Teprotumumab in thyroid eye disease

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Abstract:

Thyroid eye disease (TED) is an inflammatory condition involving the periocular and orbital soft tissues, affecting most commonly patients with hyperthyroid disorders. Traditional treatments used for the active phase of the disease range from conservative lubrication for mild symptoms to systemic immunomodulating drugs for moderate-to-severe symptoms. Teprotumumab (Tepezza) is a monoclonal antibody with an inhibitory effect on insulin-like growth factor 1 and is the first Food and Drug Administration (FDA) approved targeted medical therapy for reducing the inflammatory signs and symptoms associated with TED. Two large multicenter, randomized, double-masked, placebo-controlled trials have confirmed the efficacy and safety of teprotumumab in patients with active, moderate-to-severe TED. Recent reports and publications have also demonstrated the efficacy of teprotumumab in a wider range of patients. In this review, we summarize the clinical features and pathophysiology of TED, disease course, and traditional management methods. We further detail the development of teprotumumab, the founding studies that brought it to its FDA approval, adverse events profile, and ongoing as well as future investigations.

Keywords:

Autoimmune, graves, orbitopathy, proptosis, targeted, teprotumumab, thyroid

Introduction

Thyroid eye disease (TED) is an autoimmune inflammatory condition, occurring most commonly in patients with Graves' disease or hyperthyroidism, but can also be seen in patients with euthyroid or hypothyroidism in 5%–10%.[1]

Graves' disease is a systemic autoimmune disorder caused by autoantibodies against thyroid-stimulating hormone receptor (TSH-R) which leads to stimulation of the thyroid gland with the secretion of abnormally high amounts of triiodothyronine and thyroxine causing hyperthyroidism.[2] The hyperthyroid state manifests with a variety of systemic symptoms including tachycardia, palpitations, fatigue, tremors, weight loss, hair loss, diarrhea, sleep disturbances, and anxiety.[3]

The most common extrathyroidal manifestation of Graves' disease is the ocular involvement known as TED. TED affects approximately 25%–50% of Graves' patients, with a median age of 43 years.[1,4] In most patients (~70%), the ocular symptoms will manifest sometime within the 1st year after Graves' onset, but TED can also be the initial presentation of a thyroid disorder. In a minority of cases, TED can be associated with other dysthyroid conditions such as Hashimoto's thyroiditis or euthyroid autoimmune disease.[5] TED is more common in females, occurring annually in 16 per 100,000 women, compared to 3 per 100,000 men.[6] Risk factors include a combination of genetic disposition and environmental factors such as smoking, stress, radiation exposure, Vitamin D, and selenium deficiency.[5] Cigarette smoking is known to raise the incidence, symptom severity, disease duration, and resistance to treatments.[4] It is therefore very important to educate and guide patients toward smoking cessation to reduce the morbidity associated with this disease.

Thyroid Eye Disease Pathophysiology and Clinical Features

The pathophysiology of TED is not fully understood; however, studies have shown that orbital fibroblasts are involved in the dysregulated immunologic processes.[7-9] The

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orbital fibroblasts in TED patients have been shown to have overexpression of TSH-R (the receptor most implicated with the pathologic process causing Graves' disease), insulin-like growth factor 1 (IGF-1) receptor (IGF-1R), and their respective activating autoantibodies.[9-11] IGF-1R is also known to interact with TSH-R, creating complexes that have synergistically enhancing effects on each other and fibroblast activation.[12,13] The stimulation of orbital fibroblasts leads to the production of pro-inflammatory cytokines which activate an inflammatory cascade, resulting in orbital soft-tissue enlargement and fibrosis.[14] The activated orbital fibroblasts can differentiate into adipocytes which cause orbital fat hypertrophy and can differentiate into myofibroblasts which cause the muscle enlargement.[7,15] There is also an increased release of hyaluronic acid which leads to orbital soft tissue and extraocular muscle swelling.[14] This increase in intraorbital tissue volume against the tight bony orbit can result in globe proptosis, extraocular muscle restriction, venous congestion, and rarely, optic nerve compression.

