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Teprotumumab, a Human Monoclonal Antibody Insulin-like Growth Factor-1 Receptor Inhibitor for Thyroid Eye Disease

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Graves' ophthalmopathy (GO) is an auto-inflammatory disease associated with Graves' disease (GD).[1] Also called thyroid-associated orbitopathy (TAO), both are members of the emerging acronym in the literature called thyroid eye disease or TED.[1,2] Greater than 90% of patients with Graves' orbitopathy have GD, a complex inflammatory autoimmune condition caused by thyrotropin (TSH) receptor autoantibodies.[3]

Graves' disease is common throughout the world. Women in their third to fifth decade are primarily affected with an overall prevalence of 0.5%. Approximately 15% of patients with GD who do not present with GO at baseline will typically develop it within 3 to 6 months.[3] Eyelid retraction, restrictive strabismus, proptosis, exposure keratopathy, and optic neuropathy of TAO most often present with Graves' hyperthyroidism.[4] Persons also experience disabling vision effects and facial disfigurement, which has a significant negative impact on quality of life and mental health.[3,5] Only 3% to 5% of patients will progress to severe disease involving ulceration of the cornea, vision-threatening optic neuropathy, and cornea decompensation.[2] For most patients, predisease orbital anatomy will not be restored, and for some, surgery will be required to reduce disfigurement and restore vision. Since the 1960s, immunosuppression with steroids has been the primary medication therapy during active disease.[5]

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PATHOPHYSIOLOGY

Thyroid-associated orbitopathy begins as an acute active phase mediated by the immune system. Activation of orbital fibroblasts results in the expression of insulinlike growth factor-1 receptor (IGF-1R) and TSH receptor, which leads to the production of proinflammatory cytokines. Upregulation of cytokines leads to increased hyaluronan production by orbital fibroblasts and enlarges orbital soft tissues. Hypertrophy of the extraocular muscles and expansion of the orbital fat component lead to the characteristic clinical findings of strabismus, eyelid retraction, and proptosis. This active phase can last up to 24 months and is often followed by an inactive phase.[2,4] However, the active phase can last longer particularly in smokers. Smoking and exposure to secondhand smoke worsen GD and GO.[1,2,4]

Historical models of GD and TAO have focused almost entirely on autoimmune reactivity directed against the TSH receptor. Emerging is the theory that IGF-1R is a second participating antigen in TAO by virtue of its interactions with IGFs and anti–IGF-1R antibodies generated in GD.[6] Strong evidence supports IGF-1R in the pathogenesis of TAO, which has opened a pathway for new drug therapy development specifically for TED.[7]

PATIENT PRESENTATION

Table 1 describes the most common signs and symptoms of TED. Patients usually appear with exophthalmos and fatigue and report discomfort with reading, pain with eye movement, and diplopia. Some patients can experience milder forms of TED, which can go unnoticed and resolve without development of obvious symptoms. Assessment of TED across the possible continuum of mild, moderate, or severe is described in Table 2. Many patients will experience cosmetic concerns and distress with changes in appearance and vision. The goal of care is to limit the progression of the inflammatory phase of TED to reduce orbital pathology and risk of vision loss.[1] The care team

Table 1. Common Signs and Symptoms of TED

Signs	Symptoms
Upper eyelid retraction Proptosis Erythema Conjunctiva edema Strabismus Lacrimal gland enlargement	Double vision Photophobia Pressure sensation behind the eyes Excessive tearing Dry eye sensation Anxiety, depression, fatigue Difficulty reading

Abbreviation: TED, thyroid eye disease.
Sources: Ali et al[2] and Hodgson and Rajaii.[4]

should always include an endocrinologist and an ophthalmologist to drive best patient outcomes for this complex autoimmune disease that will require lifelong monitoring for disease reactivation after treatment and for many lifelong hormone replacement therapies.[3]

