



## A NEW FRONTIER IN THE CO-MANAGEMENT OF

# THYROID EYE DISEASE

Thyroid eye disease, also known as Graves' orbitopathy, is a potentially serious, progressive autoimmune disease that most often occurs in people living with hyperthyroidism, but may occur in people who are hypothyroid or euthyroid.

### **Burden of Disease**

The incidence of thyroid eye disease (TED) is estimated to be approximately 16 per 100,000 females, with an incidence in males of about one-fifth that number. TED has an enormous psychosocial impact on patients' lives. The changes in physical appearance, such as eyelid retraction, proptosis, and ocular misalignment, can engender distress, anxiety, and anger. Support groups can help patients with disease self-management in the long term.

### **Pathophysiology**

TED is characterized as a systemic autoimmune process that involves loss of immune tolerance within the thymus and within critical autoantigens such as thyroid stimulating hormone receptor and the IGF-1 receptor contribute to TED. Activated T-cells and B-cells and their communication with antigen-presenting cells, eg, fibrocytes, monocytes, macrophages, and dendritic cells, are also implicated in the pathophysiology of TED. Women are more likely to develop TED than men. Other risk factors include genetics, a history of tobacco smoking, advancing age, poorly controlled thyroid function, and stress.

### **Patient Evaluation**

Patients with TED present with a range of symptoms, including dry eyes, photophobia, periorbital inflammation, blepharoplasty, and compressive optic neuropathy; therefore, identifying and diagnosing TED can be challenging. Since clinical hyperthyroidism increases the suspicion for TED, endocrinologists are key to the initial diagnosis and management. Comprehensive eye examination is vital to diagnosis, looking for proptosis, examining tear film and adequacy, and periorbital edema. Orbital imaging is also important to define the tissue compartments involved. Laboratory examination includes a second-generation serum TSH, FT4, and T3 and determining the presence of detectable anti-TSH receptor antibodies, TSIs, TRABs.

### **Nonpharmacologic and Pharmacologic Treatment**

It is crucial to establish a goal for therapy that includes assessment of risk vs benefit, considers comorbidities, and addresses patient preferences and values. Therapy depends also on disease stage, severity, symptoms, and measurable endpoints (eg, proptosis reduction). Comanagement by an endocrinologist and ophthalmologist is important to ensure that therapeutic approaches include attention to both thyroid (hyperthyroidism vs hypothyroidism) and ophthalmic issues. Antithyroid medications such as methimazole play an important role in establishing euthyroid function. Relief of eye symptoms with supportive therapy (eg, artificial tears) can be a realistic short-term goal for patients with active disease. Later stage and more severe disease may warrant medical therapies or surgical interventions.

### **Clinical Trial Experience**

Teprotumumab offers a pharmacologic option that improves symptoms, as well as signs such as double vision and proptosis. This biologic agent was approved in January 2020 based on data from 2 key trials. Patients in both trials had active, moderate to severe TED (CAS  $\geq$  4); were euthyroid; with symptom onset within 9 months from baseline. Trial design was a placebo-controlled, double-masked trial, with 2 treatment arms (teprotumumab vs placebo). The primary and secondary responses were adjudicated



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at week 24, following 8 infusions, given at 3 weekly intervals. The primary response in the initial phase 2 trial was the aggregate of a reduction of  $\geq 2$  points on a 7-point CAS scale and a  $\geq 2$  mm reduction in the study eye without similar worsening in the fellow eye. In the second trial, the primary response was simplified to improvement from baseline of  $\geq 2$  mm of proptosis in the more severely affected eye. At 6 weeks, 56% of patients receiving teprotumumab had achieved the primary response compared with 7% of those receiving placebo. The most commonly occurring adverse events included muscle spasms involving the lower extremity, nausea, alopecia, mild diarrhea, generalized fatigue, hyperglycemia in patients with baseline carbohydrate intolerance or diabetes mellitus, and hearing abnormalities.

### **Surgical and Radiation Options**

Orbital radiation remains a controversial option for treating patients with TED and is associated with study results that are not definitive. Excluding patients with severe hypertension or diabetic retinopathy is very important for this treatment modality. Orbital decompression surgery has increasingly adopted minimally invasive techniques that have improved outcomes (ie, proptosis reduction) and reduced the risk for adverse events (eg, double vision). Orbital decompression surgery may be appropriate for patients with nonprogressive, stable disease of at least 3-6 months where there is no increase in proptosis and no change in double vision. Strabismus surgery may also be warranted for patients with diplopia. Eyelid surgery is an option to correct lower eyelid retraction.

### **Additional References**

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