

Efficacy and Safety of Teprotumumab in Thyroid Eye Disease

Honeylen Maryl Teo ¹
Terry J Smith^{2,3}
Shannon S Joseph²

¹Eye Institute, St. Luke's Medical Center, Metro Manila, Philippines; ²Department of Ophthalmology and Visual Sciences, W.K. Kellogg Eye Center, University of Michigan Medical School, Ann Arbor, MI, USA;

³Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

Abstract: Thyroid eye disease (TED; also known as thyroid-associated ophthalmopathy) is an autoimmune condition with disabling and disfiguring consequences. Teprotumumab is the first and only medication approved by the United States Food and Drug Administration for the treatment of TED. We review the efficacy and safety of teprotumumab in TED, highlighting results from the 2 randomized, double-masked, placebo-controlled trials. Post-approval case reports of teprotumumab use in patients with compressive optic neuropathy (CON) and inactive TED were similarly favorable to those from the trials. The preliminary results of teprotumumab for CON and inactive TED should be investigated in formal clinical trials. Teprotumumab should be avoided in pregnancy. Evidence also suggests that teprotumumab may exacerbate pre-existing inflammatory bowel disease, worsen hyperglycemia, and be associated with hearing impairment. Patients at risk for these adverse events need to be closely monitored with baseline and periodic assessments.

Keywords: monoclonal antibody, anti-IGF-IR, thyroid-associated ophthalmopathy, Graves' ophthalmopathy, autoimmune

Introduction

Thyroid eye disease (TED, also known as thyroid-associated ophthalmopathy) is a disabling and disfiguring autoimmune condition.¹ The pathophysiology of TED involves a complex interplay between autoantigens including the thyroid stimulating hormone receptor (TSHR) and the insulin-like growth factor-I receptor (IGF-IR), generation of autoantibodies to these receptors, T and B lymphocytes, and various cytokines. These interactions lead to the activation of orbital fibroblasts which are responsible for the characteristic soft tissue changes of TED.^{1,2} Specifically, the discovery that IGF-IR forms a physical and functional complex with TSHR and that inhibition of IGF-IR results in attenuation of downstream signaling initiated by either receptor supports a central role of IGF-IR in TED pathogenesis.³

Most patients with TED have underlying Graves' disease (GD). The pathophysiology of GD also remains to be fully understood. TSHR autoantibodies play a central role in GD pathogenesis, and the titer of these autoantibodies positively correlate with TED activity and severity.^{4–8} Further, autoantibodies generated in patients with GD also bind to IGF-IR and can initiate signaling through the TSHR/IGF-IR complex.⁹ Similar to that seen in TED pathogenesis, TSH and IGF-I pathways interact in thyroid epithelial cells and both are important in regulating thyroid hormone synthesis and participate in GD pathogenesis.⁹ The attainment and maintenance of the euthyroid state is associated with improvement of TED. Current

Correspondence: Shannon S Joseph
1000 Wall Street, Ann Arbor, MI, 48105, USA
Tel +1-734-936-9503
Email sjshan@med.umich.edu

treatment options for hyperthyroid GD include radioactive iodine (RAI) thyroid ablation, antithyroid drug (ATD), and surgical thyroidectomy, though RAI may potentially cause the development or worsening of TED.¹⁰

Based on accumulating evidence supporting the critical role of IGF-IR in TED pathogenesis, teprotumumab was developed as a potential therapy. Teprotumumab is a fully human monoclonal IgG1 antibody against IGF-IR,¹¹ and is the only medication thus far approved by the United States (US) Food and Drug Administration (FDA) for TED.¹² In this article, we review the efficacy and safety of teprotumumab in the treatment of TED, highlighting results from 2 randomized, placebo-controlled, multicenter clinical trials as well as case reports from its post-approval use. All reports were identified through literature searches using the PubMed database.

Efficacy of Teprotumumab in TED

Teprotumumab for Active, Moderate to Severe TED: Results of the Clinical Trials

Two multicenter, double-masked, placebo-controlled trials were performed evaluating the efficacy and safety of teprotumumab in TED (Phase 2 NCT01868997; Phase 3 NCT03298867). Both trials enrolled patients with active, moderate to severe TED. Inclusion criteria included TED of ≤ 9 months duration at screening, CAS of ≥ 4 points on a 7-point scale in the more severely affected (study) eye, and no history of surgical or medical treatment for TED. History of oral glucocorticoid with a cumulative dose of ≤ 1 g of methylprednisolone or equivalent was allowed, after a 6-week washout period. The phase 3 trial also excluded patients with prior treatment with teprotumumab or selenium supplementation within 3 weeks of the screening period. The treatment regimen involved 8 infusions of either placebo or teprotumumab starting with the initial dose of 10mg/kg body weight administered at week 0, then increased to 20mg/kg, which was given every 3 weeks from weeks 3 to 21. The endpoints were assessed at week 24 (3 weeks after the final infusion).^{13,14}

The outcome measures used in these clinical trials included proptosis reduction, improved soft tissue inflammation as measured by clinical activity score (CAS), diplopia improvement, and quality of life (QOL) as measured by the Graves' ophthalmopathy-specific quality of life (GO-QOL) score.^{13,14} Intention-to-treat analysis was performed in both trials. A subsequent study by Kahaly et al reported the results of subgroup analyses using

pooled data from both trials and off-treatment follow-up.¹⁵ We review the findings of both trials and the subsequent analysis below.

