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Teprotumumab: a novel therapeutic monoclonal antibody for thyroid-associated ophthalmopathy

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Abstract

Introduction—Thyroid-associated ophthalmopathy (TAO) is a disfiguring, potentially blinding, and sub-optimally managed autoimmune condition. Current therapy of active TAO consists most frequently of glucocorticoid steroids, orbital radiation, or B-cell depletion; all of which are associated with substantial side effects. Teprotumumab (Tepezza) is a human monoclonal antibody against the insulin-like growth factor type I receptor (IGF-IR), recently evaluated in 2 clinical trials for active moderate-to-severe TAO that was recently approved by the United States Food and Drug Administration (FDA) for use in TAO.

Areas Covered—This article reviews phase II and III placebo controlled, double masked, prospective, multicenter studies assessing the efficacy and safety of teprotumumab for the treatment of active, moderate-to-severe TAO.

Expert Opinion—Teprotumumab has demonstrated substantial and rapid improvement in Clinical Activity Score and proptosis reduction in TAO compared to placebo. Subjective diplopia and quality of life were also improved in both clinical trials. Teprotumumab exhibited a favorable safety profile, with transient hyperglycemia, muscle cramps, and auditory side effects being associated with the drug; these were usually transient. The trial findings indicate that teprotumumab is a promising, potential first line therapy for treating active TAO.

Keywords

IGF-IR; Graves' disease; thyroid associated ophthalmopathy; thyroid eye disease; R1507; RV001; teprotumumab; Tepezza

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Declaration of interest

T Smith was issued U.S. patents for the use of inhibitors of IGF-IR in Graves' disease, TAO and other autoimmune diseases. US Patents covered therapeutic targeting of IGF-I receptor)10/140003, 13710635.8, 03/00187, 10/046,651, 10/038509. These are held by the Los Angeles Biomedical Foundation and UCLA School of Medicine. He serves as a paid consultant for Horizon Therapeutics and Immunovant. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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1. Introduction

Thyroid-associated ophthalmopathy (TAO) is a progressive autoimmune disease that leads to the enlargement of orbital fat and extraocular muscles, potentially disrupting orbital architecture and causing vision loss. TAO is the most common, and most serious, extra-thyroidal manifestation of Grave's Disease (GD). Clinically apparent TAO is observed in approximately one-half of patients with GD [1]. Of those, the majority exhibits only mild disease. In the United States, the annual incidence of TAO is 16/100,000 in females and 2.9/100,000 in men [2].

The clinical course of TAO was first described by Francis Rundle in 1945 [3]. The initial, active phase of TAO is characterized by inflammation and expansion of the periorbital and orbital tissues. Clinically, this manifests as ocular protrusion (proptosis), orbital pain, eyelid swelling, conjunctival injection and edema (chemosis), increased scleral show (eyelid retraction), ocular surface dryness, restricted eye movements, double vision (diplopia), and rarely, compressive optic neuropathy (Figure 1). The active phase most frequently lasts between 1 and 3 years before the inflammation plateaus and eventually leads to the stable phase, which may be dominated by the consequences of fibrosis and an absence of clinical change [3,4]. An ophthalmic examination is performed to quantify the severity of clinical signs (mild, moderate-to-severe, or sight-threatening) and to determine the activity of TAO. The latter is frequently reported using scoring systems such as the Clinical Activity Score (CAS) [5]. 5–10% of all cases of TAO are characterized as being moderate-to-severe [6]. Once the inactive phase is reached, clinical signs rarely remit, leaving patients with lasting functional and cosmetic deficits that may require orbital, extraocular muscle, and/or eyelid surgery.

Orbital fibroblasts play an essential role in the pathogenesis of TAO. These cells demonstrate the potential to differentiate into adipocytes and myofibroblasts and to produce hyaluronic acid [7–10]. The increased volume of fat and muscle, and elevated water content in the orbit leads to many of the clinical manifestations of TAO. Additionally, orbital fibroblasts can interact with immune cells and propagate an inflammatory response, largely as a consequence of a fibroblast subset comprising $CD34^+$ fibrocytes [11–13].

