucocorticoids remain the agent of choice in the control of TED activity. The objective of this review is to discuss the paradigm and options in medical management of TED.

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1. Introduction

Thyroid eye disease (TED) or thyroid-associated ophthalmopathy (TAO) is the most common cause of orbital disease in adults and is a significant cause of morbidity in patients with Graves' disease (Scott and Siatkowski, 1999; Wiersinga and Bartalena, 2002). Approximately 25–50% of patients with Graves' hyperthyroidism have TED, which can be sight-threatening due to dys thyroid optic neuropathy or corneal breakdown in 3–5% of patients (Bartalena et al., 2000; Bahn and Heufelder, 1993). Although the disease most commonly occurs in patients with a history of hyperthyroidism, 10% of affected patients are euthyroid (6%), hypothyroid (1%) or have Hashimoto’s thyroiditis (3%) at the time of diagnosis (Bartley et al., 1996; Burch and Wartofsky, 1993). Most patients can be managed with nonsurgical treatments alone, and those requiring surgical intervention often benefit from concurrent medical therapy. This review will not address the surgical treatments of TED but rather will focus on the medical management of TED.

2. Signs and symptoms

Clinical signs and symptoms arise from soft tissue enlargement leading to increased pressure within the bony orbit (Bahn and Heufelder, 1993). A majority of patients have expansion of both extraocular muscle and adipose tissue, although some patients have a predominance of one type of tissue (Forbes et al., 1986). Eyelid retraction is the most common sign of TED occurring in 75–91% of patients (Rose et al., 2005) (Fig. 1). The exact mechanism of upper eyelid retraction is unclear, although overactive sympathetic stimulation of Muller’s muscle, scarring between the levator muscle and surrounding tissues, and overaction of the levator muscle as it contracts against a tight inferior rectus muscle are possible components (Rose et al., 2005; Waller, 1982; Small, 1995). Exophthalmos develops as orbital contents expand. CT imaging can delineate between TED that results predominately from fat expansion (type 1) and TED that results predominately from extraocular muscle enlargement (type 2) (Rose et al., 2005). Patients at high risk of compressive optic neuropathy are those with enlarged extraocular muscles that crowded orbital apex. Moreover, such individuals who also lack or have minimal exophthalmos are at highest risk of compressive optic neuropathy. Strabismus is restrictive rather than paralytic, and is due to inflammation, swelling and fibrosis of extraocular muscles, particularly the inferior and medial rectus muscles. The increased exposure of the eye from either eyelid retraction, exophthalmos and a poor Bells’ reflex may lead to corneal dryness, pain, decreased blinking, lagophthalmos, chemosis, photophobia, and corneal ulcers. Periorbital edema may reflect vascular compression within the orbit and decreased lymphatic and venous drainage. Individuals with anatomic variability in size and shape of the orbit or variations in lymphatic or venous drainage may be at increased risk of manifesting the signs and symptoms of TED (Chan et al., 2009).

3. Pathogenesis

The immunologic mechanism of TED is thought to be initiated by autoreactive T lymphocytes directed against antigens that
are common to the thyroid and orbit. The thyrotropin receptor and the insulin-like growth factor I receptor are the commonly implicated shared autoantigen although confirmatory research is ongoing (Tsui et al., 2008). The autoantigen calsequestrin in extraocular muscles and collagen XIII in orbital fibroblasts are reported to be diagnostic markers of TED and may also contribute to the disease process (Gopinath et al., 2007, 2009). Mononuclear cell infiltration consisting of helper/inducer CD4+ and suppressor/cytotoxic CD8+ T lymphocytes, B lymphocytes, plasma cells, and macrophages occurs in the extraocular and levator muscles, adipose tissues, and lacrimal gland of those with TED (Bahn, 2000; Chen et al., 2008).

Early in the disease, type 1 helper T cells predominate and secrete cytokines (interleukins, interferon-γ, and tumor necrosis factor). Later in the disease process, type 2 helper T cells predominate and propagate production of antibodies that stimulate the receptors expressed on orbital fibroblasts and adipocytes (Aniszewski et al., 2000). Cytokines, auto-immunoglobulins, and CD4+ T cells expressing the CD40 ligand directly activate orbital fibroblasts to produce glycosaminoglycans (Feldon et al., 2005; Korducki et al., 1992). The cytokine cascade, fibroblast proliferation, and expansion of adipose tissue within the rigid confines of the bony orbit result in cosmetic and sight-threatening consequences.