Both clinical trials demonstrated significant proptosis reduction in response to teprotumumab, regardless of sex and smoking status. Proptosis response was defined as reduction of ≥ 2 mm in the study (more severely affected) eye, without similar worsening in the fellow eye. At week 24, there were significantly more patients who experienced proptosis response with teprotumumab compared to placebo in both clinical trials and pooled data (phase 2: 69% or 29/42 versus 20% or 9/45, $p < 0.001$; phase 3: 83% or 34/41 versus 10% or 4/42, $p < 0.001$; pooled data: 77% or 65/84 versus 15% or 13/87; $p < 0.0001$).^{13–15}

The mean proptosis reduction from baseline was also greater with teprotumumab than placebo in both clinical trials (phase 2: -2.46 ± 0.20 mm versus -0.15 ± 0.19 mm; phase 3: -2.82 ± 0.19 mm versus -0.54 ± 0.19 mm; both with $p < 0.001$).^{13,14} In phase 2, more patients had ≥ 4 mm and ≥ 3 mm proptosis reductions from baseline with teprotumumab compared to placebo ($p < 0.001$).¹³ These levels of mean proptosis reduction are similar to results attained with single-wall orbital decompression surgery.^{16,17} In addition, the inter-group difference in the proptosis reduction increased at subsequent time points ($p < 0.001$). Patients with the most severe proptosis at baseline were found to manifest the most significant reductions with teprotumumab therapy. The onset of therapeutic proptosis reduction was rapid. In the phase 2 trial, at week 6, significant proptosis reduction was evident with teprotumumab compared to placebo (43% or 18/42 versus 4% or 2/45; $p < 0.001$). The median time to response with teprotumumab was 6.4 weeks.^{13,14}

Both clinical trials also demonstrated that teprotumumab significantly reduced inflammatory signs. CAS reduction was significantly greater for teprotumumab than placebo at all trial visits ($p < 0.001$ for all comparisons) and at week 24 (phase 2: -3.43 versus -1.85 points; phase 3: -3.7 versus -2.0 points; both $p < 0.001$). CAS reduction of ≥ 3 points was more frequent with teprotumumab versus placebo at every level of response ($p < 0.001$). At week 24, more teprotumumab-treated patients had CAS of 0 or 1 compared with placebo, indicating minimal TED activity (phase 2: 69% versus 21%; phase 3: 59% versus 21%; both $p < 0.001$).^{13,14}

Overall response was defined as ≥ 2 mm proptosis reduction and ≥ 2 points CAS reduction from baseline in the study eye, without a similar increase in both parameters in the non-study (fellow) eye at week 24. Overall

response was the primary outcome in the phase 2 trial and a secondary outcome in the phase 3 trial. In both trials, more patients experienced an overall response with teprotumumab compared to placebo (phase 2: 69% or 29/42 versus 20% or 9/45; phase 3: 78% or 32/41 versus 7% or 3/42; both $p < 0.001$).^{13,14}

Teprotumumab resulted in greater reduction in the Gorman diplopia score compared with placebo. In the phase 2 trial, more patients experienced reduction in diplopia from baseline with teprotumumab (68% or 26/38 versus 26% or 10/39; $p < 0.001$). The response with teprotumumab was noted across all trial visits and occurred regardless of baseline diplopia severity.^{13,14} In phase 3, more teprotumumab-treated patients experienced a diplopia response, defined as ≥ 1 reduction on the Gorman diplopia scale from baseline (68% or 19/28 versus 29% or 8/28; $p < 0.001$). In line with these clinical findings, orbital imaging obtained at week 24 of teprotumumab treatment in 6 patients in the phase 3 trial showed significant reduction (mean 35%) in extraocular muscle volume.¹⁴ These findings are consistent with the known role of the IGF-IR signaling pathway in activating fibrocytes and orbital fibroblasts leading to tissue volume expansion.^{1,2,18}

Lastly, both clinical trials demonstrated a positive impact of teprotumumab on QOL of TED patients, which was measured using GO-QOL, the 16-item (8 items each for the 2 subscales of visual function and psychosocial function from altered physical appearance) validated questionnaire. A clinically meaningful change in GO-QOL is a difference of ≥ 6 points in one or both subscales.¹⁹ Pooled data from both trials showed that teprotumumab significantly improved the GO-QoL subscale of visual functioning (least squares [LS] mean 16.8 with standard error [SE] of 2.0 versus 6.1 with SE of 2.0; 10.7 difference, 95% CI of 5.4–16.0; $p < 0.001$) and physical appearance (LE mean 13.5 SE 1.9 versus 5.8 SE 1.8, 7.7 difference, 95% CI of 2.9–12.6, $p < 0.002$).²⁰ In both trials, the GO-QOL overall score improved significantly with teprotumumab (phase 2: 17.7 \pm 2.4 versus 6.8 \pm 2.3 points, $p < 0.01$; phase 3: 13.79 \pm 2.07 versus 4.43 \pm 2.10 points, $p < 0.001$; pooled for both trials LS mean 15.6 SE 1.6 versus 5.9 SE 1.5, 9.6 difference, 95% CI of 5.5–13.7, $p < 0.001$).^{13,14,20}