Orbital fibroblasts express the thyroid-stimulating hormone receptor (TSHR), the immune tolerance of which when lost results in the production of activating autoantibodies against the receptor. Thyroid-stimulating immunoglobulins (TSIs) are a subset of antibodies against the TSHR. Although the relationship is not completely understood at this time, the activation of TSHR displayed on orbital fibroblasts by TSIs may be involved in the pathogenesis of TAO [11].

Orbital fibroblasts also express the insulin-like growth factor receptor type 1 (IGF-1R), which forms a physical and functional complex with TSHR [14]. Inhibiting IGF-1R attenuates the downstream effects of IGF-I- and TSH-dependent signaling in orbital fibroblasts [14, 15]. Therefore, IGF-1R is a potentially useful therapeutic target for the management of TAO. This review summarizes clinical data supporting the use of

teprotumumab (also known as RV001, R1507), an inhibitory human monoclonal antibody with absolute specificity for IGF-IR, for treating active TAO.

2. Overview of the Market

Glucocorticoid steroids are the most commonly used drugs for treatment of active TAO [16]. The side effects of systemic steroids are substantial, including impaired glucose tolerance, hypertension, iatrogenic Cushing's syndrome, osteoporosis, psychiatric maladies, impaired renal function, gastrointestinal side effects, glaucoma, cataract formation, and infection [16]. High-dosage pulse intravenous steroids are more effective than oral steroids and are better tolerated with fewer side effects [16]. These high-dosage steroids are associated with severe, occasionally fatal liver toxicity [16–18].

Use of external beam radiotherapy is advocated by some, both as standalone treatment and in combination with glucocorticoids [19]. Radiotherapy appears to be equivalent to that of glucocorticoids [20], with the combination of treatments potentially being more effective than either modality alone [21]. Orbital radiation has been shown to be rather safe overall, but can cause significant ocular side effects including cataracts, retinopathy, and a theoretical potential for radiation-induced malignancy continues to be concerning [22, 23].

Biological medications have been repurposed for use in active TAO. Effectiveness of rituximab (anti-CD20) remains uncertain, with one recent prospective double masked study demonstrating CAS improvement relative to glucocorticoids [24], while another finding no difference versus placebo [25]. Tocilizumab (anti-IL6 receptor monoclonal antibody inhibitor) demonstrated improvement in CAS in moderate-to-severe active TAO but failed to reduce proptosis [26]. Mycophenolate mofetil (inosine monophosphate dehydrogenase inhibitor) as monotherapy or in combination with glucocorticoids may prove superior to glucocorticoid monotherapy [27].

3. Teprotumumab Overview

Teprotumumab is a 150 kDa fully human monoclonal IgG1 antibody with absolute specificity against IGF-1R [4]. It binds to the extracellular region of the IGF-1R in a cysteine-rich domain with high affinity, blocking IGF-I and IGF-II from binding to the receptor [4]. After binding, the IGF-1R-teprotumumab complex is internalized and degraded [4].

Teprotumumab administered at a dosage of 9mg/kg has a half-life of 4–8 days [28]. The clearance of teprotumumab follows a dual elimination model that is non-linear (saturable) at low concentrations and linear (non-saturable) kinetics at higher concentrations [28].

4. Clinical Efficacy

A multicenter, double-masked, placebo-controlled phase II clinical trial (NCT01868997) studying the use of teprotumumab in active, moderate-to-severe TAO demonstrated clinically meaningful responses [29]. The primary outcome was the rate of clinical response, defined as a reduction in CAS by ≥ 2 points and a reduction in proptosis by ≥ 2 mm in the

more severely affected eye, without worsening in the contralateral eye at week 24. During the study period, infusions of placebo or teprotumumab (initial 10mg/kg dose followed by 20mg/kg if tolerated) were given every three weeks. In the intention-to-treat cohort, 69% (29/42 patients) receiving teprotumumab vs. 20% (9/45 patients) receiving placebo had a clinical response at 24 weeks ($p < 0.001$) [29]. Treatment onset was rapid with 43% of patients receiving teprotumumab vs. 4% of patients receiving placebo reaching the primary outcome at 6 weeks [29].