THERAPY

Glucocorticoids have been the standard of care for moderate to severe active disease since the 1960s.[2,4] Steroid therapy modulates the immune system to reduce inflammation and activation of proinflammatory cytokines in orbital fibroblasts. Comparative studies of intravenous (IV) versus oral corticosteroids have shown IV therapy to be more effective and that patients required fewer eye surgeries compared with oral therapy. There are contraindications to glucocorticoid therapy, including hepatitis, liver disease, uncontrolled diabetes, hypertension, and severe cardiovascular disease. Orbital radiotherapy has also been an important adjuvant to steroid treatment of TAO.[4] For more than 60% of patients receiving this therapy, normal anatomy will not be restored, and TAO recurrence occurs frequently once glucocorticoids are withdrawn. Some evidence suggests that the addition of antiproliferative agents may help prevent deterioration after steroid cessation.[3]

For mild TED, an oral selenium supplement is suggested related to low risk and potential benefits.[2,4] However, in active, moderate-to-severe, and vision-threatening TAO, IV corticosteroids remain a first-line therapy with, for some, low-dose radiation.[2] Surgery may be required if there is an immediate risk to vision from optic neuropathy. The optic nerve is at a high risk for compression and vascular compromise related to where the nerve enters the orbit and proximity to the origins of the surrounding extraocular muscles. For cases where high-dose IV steroids are not effective, orbital decompression may be required.[3]

The targeting IGF-1R with specific biologic agents has resulted in a paradigm shift in the therapy of TAO.[4] Biologic agents have demonstrated potential as therapeutic alternatives or adjuncts for the treatment of TAO.[3,4] Table 3 describes 3 of these agents and their activity: rituximab, tocilizumab, and teprotumumab. Evidence for use of rituximab is mixed and requires future studies to determine its efficacy for TAO. Use of tocilizumab has demonstrated improvement in disease states; however, clinical trials were limited by size.[4]

Teprotumumab, a human monoclonal antibody IGF-1R inhibitor, was approved by the US Food and Drug Administration as Tepezza (Horizon Therapeutics, Ireland DAC) in January 2020 as the first drug specifically for TED.[8] Teprotumumab binds to the insulin growth factor[1] (IGF-1R) receptor, which inhibits the activation of IGF-1R signaling, in orbital fibroblasts, which drives GO inflammation.[1] In patients with recently diagnosed GO (up to 9 months of previous symptoms and no previous treatment), teprotumumab provided clinically and statistically significant improvement in diplopia, proptosis, and quality of life.[1]

Approval was based on the results of 2 studies of 170 patients with active TED randomized to receive either Teprotumumab or a placebo. Of the patients who were administered Teprotumumab, 71% in study 1 and 83% in study 2 demonstrated a reduction in proptosis (eye protrusion) of greater than 2 mm as compared with 20% and 10% of subjects who received placebo, respectively, and demonstrated safety and efficacy in reducing disease activity and severity.[8] Adverse events were mild to moderate and resolved spontaneously, either during or soon after the treatment phase was completed. Some subjects, primarily those with diabetes mellitus, experienced hyperglycemia, but there were no reported cases of ketoacidosis. Other adverse events included leg muscle cramps and hearing abnormalities that resolved spontaneously. Other adverse events included hair loss, diarrhea, and reactivation of inflammatory bowel disease in an individual with a history of ulcerative colitis. Emerging evidence suggests that teprotumumab may be effective for both compressive optic neuropathy and chronic, stable TAO and for pretibial

Table 2. Grading TED and Selected Interventions

Grade	Findings	Selected Interventions
Mild	Low soft tissue involvement Mild and transient diplopia	• Smoking cessation • Monitoring • Topical lubricants • Selenium (low risk/ potential benefit)
Moderate	Increased soft tissue involvement Inflammation	• Smoking cessation • Drug therapy • Monitor vision • Orbital radiotherapy
Severe	Corneal ulceration Optic nerve neuropathy Vision loss	• Smoking cessation • Drug therapy • Decompressive surgery • Orbital radiotherapy

Abbreviation: TED, thyroid eye disease.
Sources: González-García and Sales-Sanz[1] and Hodgson and Rajaii.[4]