The effects of teprotumumab on TED appeared to be durable. Of 37 patients completing the intervention period of the phase 2 trial, 49% (18/37) maintained a response at week 72 (51 weeks after the final dose).²¹ Of the 79

patients who completed the phase 3 trial, 13% (5/39) of those treated with teprotumumab were non-responders and were re-treated. Twenty-three percent (9/39) of teprotumumab patients who experienced disease flare during the follow-up period were also re-treated in the OPTIC-X trial. Ninety-three percent (37/40) of placebo-treated patients subsequently received teprotumumab.¹⁵ During the treatment and follow-up periods of both trials, 11 patients in the placebo group received additional medical and surgical treatments for TED. Of these, 6 underwent orbital decompression surgeries. 8 patients treated with teprotumumab had additional treatments, 3 of whom underwent orbital decompression surgeries.¹⁵

In summary, teprotumumab is associated with a rapid and clinically significant reduction in proptosis, tissue inflammation, and diplopia; with improvement in quality of life. The improvements by teprotumumab in the study and fellow (contralateral) eye were similar. The response to teprotumumab appears to exhibit durability, though disease flare can occur.^{13,14} The numbers needed to treat (number of patients who need to be treated with teprotumumab in order to attain one additional respective positive outcome) were 1.6 for proptosis response, 1.7 for overall response (treatment difference 60%, 95% CI 48–72), 2.5 for disease inactivation (treatment difference 40%, 95% CI 27–53), 2.5 for diplopia response (treatment difference 39%, 95% CI 23–55) (all $p < 0.0001$).¹⁵ Although no published studies have directly compared teprotumumab with other treatment modalities, aggregate results concerning glucocorticoids, orbital radiotherapy (ORT), and other monoclonal antibodies in TED indicate their inferiority.^{22–30} A meta-analysis including randomized controlled trials showed that the use of intravenous glucocorticoids resulted to a mean CAS reduction of 2.5, TED inactivation in 59%, and diplopia improvement in 36% of patients; intravenous glucocorticoids had little (1.14mm) to no effect on proptosis reduction.^{24,25} ORT improved extraocular muscle motility (odds ratio of 4.88, 95% CI 1.93–12.34) but had no significant effect on proptosis reduction, CAS reduction, or the need for additional treatment in moderate to severe TED.^{26,27} Two randomized controlled trials showed that rituximab had no significant effect on proptosis reduction and diplopia in patients with active, moderate to severe TED. While Stan et al reported no difference between rituximab and placebo in CAS reduction at 24 and 52 weeks, Salvi et al showed the superiority of rituximab over intravenous glucocorticoids in reducing CAS at 24 weeks. The favorable finding by Salvi et al may be due to the shorter TED duration (mean of 4.5 months compared

with mean of 11.2 months for the Stan et al trial) and the fewer patients who underwent previous radioactive iodine therapy.^{28,29} The effect of tocilizumab versus placebo on CAS reduction and proptosis reduction at week 40 was not significant. Tocilizumab had no effect in patients with steroid-resistant, moderate to severe TED on diplopia or quality of life.³⁰

Teprotumumab for Compressive Optic Neuropathy in TED

Compressive optic neuropathy (CON) can occur in TED as a consequence of enlarged extraocular muscles at the orbital apex, and less commonly from stretching of the optic nerve from severe proptosis. Patients with CON were excluded from both clinical trials. Nevertheless, since the FDA approval of teprotumumab, 6 publications have reported on 15 cases demonstrating favorable effects of teprotumumab for CON (Table 1).^{31–36}

All 15 patients had failed to improve with or were not candidates for conventional treatments including systemic corticosteroids, orbital radiotherapy, and/or surgical decompression. All had poor optic nerve function, which was characterized by decreased visual acuity (VA) and/or color vision, presence of relative afferent pupillary defect (RAPD), and visual field (VF) defect. For this review, a patient was considered to have “resolution of CON” with treatment if they had a final VA of 20/20 or baseline VA in the involved eye, normal color vision, and resolution of abnormal optic nerve function findings including RAPD, optic nerve changes, or VF defect. A patient was considered to have “improved CON” if they had improved yet persistently abnormal optic nerve function. Of the 15 reported cases, 9 had complete resolution of CON while 6 cases had improved CON.^{31–36} The onset of improvement was as early as after 2 doses of teprotumumab in 6 of these cases.^{32,36}