A phase III confirmatory trial (NCT03298867; "OPTIC") was recently completed in the spring of 2019 [30]. Inclusion criteria were identical to the phase II study. The primary outcome was reduction of proptosis (≥2mm) at week 24. In this study, 83% receiving teprotumumab vs. 10% receiving placebo achieved the primary outcome at 24 weeks ($p < 0.001$) [30]. Proptosis non-responders in the OPTIC study were allowed to enter an open label extension study (NCT03461211; "OPTIC-X") to receive eight additional teprotumumab infusions over 24 weeks. Completion of the OPTIC-X study is anticipated in 2022.

5. Safety and Tolerability

Teprotumumab was developed for treatment of solid malignancies. The safety, pharmacodynamics and tolerability of teprotumumab were therefore initially studied in the cancer space. In a phase 1 clinical trial, thirty-seven patients with advanced solid tumors not amenable to standard therapy received up to 9mg/kg of weekly teprotumumab without evidence of dose-limiting toxicity [28], although two patients developed serious adverse events (hyperbilirubinemia and cerebral ischemia). A larger phase 1b trial involving teprotumumab in combination with other chemotherapeutics also demonstrated that the medication was generally well tolerated [31]. The most frequent severe adverse effects were fatigue, pancytopenia, and gastrointestinal distress. On the basis of several trials, teprotumumab was judged to be well tolerated but without sufficient efficacy to continue its developmental program for advanced solid tumors [32]. Despite the apparent tolerability of the drug, virtually all developmental programs for cancer therapeutics have been discontinued.

Both clinical trials of TAO also demonstrated the safety of teprotumumab. Hyperglycemia, muscle cramps and hearing abnormalities were identified as treatment-related adverse events [29,30]. Elevated blood glucose was reversible and usually managed easily with blood glucose monitoring and medication adjustment [29,30]. Hyperglycemia is commonly experienced with IGF-1R inhibition [29,30,33]. Importantly, these adverse events were most frequently transient.

6. Regulatory Affairs

No medications have been approved for management of this condition in the past. Prior to approval, the FDA designated teprotumumab breakthrough, orphan drug, and fast track status for use in TAO. A Biologics License Application was submitted to the FDA on July

10, 2019. On January 21st, 2020 the FDA approved teprotumumab for the treatment of active TAO.

7. Conclusions

Teprotumumab is a therapeutic human monoclonal antibody inhibitor of IGF-1R that has been evaluated in two recently completed clinical trials in active, moderate-to-severe TAO. Teprotumumab is currently the only FDA approved medication for use in TAO. The drug reduced both the activity and severity of TAO compared to placebo when administered every three weeks over a 24-week treatment period in phase II and phase III clinical trials. A crossover phase III study is currently underway to demonstrate drug effectiveness in non-responders and those who relapsed after the 24-week therapeutic phase. Teprotumumab exhibits a favorable safety profile. Follow-up assessment of patients is currently underway to determine the durability of the benefits of teprotumumab.

8. Expert Opinion

The low annual incidence, heterogeneity of presentation, and the historic inability of preclinical animal models to replicate human disease with high fidelity have resulted in incomplete understanding of and development of effective treatment. Consequently, inflammation associated with TAO is treated with high-dose glucocorticoids, external beam radiotherapy, or biological agents repurposed from other diseases. These therapies can improve symptoms is some patients but are unreliable and fail to alter the disease course or need for surgical intervention. Further, all carry substantial side effects. Therefore, an unmet need has existed for better treatment of TAO.

The discovery of a physical and functional relationship between IGF-IR and TSHR and the dependence of TSHR signaling on the activity of IGF-IR represents a pivotal development in our understanding of the pathogenesis of TAO [14]. It identified IGF-IR as a putative therapeutic target, not only for TAO but potentially for other autoimmune diseases as well [35]. Therefore, teprotumumab, a monoclonal antibody inhibitor of IGF-IR repurposed from the cancer space became, a plausible therapeutic agent for TAO.