### 4. Evaluation of thyroid eye disease

#### 4.1. Disease phase

A primary objective in the evaluation of a patient with TED is to determine the patient’s disease phase as a function of two variables: activity and severity. Discriminating between active and inactive disease is a crucial step in treatment decision making. Activity can be thought of as the degree to which the body is reacting to autoantigen. Patients with a Clinical Activity Score (CAS) ≥ 3/7 should be considered as having active TED (Mourits et al., 1989, 1997). Qualitatively, activity can be considered inactive, moderately active and severely active.

**Clinical Activity Score (Mourits et al., 1997):**

| Pain | 1. Painful, oppressive feeling on or behind the globe, during the last 4 weeks |
| Redness | 2. Pain on attempted up, side or down gaze during the last 4 weeks |
| Swelling | 3. Redness of the eyelid(s) |
| Swelling | 4. Diffuse redness of the conjunctiva, covering at least one quadrant |
| Swelling | 5. Swelling of the eyelid(s) |
| Swelling | 6. Chemosis |
| Swelling | 7. Swollen caruncle |
| Swelling | 8. Increase of proptosis of ≥ 2 mm during a period of 1–3 months |
| Impaired function | 9. Decrease of eye movement in any direction ≥ 5 deg during a period of 1–3 months |
| Impaired function | 10. Decrease of visual acuity of ≥ 1 line(s) on the Snellen chart (using a pinhole) during a period of 1–3 months |

**Severity on the other hand is the physical sequelae of activity, however, those changes may remain despite control of activity; e.g. a person may have chronic diplopia and exophthalmos although she/he has inactive disease (Fig. 2). The Consensus Statement of the European Group on Graves’ Orbitopathy recommends stratifying disease severity into the following categories to help guide treatment (Bartalena et al., 2008):**

1. **Sight-threatening TED:** patients with dysthyroid optic neuropathy (DON), eyeball subluxation, choroidal folds and/or corneal breakdown; these patients warrant immediate intervention. Treatment for DON may include steroids, surgery or both (Marcocci et al., 2001; Macchia et al., 2001; Kauppinen-Makelin et al., 2002; Kahaly et al., 2005).

2. **Moderate to severe TED:** patients without sight-threatening disease, but whose eyes have sufficient impact on quality of daily life to warrant the risk of rehabilitative surgery (if inactive) or the risks of immunosuppression and/or orbital radiotherapy (if active). Common symptoms include: lid retraction ≥ 2 mm, exophthalmos ≥ 3 mm above normal for race and gender, moderate to severe soft tissue involvement, and intermittent or constant diplopia.

3. **Mild TED:** patients with features that have minor impact on quality of daily life. Watchful waiting is appropriate for the majority of patients. Risk of immunosuppression or surgery is typically not justified in this group unless there is progression. Common symptoms include: minor lid retraction < 2 mm, exophthalmos < 3 mm above normal for race and gender, mild soft tissue involvement, transient or no diplopia, and corneal exposure responsive to lubricants (Bartalena et al., 2000). Even minor disfigurement can impact the patient’s quality of life, and intervention may be offered to patient if individualized analysis of risks and benefits favor treatment.

#### 4.2. Imaging

CT imaging is often adequate for those with TED. It is not essential in all patients, but should be considered in those with atypical presentations, e.g. strabismus affecting the lateral rectus, non-axial globe proptosis, suspected optic neu-
ropathy and before orbital decompression (Rose et al., 2005).

4.3. Serum markers

Laboratory makers provide diagnostic as well as therapeutic assistance. Therapeutically, serum markers guide and gauge response to treatment, and may help identify patients at risk for disease progression. Recent research has focused on the pathogenic role of thyrotropin receptor autoantibodies (TRAb) or thyroid stimulating hormone stimulating antibodies (TSAb), in Graves’ disease. The thyroid stimulating hormone receptor (TSHR) is over-expressed in orbital fibroblasts and adipose tissue in TED patients (Heufelder, 1995; Paschke et al., 1995; Crisp et al., 1997; Spitzweg et al., 1997). Higher levels of TSHR mRNA expression are found in patients with clinically active disease when compared to patients with inactive TED (Wakelkamp et al., 2003). Autoantibodies to thyroid antigens are associated with TED at the onset of the disease (Tsui et al., 2003; Gopinath et al., 2007, 2009; Stiebel-Kalish et al., 2010). The increased level of autoantibodies and TSHR expression in patients with TED suggests that serum markers may be useful in confirming the diagnosis.