Data on proptosis reduction and CAS improvement were also available in 13 of the 15 reported cases. Twelve of 13 cases had ≥ 2 mm proptosis reduction in the involved eye (range, 2mm to 10mm). All 13 cases had a final CAS of 0 to 1 (CAS reduction range, 4 to 7). As observed in the clinical trials, the onset of response was rapid. After only 2 doses, proptosis reduction was noted in 5 of 13 cases and CAS improvement in 9 of 13 cases.^{31–34,36} In addition, these responses persisted at 3–33 weeks after the final 8th dose.^{31–33,36} Radiographic data was available for 7 cases, and all showed reduction in both extraocular muscle size and apical crowding, supporting the clinical evidence of

CON resolution or improvement. While these reports suggest that teprotumumab may be an effective therapy for CON, further studies should help identify clinical factors that would be predictive of a positive response to teprotumumab, including duration and/or severity of CON. For example, teprotumumab may only have favorable results in CON when the optic nerve has not yet reached the irreversible atrophic state.

Teprotumumab for Inactive TED

Patients with inactive TED were also excluded from both clinical trials. However, 2 subsequent reports of 5 patients have demonstrated favorable effects of teprotumumab in chronic inactive TED (Table 2). Ugradar et al reported 4 consecutive patients with “non-inflammatory” TED, each with CAS of ≤ 1 for at least 4 months, diplopia scores of 0, but all had persistent bilateral proptosis. All four patients, each without previous history of orbital surgery or radiotherapy, were treated with teprotumumab. After 8 infusions, all 4 patients demonstrated ≥ 2 mm proptosis reduction (mean reduction 2.6mm, standard deviation 1.2, $p < 0.01$) in the more severely affected eye. The CAS and diplopia scores remained 0 throughout the treatment. It is important to note that while these four patients described by Ugradar et al were defined as clinically “non-inflammatory” based on CAS of ≤ 1 , the duration of disease were only 4, 5, 7, and 12 months. Thus, it is conceivable that patients may have early, mildly active disease rather than chronic, inactive disease. This issue highlights the imprecision of judging TED activity on the basis of CAS. A separate report by Ozzello et al described the case of a 50-year-old man with asymmetric bilateral proptosis of ≥ 3 years duration that had been stable for 2 years. Treatment with teprotumumab was associated with 5mm bilateral proptosis reduction after 2 infusions. CAS improved from 1 to 0 with the resolution of orbital pain after 3 infusions.^{37,38}

Currently, chronic, inactive TED is predominantly managed with surgical rehabilitation as needed. The reports above suggest the potential of teprotumumab as disease-modifying in chronic inactive TED.^{37,38} While the initial findings of Ugradar et al showed IGF-IR overexpression in orbital fibroblasts of “non-inflammatory” TED compared to controls,³⁷ more rigorous clinical studies are required to fully elucidate the role of teprotumumab in treating inactive TED. A 24-week, randomized, placebo-controlled, multicenter trial (Phase 4 NCT04583735) to evaluate the efficacy and safety of

Table 1 Clinical and Demographic Details of Patients with CON Treated with Teprotumumab

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15
Reference	Sears ^{31,36}	Slentz ³²	Hwang ³³	Chiou ³⁴	Diniz ³⁵	Diniz ³⁵	Sears ³⁶								
Sex	M	M	F	F	F	F	F	F	F	F	F	F	M	M	M
Age (years)	45	62	81	68	83	90	76	84	62	73	55	73	57	40	76
Smoker	Prior	Y	U	N	U	U	N	N	N	Prior	N	N	N	N	N
Duration of active TED (months)	18	6	8	3	4	72	>120	~12	6	12	2	2	120	10	20
Prior treatment	SS, RT OD	None	SS	SS	SS	SS	SS, SD OU	SS	SS	SS, SD OU	SS, SD OD	SS	SD OU, SS, RT OU	SS	SS, SD OD
Laterality of CON	OU	OD	OU	OS	OS	OS	OU	OU	OU	OS	OS	OD	OU	OS	OU
Final VA															
OD	20/20	20/20	20/40-	20/25	U	U	20/800	20/800	20/50	20/20	20/25	20/20	20/25	20/20	20/70
OS	20/20	20/20	20/30-	20/25	20/60	20/50	20/800	20/800	20/30	20/20	20/25	20/20	20/30	20/20	20/200
Resolved RAPD	Y	N/A	Y	N/A	Y	Y	N/A	N/A	N/A	N/A	Y	Y	Y	Y	IMP
Normal final color vision	Y	N/A	Y (OD) IMP (OS)	N/A	IMP	Y	N/A	N/A	Y	Y	Y	N/A	Y	Y	IMP
Final proptosis reduction OD, OS (mm)	3.5, 7	5, 5	5, 4.5	4.5, 3	U	U	3, 2	3, 3	4, 5	9, 10	3.5, 4.5	7, 7	1, 1	7, 9	3, 3
Final CAS reduction	4	5	6	6	U	U	6	4	4	5	4	7	4	7	6
Reduced EOM size and apical crowding on imaging	Y	Y	Y	U	U	U	U	Y	Y	U	Y	U	U	Y	U
Length of follow-up after 8th dose (weeks)	30	4	0	N/A	N/A	N/A	16	3	22	16	0	0	22	33	5

Note: The words in bold letters are headers of each column.