TED clinical signs and symptoms are the result of varying degrees of inflammation in the orbital and periocular soft tissues. The disease is most often bilateral but can also be unilateral. Common ocular clinical findings include upper eyelid retraction, globe proptosis, conjunctival and eyelid edema, erythema, congestion, caruncular inflammation, and elevated intraocular pressure.[16] Patients' symptoms can range from mild to severe to sight threatening dependent on the degree of inflammatory activity in the orbit. The most common patient symptoms include dryness, surface irritation, excessive tearing (due to exposure from proptosis and lid retraction and/or lacrimal gland inflammation), transient or constant diplopia (caused by restrictive myopathy), and ocular pain or pressure.[1] Severe features which can be vision threatening are optic nerve compression, called dysthyroid optic neuropathy (DON), or exposure keratopathy, which in extreme cases can cause corneal ulceration. These extreme features are rare and can develop in approximately 5% of TED patients.[4,17]

Another important aspect of this disease is the psychosocial burden. Studies have shown TED patients to suffer from decreased quality of life (QoL), difficulties with their jobs and interpersonal interactions, and overall higher rates of anxiety and depression than the general public.[16,18]

Disease Course and Management

TED is a self-limiting disease which manifests in two consecutive stages: initial progressively active inflammatory period followed by a stable quiescent period. The early active stage lasts an average of 1 year in nonsmokers and 2–3 years in smokers.[16] During this period, patients will suffer from inflammation-related signs and symptoms in the orbit and periocular soft tissues as mentioned above. In most patients, the active symptoms will spontaneously gradually resolve or regress within 2–5 years from onset, reflecting the self-limiting nature of this disease. However, some features including proptosis and diplopia may persist as a result of fibrotic changes in the tissues.[1]

The clinical activity score (CAS) is a grading system applied by the European Group on Graves' Orbitopathy for the assessment of disease activity level. The CAS is useful for evaluating if patients are at the active or inactive stage of the disease, following their progression or improvement at each visit, as well as help with management decisions.[16,19]

Orbital imaging studies with computed tomography (CT) or magnetic resonance imaging (MRI) can be helpful to confirm the clinical diagnosis and assess treatment response or disease progression. CT is better to evaluate bony structures, and MRI is more sensitive to soft-tissue changes. Typical findings in TED will be edema of the retro-orbital contents and enlargement of extraocular muscles' belly with sparing of the tendinous attachments.[20]

Management of TED is divided between the active and nonactive phases. Balancing systemic thyroid levels and smoking cessation are always attempted as first-line initial intervention.[21] For patients in the active phase suffering from various inflammatory-related symptoms, a range of treatment options can be offered: for mild disease manifesting as ocular dryness/irritation, conservative solutions such as lubrication, topical cyclosporine, and oral selenium supplement can be adequate.[21] For moderate-to-severe symptoms such as keratopathy, proptosis, lid retraction or transient/constant diplopia, and systemic immunomodulatory agents to reduce inflammation are the mainstay of treatment. Historical treatment options have included oral/intravenous high-dose corticosteroids, rituximab, or orbital radiation.[21-24] Surgical intervention in the active phase with orbital decompression is usually reserved for extreme cases with sight-threatening conditions such as DON or severe keratopathy or cases refractory to medical treatments.[21]

When patients are in the inactive chronic phase of TED, the disease has stabilized and is not expected to progress. At this point, surgical interventions can be performed. This can include orbital decompression, followed by strabismus surgery and finally correction of eyelid retraction, depending on patients' signs and symptoms.

Teprotumumab

As previously discussed, the exact pathophysiology of TED is not completely understood but is known to involve stimulation of TSH-R and IGF-1R, which are overexpressed in TED, on orbital fibroblasts.

Teprotumumab (trade name Tepezza, developed by Horizon Therapeutics) is a fully human monoclonal antibody with an inhibitory effect on IGF-1R. The proposed mechanism of action is inhibition of orbital IGF-1R activation and IGF-1R/TSH-R signaling complex with a decrease in the downstream inflammatory signs and symptoms of TED. Teprotumumab is

given intravenously (initial dose of 10 mg/kg, remainder doses of 20 mg/kg) every 3 weeks for a total of eight infusions (total treatment time of 6 months).