In addition to the commonly tested serum markers, free T4, T3, thyroglobulin, and TSH, there are several additional variables that correlate with TED. Thyroglobulin (TgAb) and thyroid peroxidase (TPOAb) are both auto-immunoglobulin markers of TED. TgAb are less prevalent and less useful than TPOAb for prediction of thyroid dysfunction (McLachlan and Rapoport, 2004). The thyrotropin binding inhibitory immunoglobulins (TBII) assay quantifies the titer of auto-immunoglobulins that inhibit the binding of TSH to purified or recombinant TSHR, thereby measuring both thyroid stimulating antibodies (TSI) and thyroid blocking antibodies. Alternatively, a bioassay can be used to distinguish between stimulating- and blocking-autoantibodies via their effect on cyclic adenosine monophosphate (cAMP) in a cell line transfected with the receptor (Stan and Bahn, 2010). It is possible that yet unrecognized or undetected neutral TSHR antibodies or subsets of TSHR-directed antibodies play a role in orbital fibroblast signaling.

Older studies reported limited utility of TSHR antibody levels (Gerding et al., 2000; Feldt-Rasmussen et al., 1981; Teng et al., 1977; Wall et al., 1979; McKenzie, 1967). These studies have been criticized for using first generation TBII assays or long-acting thyroid stimulator assays (now known to be insensitive) and including patients with inactive disease (Stan and Bahn, 2010). Despite the insensitive assays, a few of these older studies did report correlation between long-acting thyroid stimulatory activity and severity of TED (Lipman et al., 1967; Morris et al., 1988; Kosugi et al., 1990).

Several newer studies investigated whether auto-immunoglobulins correlated with symptoms of TED. Two reports found a positive correlation between the prevalence of TED and levels of TSI but not levels of TBII (Khoo et al., 1999; Noh et al., 2000). Later report by Goh et al. supported this finding: TSI was a positive predictor, while TPOAb and TgAG were both negative predictors of chronic lid retraction, lid swelling, proptosis, and extraocular myopathy (Goh et al., 2004). Also, Kho et al. detail that absent autoantibodies to TPO coupled with high TSI levels identify a group at high risk for TED (Khoo et al., 1999). The simultaneous presence of TBII and TSAb (odds ratio: 4.9 activity, 9.0 severity) was significantly associated with higher activity and severity of disease than the presence of TBII without measurable TSAb (odds ratio: 2.1 activity, 2.0 severity) (Eckstein et al., 2004). Gerding et al. also found a highly significant correlation between the CAS and both TBII and TSI (Gerding et al., 2000). Recent report by Dragan et al. supports the correlation between TSI values and changes in clinical severity score (Dragan et al., 2006). In contrast, Kung et al. reported that the development of new or exacerbation of TED after radioactive iodine therapy did not correlate with TRAb titers (Kung et al., 1994).

Subsequent investigations focused on using TRAb levels to predict response to therapy. Eckstein et al. demonstrated that TBII titers remained detectable in 14 of 15 (93%) patients who were unresponsive to anti-inflammatory therapy compared to 22 of 52 (42%) patients who responded to therapy (Eckstein et al., 2004). Study by Kahaly et al. also demonstrated a decrease in TRAb that correlated with an improvement in CAS score after intravenous glucocorticoid therapy (Kahaly et al., 2005). Eckstein et al. followed TBII levels every 3 months for 12-24 months in 159 TED patients and were able to predict the TED progression (whether mild or severe) in 50% of patients (Eckstein et al., 2006). Further studies are needed to clarify the role of auto-immunoglobulin levels in the management of TED but preliminary studies suggest that they are useful in diagnosis and may be a predictor of progression risk.

5. Systemic thyroid disease

5.1. Anti-thyroid meds

Patients with TED or suspected TED should be referred to an internist or an endocrinologist for evaluation and management of systemic thyroid disease. Anti-thyroid drug (ATD) therapy may help reduce orbit-directed autoimmune reactions but does not alter the course of existing TED (Marcocci et al., 1992). However, medical management of thyroid function is essential as patients with uncontrolled hyper-and hypothyroidism are more likely to have severe TED than euthyroid patients (Prummel et al., 1990). No particular drug or drug regimen has demonstrated any advantages in the management of TED (Bartalena et al., 2008).