Abbreviations: M, male; F, female; Y, yes; U, unknown; N, no; TED, thyroid eye disease; SS, systemic steroid; RT, radiotherapy; OD, right orbit or eye; SD, surgical decompression; OU, both orbits or eyes; CON, compressive optic neuropathy; OS, left orbit or eye; VA, visual acuity; RAPD, relative afferent pupillary defect; N/A, not applicable; IMP, improved, not resolved; mm, millimeter; CAS, clinical activity score; EOM, extraocular muscle.

Table 2 Clinical and Demographic Details of “Non-Inflammatory” or Inactive TED Patients Treated with Teprotumumab

	Case 1	Case 2	Case 3	Case 4	Case 5
Reference	Ugradar ³⁷	Ugradar ³⁷	Ugradar ³⁷	Ugradar ³⁷	Ozzello ³⁸
Sex	F	F	F	M	F
Age (years)	22	32	47	21	50
Smoker	N	N	N	N	Y
Duration of TED (months)	12	7	4	5	24
Prior treatment	SS	SS	SS	SS	None
Final proptosis reduction after teprotumumab treatment OD, OS (mm)	3, 4	1, 2	3, 2	4, 3	6, 6 ^a
CAS at baseline	0	0	0	0	1
Reduced EOM size on orbital imaging	N/A	N/A	N/A	N/A	Y

Note: The words in bold letters are headers of each column.

Abbreviations: F, female; M, male; N, no; Y, yes; TED, thyroid eye disease; SS, systemic steroids; mm, millimeter; OD, right orbit; OS, left orbit; CAS, clinical activity score; EOM, extraocular muscle; N/A, not applicable; a, after only 3 doses; no details on subsequent doses.

teprotumumab in treating patients with chronic inactive TED is currently in the recruitment process.³⁹

Safety of Teprotumumab as a Therapy for TED

Teprotumumab is a fully human IgG1 monoclonal inhibitory antibody against IGF-IR. Since it was initially developed for cancer therapy, studies on the tolerability and adverse effects were originally performed in patients with solid tumors including sarcomas. Early phase clinical trials revealed that the drug was well-tolerated.^{40–43} There was no dose-limiting toxicity associated with weekly infusions of 9mg/kg; the maximum tolerated dose was not reached.⁴⁰ Safety results from the clinical trials for TED and post-approval reports are discussed below (Table 3).

Safety of Teprotumumab for Active, Moderate to Severe TED: Results of the Clinical Trials

Adverse events (AE) of any cause were defined as those that occurred between the administration of the first dose and 30 days after the administration of the final dose (prior to week 25). Some patients had multiple AEs. In both trials, the most common AEs reported with teprotumumab included muscle spasms (25% or 21/84), nausea (17% or 14/84), alopecia (13% or 11/84), diarrhea (12% or 10/84), fatigue (12%), hearing impairment (10% or 8/84), and hyperglycemia (8% or 7/84). AEs of special interest, which are AEs that potentially have mechanistic ties to teprotumumab, included infusion-related reactions, muscle spasms, diarrhea, hearing impairment, and hyperglycemia.^{13,14} In the pooled follow-up study of both trials at weeks 28 and 72, AEs of

special interest in the teprotumumab group included 1 case of muscle spasm, 2 cases of hearing impairment, and 2 cases of hyperglycemia.¹⁵

The severity of AEs in both trials was graded based on version 4.03 of the National Cancer Institute Common Terminology Criteria for AEs.^{13,14} Grade 1 or mild AEs are associated with asymptomatic or mild symptoms; intervention is not indicated. Grade 2 or moderate AEs limit age-appropriate instrumental activities of daily living; they require minimal, local, or non-invasive intervention.⁴⁴ Most AEs were mild to moderate in severity for both teprotumumab and placebo groups (94% or 63/67 versus 98% or 59/60). Most AEs resolved while the patients continued in their study group.^{13,14} The pooled week 28 and 72 follow-up analysis of both trials showed that AEs in 90% (26/29) of patients who received teprotumumab and 100% (9/9) patients who received placebo were mild to moderate.¹⁵

Serious AEs were uncommon in both trials. Of the serious AEs occurring in the teprotumumab group (8% or 7/84) in both trials, 4% (3/84) were considered by the trial investigators as possibly related to teprotumumab and led to study intervention discontinuation. These included infusion reaction, diarrhea, and transient (less than 24-hour) cognitive changes with a provisional diagnosis of Hashimoto’s encephalopathy.^{13,14}

Teprotumumab and Infusion-Related Reaction

Intravenous administration of monoclonal antibodies can result in infusion-related reactions. These reactions can be anaphylactic or anaphylactoid from cytokine release. Two patients in the phase 3 trial developed infusion reaction to