The efficacy and safety of teprotumumab were evaluated in two large multicenter, randomized, double-masked, placebo-controlled trials (sponsored by Horizon Therapeutics): a Phase II trial with results published in 2017 and a Phase III "OPTIC" trial published in the *New England Journal of Medicine* in 2020.[25,26] Overall, 170 patients with active (<9 months since diagnosis), moderate-to-severe TED (CAS ≥4) were randomized to either receive teprotumumab or a placebo infusion every 3 weeks for 24 weeks. Both trials found significantly better outcome results in the teprotumumab group compared to the placebo group for: proptosis reduction ≥2 mm (83% vs. 10% in OPTIC), CAS reduction ≥2 points (78% vs. 7% in OPTIC), diplopia improvement ≥Grade 1 (68% vs. 29% in OPTIC), and mean improved score on TED-related QoL (GO-QoL) questionnaire.[26] The clinical response proved to be long-lasting and sustained for at least 1 year in most patients after treatment completion (longer follow-ups have not yet been evaluated).[27] These positive results achieved by teprotumumab treatment in the two clinical trials exceeded greatly the benefits shown in previous studies of traditional treatments with corticosteroids or rituximab for active TED.[28] Based on these findings, teprotumumab has been approved by the US Food and Drug Administration (FDA) in January 2020 for use as treatment of active TED.[29]

Since the drug approval, there have been many real-world reports and publications confirming the efficacy of teprotumumab in relieving symptoms of active inflammatory disease.[30] In recent years, there have also been increasing reports of teprotumumab use in a variety of different disease conditions including chronic TED and DON.[31-33]

Teprotumumab Adverse Events

The two large clinical trials mentioned above have proven teprotumumab is safe and has a favorable side effect profile. The most common adverse events found related to teprotumumab were mild to moderate in severity and included muscle spasms (20%), nausea (10%), alopecia (10%), hyperglycemia (8%), diarrhea (8%), dry skin, nail bed changes, fatigue, menstrual changes, and hearing impairment (all ≤ 5%).[27] Particular caution should be exerted in diabetic patients with close blood sugar monitoring and in patients with preexistent hearing loss due to the known potential of hearing changes. Furthermore, patients with a history of inflammatory bowel disease should be monitored as teprotumumab can cause disease flare-ups.[28]

Teprotumumab may also cause infusion reactions occurring during or up to 1.5 h posttreatment. These can include tachycardia, blood pressure increase, dyspnea, headaches, and muscular pains. Such reactions have been reported in <5% of patients and can be handled by premedicating with antihistamines, antipyretics, or steroids and lowering the infusion rates in subsequent doses.[25,26]

Important to note are the likely teratogenic effects of teprotumumab based on the drug's mechanism of action involving inhibition of IGF-1R in various cell functions including cell differentiation and proliferation.[34] As Graves' disease and TED preferentially affect women of reproductive ages, it is important to remember that it is not advised during pregnancy, and if given to women of childbearing ages, it must be accompanied by appropriate forms of contraceptives. The FDA regulations dictate for two contraceptive methods to be initiated at least one full cycle before treatment initiation and continued for 6 months after the final dose.[35]

Teprotumumab for Chronic Thyroid Eye Disease

During the chronic phase of TED, many patients may still suffer from persistent proptosis, diplopia, pain, and other symptoms, due to fibrotic changes in the orbital soft tissues from the previous inflammatory activity.[8] The mainstay of treatment for these patients has been surgical.[36]

The pathological overexpression of IGF-1R in orbital fibroblasts known to be associated with Graves' and acute TED was also found in the chronic stages of TED.[9,12] This finding may reflect on some association between the IGF-1R pathway and the persistent orbital tissue expansion causing long-term proptosis in the noninflammatory phase.[13]

While the two large clinical trials did not include patients in the chronic stage of TED, there have been several recent publications, mostly small case reports or series, which report effective teprotumumab treatment for symptomatic patients in the stable chronic stage of TED.[33,37,38] The largest study to evaluate teprotumumab efficacy in chronic TED is a retrospective multicenter review on 31 patients with chronic stable TED (>2 years since diagnosis and no change in proptosis and diplopia in the preceding year). Results revealed 90% improvement in proptosis (≥2 mm) and 67% improvement in diplopia.[38]

A Horizon-sponsored ongoing randomized, double-masked, placebo-controlled, multicenter clinical trial is currently also investigating the efficacy of teprotumumab in patients with chronic (inactive) TED (≥2 years since diagnosis with CAS ≤1 in preceding year). They have enrolled 62 patients, and results are expected soon.