Methimazole, carbimazole, and propylthiouracil are the main drug treatments blocking thyroid hormone synthesis. They are frequently used in an attempt to achieve remission or as preparative therapy before radioactive iodine or thyroid surgery. After active concentration by the thyroid, the drugs inhibit thyroid peroxidase mediated iodination of tyrosine residues in thyroglobulin. Propylthiouracil had the additional benefit of inhibiting the peripheral conversion of thyroxine (T4) into triiodothyronine (T3). Decrease in thyrotropin receptor antibodies, IL-2 and IL-6 receptors, HLA class II expression, and intracellular adhesion molecule are seen with treatment; it is unclear whether these are direct effects of the drugs or are the result of normalization of thyroid function (Cooper, 2005; Laurberg, 2006). Serious side effects occur in less than 0.3% patients and include agranulocytosis, hepatotoxicity, and vasculitis (Cooper, 2005; Harper et al., 2004). Overall, the recurrence rate of hyperthyroidisms is 50–60%, with most cases occurring within 3–6 months of drug cessation.
Drug regimens are given either by the block-replace regimen (where a higher dose of anti-thyroid drug is given with a replacement dose of thyroid hormone) or by the titration regimen (where the anti-thyroid drug is reduced by titrating treatment against thyroid hormone concentrations). A meta-analysis by Abraham et al. summarized 26 randomized trials evaluating different ATD regimens (Abraham et al., 2005). Twelve trials examined the effect of block-replace versus titration regimens. The relapse rate of hyperthyroidism was similar in both groups; 51% in the block-replace group and 54% in the titration block-group (OR 0.86, 95% confidence interval (CI) 0.68–1.08). Adverse effects and withdrawing due to side effects (16% versus 9%) were significantly higher in the block-replace group. Trials that studied the effect of duration of therapy on relapse rates showed that when using the titration regimen for 12 months was superior to 6 months, but no benefit was seen by extending the treatment beyond 18 months (Allanic et al., 1990; Maugenre et al., 1999; Weetman et al., 1994; Garcia-Mayor et al., 1992). Authors concluded that 12–18 months of the titration regimen had fewer side effects but had the same efficacy than the block-replace regimen.

5.2. Radioactive iodine

Radioactive iodine (RAI), or $^{131}$I, can be given orally and is rapidly concentrated by thyroid follicular cells. The ionizing effect of $\beta$ particles induces an inflammatory response and subsequent necrosis of follicular cells. The typical amount of RAI given is 5–15 mCi to yield an absorbed radiation dose of 50–100 Gy. Following administration, thyroid function declines over weeks to months and symptoms can be managed with B-adrenergic antagonists or ATD in the interim. Due to its radioprotective effects, ATD are usually discontinued 4 days prior to administration of $^{131}$I (Bonnema et al., 2002). The period of interruption is intended to decrease the risk of relapse into hyperthyroidism and cardiovascular complications.

Radioiodine has been associated with disease progression in some patients with TED or newly diagnosed eye disease (15%). This risk is commonly mitigated with prophylactic steroid cover (0.3–0.5 mg of oral prednisone/kg body weight per day for 1–3 days after RAI) with taper until withdrawal at 3 months (Bartalena et al., 1998). Review of five randomized control trials examining the use of glucocorticoid prophylaxis with RAI showed that prednisolone was highly effective in preventing the progression of TED in patients with pre-existing TED (RR 0.03; 95% CI 0.00–0.24) (Acharya et al., 2008). Patients with inactive TED can receive radioiodine without steroid prophylaxis, as long as no other risk factors (i.e., smoking, high thyrotropin-receptor antibody > 7.5 IU/L) are present and hypothyroidism is avoided (Bartalena et al., 2008; Eckstein et al., 2006; Perros et al., 2005). Of those with exacerbation of TED, approximately 5% had worsening that persisted at one year and required additional treatment (Bartalena et al., 1989).

Long term hypothyroidism is common with an estimated incidence of 2–3% annually and is managed with thyroid hormone supplementation. The incidence of early hypothyroidism is associated with increased $^{131}$I dose, autoantibodies to TPOAb, hypoechogenicity on ultrasound, and enlarged gland (Ahmad et al., 2002).