Table 3 Clinical and Demographic Details of Patients Developing Adverse Events with Teprotumumab for TED

	Case 1	Case 2	Cases 3–5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
Reference	Ashraf ⁴⁸	Safo ⁴⁹	Kossler ⁵²	Kossler ⁵²	Belinsky ⁵³	Belinsky ⁵³	Belinsky ⁵³	Belinsky ⁵³	Hoang ⁶³
Sex	F	F	N/A	N/A	F	F	F	F	M
Age (years)	45	46	N/A	N/A	77	68	34	48	76
Smoker	N	N	N/A	N/A	Previous	N/A	N/A	N/A	N/A
Duration of TED (in months)	6	2	N/A	N/A	6	N/A	N/A	N/A	N/A
Prior treatment	None	SS	N/A	N/A	SS	SS, SD OD	N/A	None	None
Presenting feature	Bowel urgency, diarrhea, HC, Abd pain	Fecal urgency, HC	SNHL in 2 of 3 patients	N/A	N/A	Decreased hearing and muffled hearing (worse AS)	Difficulty hearing background noise AS	Fullness AU	Behavior changes, Confab, memory deficit, delirium, delusion
Adverse event (AE)	IBD	Ulcerative colitis (IBD)	Hearing impairment	Hearing impairment	Hearing impairment	Hearing impairment	Hearing impairment	Hearing impairment	Rapid cognitive decline ^a
Onset of AE (after x doses)	6	5	~3.6	~3.6	3	3	8	4	4
Resolution of AE	N	N	N	Imp	N	N	Y	Imp	Y

Note: The words in bold letters are headers of each column.

Abbreviations: F, female; N/A, not applicable; M, male; TED, thyroid eye disease; SS, systemic steroids; SD, surgical decompression; OD, right orbit; HC, hematochezia; Abd, abdominal; SNHL, sensorineural hearing loss; AS, left ear; AU, both ears; Confab, confabulation; AE, adverse event; IBD, inflammatory bowel disease; x, a certain number; N, No; Imp, improved, not resolved; Y, yes; a, causal relationship with teprotumumab cannot be established.

teprotumumab. Neither was anaphylactic. One patient developed the reaction during the initial infusion and discontinued the trial drug despite resolution with hydrocortisone within 2 hours. The other patient was pre-medicated thereafter, received subsequent infusions at a slower rate, and completed the study. No antidrug antibodies were detected in those patients who received teprotumumab.^{13,14} Most infusion-related reactions occur during or within 90 minutes of the first infusion and are mild in severity. These can be managed by discontinuation of the infusion, and evaluation of vital signs and airway integrity. The need for epinephrine, anti-histamine, or corticosteroids should be determined; resuming the infusion at a slower rate and titrated to tolerance is recommended. Pre-medication with anti-histamine, anti-pyretic, and corticosteroid may be considered prior to subsequent infusions, which should initially be given at a slower rate.⁴⁵

Teprotumumab and Muscle Spasm

Muscle spasm was the most frequently reported AE for teprotumumab, occurring at a higher incidence compared to placebo (25% or 21/84 versus 7% or 6/86) in both trials. IGF-I is thought to play an important role in skeletal muscle growth, repair, and prevention of degeneration.⁴⁶ Inhibition of IGF-IR may lead to muscle spasm, but the mechanism has yet to be determined. The most commonly affected body areas were the lower limbs. No clinically relevant laboratory abnormalities were identified, although serum magnesium levels were not tested. Most cases were mild in severity; moderate cases were reported for 5 patients in total in the teprotumumab group in both trials. None discontinued treatment.^{13,14,20} Treatment measures could include muscle relaxants and supplementation with vitamin B, calcium, and magnesium.

Teprotumumab and Inflammatory Bowel Disease

Teprotumumab may reactivate inflammatory bowel disease (IBD) in those patients with a history of the disease. IGF-I has been shown to induce proliferation of regulatory T cells and halt the progression of autoimmune diseases in the gut.⁴⁷ In the phase 2 trial, diarrhea was reported in 14% (6/43) of teprotumumab-treated patients. One of these 6 cases was classified as a serious AE. The patient had a 6-month history of ulcerative colitis who developed severe diarrhea while receiving teprotumumab. Another patient was diagnosed by colonoscopy with ileitis and colitis 3 months into the study and was treated and recovered from IBD while continuing to receive teprotumumab. These after study observations led to the exclusion of patients with pre-existing IBD in the phase 3 trial.^{13,14}

Subsequently, Ashraf et al and Safo et al independently reported two women in their 5th decade of life who developed new-onset IBD during teprotumumab therapy for active TED. After 5–6 infusions, both developed bowel urgency and hematochezia. Colonoscopy and biopsy confirmed the diagnosis of ulcerative colitis (UC) in both. Teprotumumab was discontinued for both while the patients underwent treatment for UC. Their gastrointestinal symptoms persisted for 1.5–2 months after the seventh infusion of teprotumumab. Of note, both patients had a family history of UC; one had at least 1 episode of bilateral uveitis of unknown etiology 2 years prior to the diagnosis of UC.^{48,49}