Table 3. Medication Therapies for TED

Agent	Actions	Outcomes
Glucocorticoids	Reduce inflammation and activation of proinflammatory cytokines in orbital fibroblasts	Intravenous route superior to oral dosing for benefits. Contraindications: hepatitis, liver disease, uncontrolled diabetes, hypertension, and severe cardiovascular disease.
Rituximab (anti-CD20)	A chimeric mouse-human monoclonal antibody	Reduces inflammation by decreasing T-cell activation in active disease. Mixed results in limited trials; efficacy still under study.
Tocilizumab (TCZ) (anti–interleukin-6 [IL-6])	Anti–IL-6 receptor monoclonal antibody	Potential benefits in reducing inflammation, proptosis, and diplopia. Effective in steroid-resistant patients with severe TED. Clinical trials' sample sizes were small; further research is needed.
Teprotumumab (anti-IGF-1R)	Recombinant, fully human monoclonal antibody of the immunoglobulin G1 subclass	Decreases proptosis and diplopia by blocking the activation of IGF-1R; this inhibits the activation of IGF-1R signaling in orbital fibroblasts, which drive GO inflammation. May reduce the need for orbital decompression surgery.

Abbreviations: GO, Graves' ophthalmopathy; IGF-1R, insulinlike growth factor-1 receptor; TED, thyroid eye disease.
Sources: González-García and Sales-Sanz,[1] Taylor et al,[3] Hodgson and Rajaii,[4] and Kahaly.[5]

myxedema. As for aggressive TAO and that which has become clinically stable, teprotumumab may prove to be therapeutically beneficial.[6,8,9]

GOING FORWARD

Before 2020, TED is a debilitating, disfiguring, and potentially blinding periocular condition for which no US Food and Drug Administration–approved medical therapy was available.[7] Teprotumumab is the first approved therapy that reduces proptosis in TED and may reduce the need for orbital decompression. In the future, we can anticipate significant improvements in the management of TED using biologic agents and targeted therapies.[4]

With increasing understanding of the immunopathogenesis of TED, it is tempting to implement biological therapies that directly target the underlying pathological mechanisms. As the research moves forward, steroids remain a mainstay of treatment in TED. However, recurrence of active disease after steroid therapy, permanent orbital anatomy changes, double vision, risk for blindness, and cosmetic disfigurement will drive discovery of more novel and effective treatments. Because TED spontaneously remits many cases over time, it is important to monitor the literature regarding the safety and efficacy of all novel therapies for mild, moderate, and severe TED.[5]

In the provision of care, smoking cessation is critical to control disease activity. Risk for GO is higher in smokers and also in patients with poor control of hyperthyroidism or very high TSH antibodies. Patients must be taught that smoking is associated with worse clinical outcomes, including risk of blindness in GO.[1,4] Although total thyroid ablation improves GO, there is not enough evidence to offer this treatment for everyone with GD.[1] Finally, radioactive iodine is not recommended for persons with active GO.[3]

Thyroid eye disease impacts quality of life, difficulty driving and reading, anxiety, and depression related to changes in appearance. Even with appropriate medical therapy, nearly 20% of patients with TAO require surgical therapy to preserve eye function and/or improve appearance. The psychosocial aspects of care cannot be overstated and must be included in the plan of care. Certainly, the approval of this first drug for the treatment of TED offers hope.[4]

Teprotumumab, an IGF-1R antibody, has demonstrated efficacy in treating active disease and is the first therapy that has demonstrated a reduction in proptosis.[4] Prescribing information can be found at https://www.hzndocs.com/TEPEZZA-Prescribing-Information.pdf. It is important to carefully review current prescribing information particularly related to the following safety issues. First, female patients should use effective contraception before beginning and during treatment with Teprotumumab and continue for 6 months after the last dose. Clinical trials with Teprotumumab have not been conducted in pregnant women; therefore, drug-associated risks for fetal harm and adverse developmental outcomes are unknown. Second, hyperglycemic reactions must be monitored in diabetic patients and those with impaired glucose tolerance; both should have glycemic control before beginning and during therapy.

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