5.3. Thyroid surgery

The goal of thyroidectomy, regardless of the type total, near total, or subtotal surgery, is to correct thyroid function while minimizing recurrence and complication rates. Hypoparathyroidism and permanent damage to the recurrent laryngeal nerve occur in at least 1–2% and rates up to 5–10% have been reported (Sosa et al., 1998). Transient hypocalcemia, wound infections, keloids, and postoperative bleeding are common complications.

Thyroidectomy has not demonstrated any advantage in the outcome of TED but is indicated for long-term control of thyroid function (Bartalena et al., 2008). Subtotal thyroidectomy carries a smaller complication rate than total or near total removal but 5–15% of patients have recurrence of hyperthyroidism (Hoffmann, 2009). Due to the high recurrence rate, total or near total thyroidectomy is typically performed. This risk of recurrence is directly related to the size of thyroid remnant, initial TSHRAb level, and the presence of TED (Werga-Kjellman et al., 2001). Total ablation may not be achieved by thyroidectomy alone. Compared to thyroidectomy alone, thyroidectomy followed by RAI is associated with better outcomes and this combination is routinely performed in order to achieve total ablation (Menconi et al., 2007).

In routine and non-urgent cases, the goal is to optimize the patient’s thyroid function before surgery. Preoperative inorganic iodine (saturated solution of potassium iodide, or SSKI) is given for 10 days to decrease blood flow to the thyroid. If the patient cannot tolerate anti-thyroid medications or requires urgent surgery, betamethasone, B-adrenergic antagonist, and SSKI can be given for 5 days before surgery (Baeza et al., 1991; Henley et al., 2006).

6. Management of thyroid eye disease

6.1. Smoking cessation

The strongest modifiable risk factor for disease progression is cigarette smoking (odds ratio among smokers versus non-smokers, 7.7 (Wiersinga and Bartalena, 2002)). A systematic review by Thornton et al. of 15 studies found dose-dependent relationship between smoking and disease severity and concluded that smokers have poorer treatment outcome (Thornton et al., 2007). In a trial of patients with newly diagnosed TED treated with either radioactive iodine or anti-thyroid drugs, smokers had the highest overall risk for the development or progression of TED irrespective of the treatment modality (Traisk et al., 2009). Smokers who undergo radioactive iodine therapy have the highest incidence of unfavorable TED outcome, and this risk is proportional to the number of cigarettes smoked per day (Stan and Bahn, 2010).

The mechanism underlying the link between cigarette smoking and TED is unclear. In vitro studies have suggested oxygen reactive species may lead to proliferation of orbital fibroblasts (Bartalena et al., 2003). Cigarette smoke extract synergized with interleukins in promoting adipogenesis in orbital tissue (Cawood et al., 2007). Smoking cessation is a crucial aspect of medical management to halt disease progression and to promote favorable treatment outcomes.
6.2. Conservative therapy

Many patients with TED can be managed with minimal intervention. Lubrication with artificial tears, gels and ointments often provide symptomatic relief. Patients may also benefit from using cool compresses, sleeping with an elevated head of bed and taping of the eyelids. If patients are symptomatic from exposure keratopathy from eyelid retraction botulinum toxin can be successfully utilized (Uddin and Davies, 2002; Shih et al., 2004) (Figs. 3A and 3B).

6.3. Intravenous corticosteroids

Glucocorticoids are used as a method of medical decompression due to their anti-inflammatory and immuno-suppressive properties. Intravenous glucocorticoid (IVGC) is a short-term and urgent treatment used to decelerate disease activity in patients with sight-threatening disease, although it may be considered in patients with active moderate to severe TED. A commonly used regimen consists of 12 weekly infusions of methylprednisolone (500 mg weekly for 6 weeks, then 250 mg weekly for 6 weeks) with a cumulative dose of 4.5 g (Kahaly et al., 2005). Patients with sight-threatening dysthyroid optic neuropathy require immediate high-dose IVGC, usually 1 g of methylprednisolone for three consecutive days with subsequent response based dose titration. If there is no improvement after 1–2 weeks, then prompt surgical orbital decompression may be considered (Bartalena et al., 2008).