Teprotumumab may exacerbate pre-existing IBD. Patients should be monitored for disease flare and the drug must be discontinued if IBD worsens. In addition, identifying treatment candidates with family histories of IBD should aid in stratifying risk as up to 12% of IBD cases are familial and family history is the strongest recognizable risk factor.^{50,51}

Teprotumumab and Hearing Impairment

Hearing impairment was one of the most common AEs associated with teprotumumab in both clinical trials.^{13,14} None of the placebo patients developed hearing impairment while nearly 10% (8/84) of the teprotumumab-treated patients did so. In the phase 2 trial, 7% (3/43) developed hearing abnormalities with teprotumumab; 1 resolved, 1 had partial improvement, and 1 required evaluation for hearing aids. One patient developed mild hyperacusis before the fifth dose; audiogram performed on week 16 revealed mild bilateral hearing loss.

The bilateral hearing impairment resolved at week 35. Another patient with moderate eustachian tube dysfunction developed moderate unilateral deafness 16 weeks after completing teprotumumab therapy; audiogram performed on week 39 showed moderate mixed hearing loss. The eustachian tube dysfunction resolved at week 68; unilateral moderate, mixed hearing loss partially improved by week 71. A third patient with pre-existing intermittent tinnitus from loud noise exposure developed moderate high frequency sensorineural bilateral hearing loss at the time of the eighth dose. Evaluation for hearing aids was recommended.^{13,46} In the phase 3 trial, 12% (5/41) developed spontaneously resolving hearing impairment with teprotumumab: 2 cases of mild to moderate hypoacusis; 1 case of moderate deafness; 1 case of mild autophony; and 1 case of mild patulous eustachian tube.¹⁴ The hearing impairments developed after 4–8 infusions. All patients in the teprotumumab group completed therapy. Of note, baseline audiograms were not part of the screening protocol in either trial. Further, not all patients who reported hearing impairment underwent formal audiology testing.^{13,14}

Kossler et al published a retrospective series of 28 TED patients treated with teprotumumab and found that 13 patients (46%) experienced hearing symptoms after a mean of 3.6 infusions. The most commonly reported symptoms were autophony, hearing loss, or muffled hearing. Three patients developed sensorineural hearing loss (SNHL) and did not experience significant improvement 3 months after drug discontinuation. One patient developed patulous eustachian tube (PET), with some improvement of her symptoms after drug discontinuation.⁵² No other details were provided for the 9 remaining patients who were reported to have hearing symptoms. Another retrospective series by Belinsky et al of 28 patients with TED treated with teprotumumab found 4 patients (14%) to have hearing symptoms after receiving at least 3 infusions. All 4 patients developed SNHL with abnormal audiogram findings.⁵³ One patient discontinued treatment after 7 infusions; the others completed all 8 infusions. In 3 patients, the hearing impairment persisted 2, 3, and 7 months after the final dose. One patient who developed hearing symptoms after 4 doses gradually improved and completed 8 doses.⁵³

The frequency, magnitude, reversibility, and mechanism of the hearing impairment associated with teprotumumab remains unclear. Studies have shown the crucial role of IGF-I in the development, survival, and maintenance of cochlear hair cells, regeneration of cochlear synapses, and synaptic neurotransmission in the cochlear nuclei.^{54–56} IGF-I appears to protect cochlear hair cells

from trauma due to loud noise, medication toxicity, and ischemia.^{54–56} It is possible that IGF-IR inhibition by teprotumumab may alter receptor signaling and result in SNHL. Eustachian tube dysfunction and autophony, which were identified in both clinical trials and one case series, may be due to atrophy of the nasopharyngeal fat pad, resulting in Eustachian tube dysregulation.^{13,14,53} Further studies are needed to better understand the association between hearing impairment and teprotumumab therapy. It may be prudent to obtain audiologic testing at baseline, during, and after completion of teprotumumab therapy. Patients should also be closely monitored for hearing symptoms through the course of treatment.^{52,53}

Teprotumumab and Hyperglycemia

Hyperglycemia is an AE of special interest associated with teprotumumab therapy,^{13,14,39–41} and was more commonly reported in patients with pre-existing diabetes mellitus or impaired glucose tolerance.¹³ This finding is likely related to reduced insulin sensitivity from IGF-IR inhibition, a co-receptor of the insulin receptor.^{13,57}

In the phase 2 trial, hyperglycemia occurred in 12% (5/43) of teprotumumab-treated patients.¹³ Hyperglycemia was consistently grade 1 (asymptomatic or mild) among non-diabetics, and grade 2 or 3 (severe or medically significant but not immediately life-threatening) among patients with baseline diabetes.⁴³ In the phase 3 trial, 5% (2/41) of patients who received teprotumumab developed grade 1 (mild) hyperglycemia. In both trials, hyperglycemia occurred in more patients who received teprotumumab compared to placebo (10% or 8/84 versus 1% or 1/86). Five out of 8 patients who developed hyperglycemia in the teprotumumab group had pre-existing diabetes mellitus or impaired glucose tolerance at baseline. In all cases, hyperglycemia was managed through diabetes medication adjustment. All events resolved either during or immediately following treatment; none led to teprotumumab discontinuation.^{13,14}