An open-label extension study to OPTIC (known as OPTIC-X) examined the efficacy of teprotumumab for nonresponders during the original trial. An additional eight teprotumumab infusions over 24 weeks were given to patients who did not have a proptosis response in the initial trials. Two out of five patients enrolled showed a proptosis response after retreatment, suggesting that a second course may be effective in refractory cases. No additional safety concerns were seen during retreatment.[32]

Teprotumumab for Dysthyroid Optic Neuropathy

The most serious manifestation of TED is DON, occurring in up to 8% of patients.[17] This can present with decreased

visual acuity and color vision, relative afferent pupillary defect (RAPD) if the disease is unilateral or asymmetric, optic disc edema, and visual field defects. Orbital imaging in these cases typically will reveal significant expansion of extraocular muscle and fat tissue. The optic nerve may appear stretched tight, and the posterior globe may show tenting.[20] DON is a sight-threatening state and therefore early diagnosis and timely treatment is crucial. The mainstay of treatment, depending on severity and rate of progression, has been high-dose corticosteroids, orbital radiation, and/or surgical decompression to achieve immediate release of pressure.[21] Each of these modalities carries its own set of risks.

Teprotumumab has shown to significantly reduce proptosis and orbital inflammatory symptoms. In the OPTIC trial, orbital imaging was included in six patients at baseline and after treatment completion at 24 weeks. All six cases uniformly demonstrated a significant reduction of orbital fat tissue and/or extraocular muscle volume (respective mean volume reduction of 17% and 35%).[26] While optic neuropathy was excluded from the original clinical trials, the medical decompressive effect of teprotumumab makes it a potentially promising therapeutic option in DON. Several case series have shown the effectiveness of teprotumumab in DON.[39-41] The largest report is a multicenter observational 10-case series of patients with proven DON who were either poor surgical candidates or who had failed previous conventional therapies. Their results showed 70% improvement in DON objective findings (visual acuity and/or RAPD resolution) and 100% improvement in subjective findings (visual acuity, color vision, and comfort) after two teprotumumab infusions.[39] Although these are preliminary reports with small sample sizes and limited follow-up periods, these recent reports suggest teprotumumab as a potentially highly effective alternative therapy for patients with DON.

Looking to the Future

Teprotumumab has marked a new milestone as being the first approved biological targeted medical therapy for TED. It has shown high efficacy in decreasing inflammatory signs and symptoms associated with TED, as well as medically decreasing orbital fat and muscle volume.

Since its FDA approval just 3 years ago, the clinical experience is rapidly growing, with an overflow of publications reporting on the high efficacy of teprotumumab in treating a wide range of TED patients. The efficacy for chronic TED state is becoming more evident and will be further evaluated in the expected results of the Horizon multicenter clinical trial for chronic inactive disease (NCT04583735). Teprotumumab treatment for DON and for TED-related strabismus is very promising from a few recent reports, yet further investigation is necessary.[38,39]

As both previous clinical trials conducted were placebo controlled, it is worth mentioning that a comparison clinical trial between teprotumumab and other medical treatments used for TED including corticosteroids and rituximab is needed. Aside from clinical benefit, this is especially relevant considering the significant cost differences of these therapies. Teprotumumab is still very expensive and obtaining insurance authorization can be time-consuming and difficult.

Further investigation is also necessary to determine the optimal dosing and duration of teprotumumab treatment in the setting of TED. Dose-ranging studies including variable concentrations, infusion frequencies, and durations have not yet been conducted. Lowering the treatment dose/duration may improve the adverse effects patients are experiencing from IGF-1R inhibition throughout the body. Prolonging treatment duration is also worth investigating as it may enhance the response during the entire acute phase of TED, which can last between 1-3 years. On the other hand, a modulated "treat-and-extend" method might prove most efficient, tailored to each patient's specific disease pattern.

Limitations

Limitations to this study include it being the English language only. In addition, teprotumumab is a relatively new drug with limited long-term follow-up on patients. As TED is a rare disease, there is overall limitation of the sample size of patients treated.

Conclusion

Teprotumumab is a powerful new therapeutic option in the challenging field of TED management. It is the only medical treatment proven to significantly reduce orbital volume. Growing evidence suggests its efficacy yield may be far wider than initially presumed and will be further revealed with continuing investigations. The treatment is relatively safe, yet careful patient selection and monitoring are important to prevent complications.

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Conflicts of interest

There are no conflicts of interest.

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