The approximate percentage of positive response to IVGC is over 70% (ranges from 33% to 100%), which is higher than the response rate to oral or local corticosteroids (Bartalena et al., 2000). Two randomized trials have shown that IV therapy is more effective than oral therapy (88% versus 63% by Marocci et al. (2001); 77% versus 51% by Kahaly et al. (2005)). In a small randomized trial, immediate decompression surgery as the first choice therapy does not appear to be associated with better outcomes compared to IVGCs as the first therapy (Wakelkamp et al., 2005).

Acute and severe organ damage has been reported in sporadic cases. Marino et al. reported seven cases of acute liver damage in patients without prior overt liver disease, three of whom died (Marino et al., 2004). The patients had been treated with either 131I or thyroidectomy and were euthyroid on levothyroxine when they underwent IV methylprednisolone acetate (IVMP). A prospective observational study of 13 patients with moderate to severe TED by Le Moli et al. demonstrated that IVMP causes dose-dependent liver damage but appears safe if cumulative dose remains under 8 g (Le Moli et al., 2007). One case report of new onset heart failure was attributed to IVMP pulse therapy superimposed on thyrotoxicosis-related hemodynamic instability (Gursoy et al., 2006). Due to these serious risks, patients should be screened for co-morbid medical conditions and monitored closely during the course of therapy.

6.4. Oral corticosteroids

Oral glucocorticoids are frequently used in the treatment of TED although they are associated with systemic side effects. The long term consequences are more pronounced since oral therapy is typically given for a longer period of time than intravenous or local glucocorticoids. Oral glucocorticoids can be given at high doses, such as prednisone 80–100 mg/day (or about 1 mg/kg body weight) followed by 10 mg/week taper (Kahaly et al., 2005; Brauer and Scholz, 2004). Need to mention typical duration of therapy mentioned in studies.

Cushionoid features, increased risk of diabetes, infections, osteoporosis, hypertension, hirsutism, and cataract formation limit their long term use. Monitoring of glycemic and blood pressure is especially crucial in patients with pre-existing diabetes or hypertension. During treatment with high dose GC, thiazide and loop diuretics should be used cautiously to avoid hypokalemia. Prolonged oral GC therapy > 5 mg average daily dose of prednisone for > 3 months requires bisphosphonates or other antiresorptive drugs (Tamura et al., 2004). Therapy should be tapered slowly upon cessation to avoid flares and cortisol deficiency.

Approximately 60% of patients have favorable effects of high dose oral GC (reports range from 40% to 100%) (Bartalena et al., 2000). Open trials or randomized studies comparing oral GC with other treatments have shown a favorable response in about 33–63% of patients with soft tissue changes, recent onset eye muscle involvement, and DON (Bartalena et al., 1983; Prummel et al., 1993; Kung et al., 1996; Kahaly et al., 1996).
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6.5. Local corticosteroids

Retrobulbar or subconjunctival glucocorticoid injections are less effective than oral or IV GCs but can be considered when oral or IVGCs are contraindicated. Risks of this invasive procedure include exacerbation of proptosis, infection, globe perforation, corneoscleral or conjunctival melting, occlusion from embolization, pressure induced optic nerve compression, depigmentation, granuloma reaction to methyl cellulose, fat atrophy, and elevated IOP (Nozik, 1976).

Several studies have reported varied degrees of success with local corticosteroid deposition. Marocci et al. compared 30 patients treated with systemic GC tapered over 6 months versus 44 patients treated with retrobulbar injections (14 methylprednisolone bilateral injections at 20–30 day intervals). All patients were also treated with irradiation (total dose 2000 rads). The treatment group receiving local GC had 25% favorable result rate, while the group receiving systemic CS had 60% favorable result rate (Marocci et al., 1987). The authors concluded that although response rate is lower with local administration, the adverse effects are milder than with systemic GC administration. Poonyathalang et al. also studied the efficacy of retrobulbar triamcinolone injections once weekly for 4 weeks in 27 eyes of 19 previously untreated patients. At 3 months, a reduction of ≥ 1 mm of proptosis was seen in 56% of the eyes, no change in 37%, and a worsening in 7%. Results were stable at 6 months follow-up. EOM function was improved in 41% of patients at 3 months. Eight eyes were noted to have increase in IOP that responded to topical glaucoma medications (Poonyathalang et al., 2005).