In summary, hyperglycemia can occur during teprotumumab therapy, especially in patients with pre-existing impaired glucose tolerance. Prior to initiating treatment with teprotumumab, baseline glucose and HbA1c testing and optimizing glycemic control are strongly recommended. During teprotumumab treatment, patients with history of diabetes or pre-diabetes should be closely monitored for the development of hyperglycemia and treated accordingly in collaboration with endocrinologists or primary care providers.^{13,14,58}

Teprotumumab in the Pregnant and Pediatric Populations

IGF-I is an important mediator of normal and abnormal growth, and the IGF-I pathway plays a critical role in both intrauterine and postnatal development or growth. Although IGF-I insufficiency is relatively well-tolerated in adulthood, insufficiency can lead to severe consequences in utero through adolescence.⁵⁹ Mutations in the human IGF-I gene that result in abnormal circulating levels of IGF-I are associated with intrauterine and postnatal growth failure, sensorineural deafness, and mental retardation.^{60,61}

No controlled studies have been conducted in pregnant or lactating women or in children. However, animal studies suggest that teprotumumab may lead to increased fetal loss, as well as external and skeletal abnormalities.⁶² Therefore, teprotumumab use should be avoided during pregnancy. It is important to screen women for pregnancy prior to initiating treatment and implement effective (such as double barrier) contraception prior to initiation, during, and for 6 months after treatment with teprotumumab.⁶² The authors also strongly recommend that teprotumumab not be used in pediatric patients.

Teprotumumab and Cognitive Changes

Two patients treated with teprotumumab developed cognitive changes. However, a causal relationship could not be established in either case. The phase 2 trial disclosed 1 case of cognitive changes in a 61-year-old man who developed multiple episodes of transient mental confusion lasting less than 24 hours after 6 doses, without other neurologic symptoms. Brain imaging failed to demonstrate pathologic findings. Lab work revealed elevated thyroid peroxidase antibody. Based on the strong family history of autoimmune thyroid disease and intermittent fluctuating nature of the symptoms, a provisional diagnosis of Hashimoto's encephalopathy was made. Teprotumumab was discontinued even though the association between treatment and these cognitive changes was uncertain.^{13,46}

A case report by Hoang et al described a 76-year-old man with Graves' disease, rendered euthyroid with methimazole, who developed 6 weeks of rapidly worsening cognitive decline after the fourth infusion of teprotumumab. The patient developed intermittent behavioral and mental changes including confabulation, memory deficit, and delirium. Teprotumumab was discontinued. Acute neurologic etiologies were ruled out with normal brain

imaging and laboratory tests. The neurologic condition did not respond to systemic steroids or intravenous immunoglobulins but resolved following plasmapheresis. Causal relationship of this neurologic presentation with teprotumumab was not established.⁶³

Conclusion

Teprotumumab has been shown to be effective in the treatment of active, moderate to severe TED in the phase 2 and phase 3 clinical trials. Subsequent case reports suggest that the drug may also be effective in treating CON and chronic inactive TED. The therapeutic effects of teprotumumab on TED have rapid onset and appear durable. Results from the case reports will need confirmation in larger studies of patients with CON and inactive TED. There have been no clinical studies comparing teprotumumab with other treatment modalities traditionally used to treat TED (eg medical therapy including corticosteroids, other biologics, and surgical management). Future studies could focus on these comparisons as well as cost-effectiveness analysis of teprotumumab.

Obtaining detailed medical history prior to initiating therapy with teprotumumab is important. This includes details of risk factors for IBD, hearing impairment, hyperglycemia, and ruling-out pregnancy. Teprotumumab is contraindicated in pregnancy. The drug may also exacerbate pre-existing IBD and be associated with hyperglycemia and hearing impairment. Patients with pre-existing IBD should be monitored for disease flare, in which case the drug should be discontinued. Hyperglycemia should be carefully monitored, and diabetes medication should be adjusted as indicated for maintaining optimal glycemic control. Patients should also be closely monitored for the development of hearing impairment. Obtaining routine baseline and periodic pre-infusion audiologic assessment is prudent.

Disclosure

Dr. Terry J. Smith has been issued the following US patents, held by University of California Los Angeles and Los Angeles Biomedical Institute and covering the use of insulin-like growth factor I receptor inhibition and teprotumumab in Graves' disease and other autoimmune diseases: 6936426, 7998681, 8153121, and 8178304. He receives consulting fees from Horizon Therapeutics and Immunovant outside the submitted work. His institution received research support from Horizon Therapeutics for participating in the clinical trials of teprotumumab for TED. Dr. Shannon S. Joseph receives consulting fees

from Horizon Therapeutics outside the submitted work. The authors report no other conflicts of interest in this work.

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