In phase II and phase III clinical trials, teprotumumab demonstrated a rapid reduction of both proptosis and clinical activity score compared to placebo for active, moderate-to-severe TAO. The medication was well tolerated. Although some experts in the field advocate that a randomized trial comparing teprotumumab to intravenous steroids is needed [36], the aggregate findings concerning teprotumumab prompt the authors to conclude that teprotumumab represents a potential first line and paradigm changing medical treatment for active TAO. With our current knowledge, the drug may be best suited for active disease where steroids are being considered, especially those at a high dosage. The efficacy of teprotumumab in inactive disease is undetermined. The drug offers an advantage over the currently available pharmacological and surgical options by its restoration of function and appearance in many cases. Although data from the phase III extension study and longer-term assessments are pending, teprotumumab appears to alter the natural progression of disease over the duration studied in the clinical studies already published [29, 30]. The side effect

profile of teprotumumab appears to be considerably better than that of steroids, radiotherapy, and rituximab. Given its recent approval by the FDA, we proffer that the drug will gain wide acceptance in medical and patient communities.

9. Drug Summary

9.1 **Drug Name (generic)**: Teprotumumab (RV001, R1507)

9.2 **Clinical Phase**: FDA Approved

9.3 **Indication**: Active thyroid associated ophthalmopathy (Janupaiary 21st, 2020)

9.4 **Pharmacology description / mechanism of action**: human monoclonal inhibitory antibody against the insulin-like growth factor I receptor (IGF-1R).

9.5 **Route of administration**: intravenous infusion

9.6 **Chemical structure**: Proprietary

9.7 **Pivotal trials:**

9.7.1 NCT01868997 (Phase 2) [29]

9.7.2 NCT03298867 (Phase 3) – OPTIC [30]

9.7.3 NCT03461211 (Phase 3) – OPTIC-X

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Article Highlights

- Teprotumumab is a therapeutic monoclonal antibody that inhibits the insulin-like growth factor type I receptor (IGF-IR).
- It was studied in phase II and phase III trials for moderate-to-severe active thyroid-associated ophthalmopathy (TAO).
- Teprotumumab demonstrated substantial and rapid improvement in clinical activity, diplopia and proptosis reduction.
- Teprotumumab is the only FDA approved therapy for TAO.
- Teprotumumab exhibited an overall favorable safety profile.
- Its long-term durability is currently being evaluated.

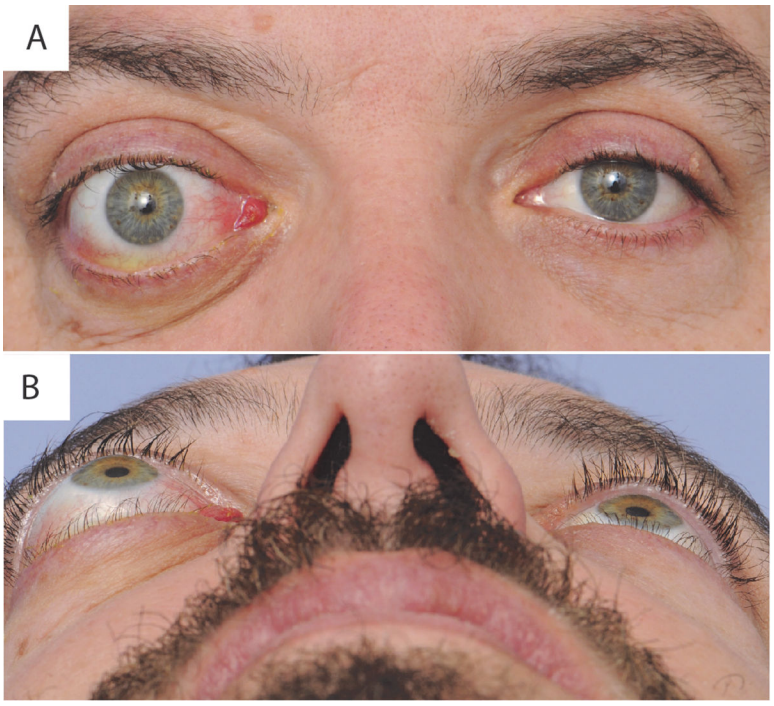

Figure 1:
Thyroid associated ophthalmopathy. A) Portrait view demonstrates axial anterior displacement of the right globe (proptosis), conjunctival injection most prominent along the rectus muscle insertions, lower eyelid retraction, upper eyelid temporal flare, and caruncular edema. B) Worm's eye view demonstrating the degree of right proptosis relative to the left eye. Note: patient permission was obtained.