There are two studies evaluating peribulbar triamcinolone injections. In a randomized control study, Ebner et al. divided 41 patients with early TED into either the treatment group receiving 4 weekly peribulbar injections (triamcinolone 20 mg injected to the inferolateral orbital quadrant) or the control group without injections. The study found an increase in the area of binocular vision without diplopia in the treatment group. The size of extraocular muscles (initially compared to final size) was significantly decreased at 24 weeks in the treatment group. No adverse ocular or systemic side effects were reported (Ebner et al., 2004). In a prospective case study by Bordaberry et al., 11 patients with moderate disease and 10 patients with optic neuropathy underwent peribulbar triamcinolone injections (20 mg injected to inferolateral or superomedial quadrants at 2 week intervals for four total doses). Mean difference of 4.57 ± 1.56 points on CAS evaluation was found between initial and post-treatment. Of the 10 patients with ON, 66% improved with peribulbar triamcinolone exclusively. Two patients had transitory increased IOP which was controlled with topical medication (Bordaberry et al., 2009).

The data from these small studies suggest that local corticosteroids may be considered as an adjunctive therapy or used in patients who cannot tolerate other forms of GC. Although local therapy has decreased efficacy compared to oral or IV corticosteroids, the lower rate of systemic effects may be an appropriate alternative for patients with co-morbid medical conditions.

6.6. Orbital irradiation

Orbital irradiation (OR) may be considered in patients with active disease with severe TED. Furthermore, in a review of 624 patients, Bartalena et al. found that recent optic neuropathy and soft tissue changes responded better than proptosis or extracocular muscle disease (Bartalena et al., 2002). OR has anti-inflammatory effects and alters the helper/suppressor T lymphocyte ratio (Bartalena et al., 1998). The most commonly delivered cumulative dose is 20 grays per eye, fractionated in 10 daily doses. OR with lower doses (10 Gy) may be effective and better tolerated than the traditional higher dose (Kahaly et al., 2000). Risk of exacerbation of inflammatory symptoms is decreased by giving glucocorticoids concomitantly (Bartalena et al., 1983).

Complications from OR are rarely reported, but are concerning. The risk of cataract formation caused by irradiation of the lens is minimized by fractionating the dose. Radiation retinopathy is a rarely reported complication. Patients with severe hypertension or diabetic retinopathy should not be treated with radiation as retinal microvascular abnormalities have been detected in a minority of these groups (Robertson et al., 2003; Viebahn et al., 1991). Evidence is unclear whether diabetic patients without retinopathy are at increased risk of developing retinal changes, thus diabetes without retinopathy should be regarded as a relative contraindication (Marocci et al., 2003; Wakelkamp et al., 2004). There is a theoretical calculated risk of 0.3–1.2% for occurrence of secondary tumors but no cases of radiation-induced tumors have been reported in Graves’ patients (Broere et al., 1999). Orbital radiation should be avoided in patients younger than 35 due to the potential carcinogenic effects (Bartalena et al., 2008).

Approximately 60% of patients have favorable response to OR (range 20–92%) (Bartalena et al., 2000). Combined treatment of OR with oral glucocorticoids is more effective than either treatment alone (Bartalena et al., 2000; Stiebel-Kalish et al., 2009). In a randomized trial comparing OR with oral glucocorticoids, both were found to be equally effective as initial treatment (Prummel et al., 1993). There is a lack of randomized studies comparing the combination of IV glucocorticoids with OR versus IV glucocorticoids alone.

The efficacy of irradiation is still controversial due to three trials that evaluated sham irradiation (Prummel et al., 2004; Mourits et al., 2000; Gorman et al., 2001). Retrobulbar radiotherapy therapy (total of 20 Gy in 10 divided fractions) was administered in the treatment groups of all studies and follow-up period ranged from 24 weeks to 1 year. The response rate of diplopia was better in the radiotherapy group as compared to the sham-irradiated group. No improvement was seen in CAS, exophthalmos and lid aperture outcomes were observed in the irradiated groups. The conflicting reports on the efficacy of OR merits further study.

6.7. Novel treatments

Advances in the understanding of the pathogenesis and immunologic basis of TED have lead to the advent of new potential treatment modalities. They include monoclonal antibodies and immunomodulators, such as rituximab, TNFα inhibitors, and somatostatin analogs, are the emerging research modalities. We will give a brief overview of the new research treatments.

6.8. Rituximab

Rituximab (RTX) is a monoclonal antibody directed against the CD20 antigen expressed on the surface of B lymphocytes. Potentially, decreasing B cell function will result in decreased
cytokine synthesis, dendritic cell function, and antibody levels, including the TSH-receptor and IGF-1 receptor antibodies. Rituximab has been shown to deplete intrathyroidal B-cells in Graves’ disease and thus may have a therapeutic role (El Fassi et al., 2007). Common adverse side effects include serum sickness, infusion reaction, and increased infections.

Several studies summarized below have shown varying degrees of benefit. Salvi et al. compared RTX with intravenous glucocorticoids in a nonrandomized pilot study in patients with mild to moderate disease (Salvi et al., 2007). Nine patients treated with RTX (1000 mg IV × 2 with 2 week interval) and 20 patients were treated with IVGC (500 mg IV for 16 weeks). Thyroid function was not affected but exophthalmos and clinical signs improved in patients treated with RTX. Patients treated with RTX had more CAS improvement than patients treated with intravenous glucocorticoids (P < .05).

In a controlled nonrandomized study by El Fassi et al., 10 patients received methimazole before RTX therapy (375 mg/m² IV on day 1, 8, 15, and 22) and 10 patients received methimazole only (El Fassi et al., 2007). Both groups were withdrawn from therapy including steroids, radiation or immunomodulators without consistent success. Two small studies have been conducted (Paridaens et al., 1989). Azathioprine (Perros et al., 1990), ciamexone (Kahaly et al., 1986; Prummel et al., 1989), Azathioprine (Perros et al., 1990), ciclosporine (Kahaly et al., 1990), and IV immunoglobulins (infusion of IgG antibodies isolated from human plasma donors) (Kahaly et al., 1996; Antonelli et al., 1992) have marginal or unproven value. Other agents approved for rheumatoid arthritis, such as abatacept (costimulatory blocker of T-cell activation), and anakinra (interleukin-1 receptor antagonist) have yet to be tested in patients with TED (Griepentrog and Garrity, 2009).

6.10. Somatostatin analogs

There are five somatostatin receptor subtypes, and all except subtype 4 are expressed in orbital lymphocytes and fibroblasts of TED patients (Pasquali et al., 2000). These receptors are thought to contribute to adipocyte proliferation. Although initial noncontrolled studies showed positive results, four randomized, placebo-controlled clinical trials with long-acting octreotide or lanreotide have demonstrated marginal efficacy in treatment of TED (Dickinson et al., 2004; Wemeau et al., 2005; Chang and Liao, 2006; Stan et al., 2006). Pasireotide (SOM230) is a new somatostatin analog undergoing development that targets a wider range of somatostatin receptors. Cell cultures show that SOM230 produced significantly greater inhibition of orbital adipocyte proliferation than octreotide and may become a promising new treatment (Cozma et al., 2007).

6.11. Other immunomodulators

There have been several reports of using novel immunomodulators without consistent success. Two small studies have shown that the combination of oral GCs and cyclosporine is superior to either treatment alone (Kahaly et al., 1986; Prummel et al., 1989). Azathioprine (Perros et al., 1990), ciclosporine (Kahaly et al., 1990), and IV immunoglobulins (infusion of IgG antibodies isolated from human plasma donors) (Kahaly et al., 1996; Antonelli et al., 1992) have marginal or unproven value. Other agents approved for rheumatoid arthritis, such as abatacept (costimulatory blocker of T-cell activation), and anakinra (interleukin-1 receptor antagonist) have yet to be tested in patients with TED (Griepentrog and Garrity, 2009).

7. Conclusion

Thyroid eye disease is a common cause of orbital disease in adults. The pathogenesis is an active area of research and many immunologic aspects of the disease have been elucidated. Research of serum markers may assist in the diagnosis, prognosis, and response to therapy through their ability to improve the classification of TED patients. Characteristic enlargement of the extraocular muscles and proliferation of adipocytes result in the clinical findings, such as eyelid retraction, exophthalmos, and strabismus of TED. All patients require management of their systemic thyroid disease. Most cases of TED can be managed conservatively. Symptomatic treatment with lubrication often suffices for those with mild TED. Individuals with moderate to severe TED may require an escalation of therapy including steroids, radiation or immunomodulation. Intravenous glucocorticoids have the best response rate and the lowest incidence of side effects and thus play a sig-
significant role in the management of moderate to severe as well as sight-threatening TED. Surgical management is required when medical management fails. An emerging understanding of the immunologic pathogenesis will likely evolve the management of TED over the next decade.

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