• Brief Report •

Efficacy of teprotumumab N01 (IBI311), an IGF-1R inhibitor, for thyroid eye disease patients who had failed glucocorticoids

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Abstract

● **AIM:** To explore the efficacy of teprotumumab N01 (IBI311), an insulin-like growth factor-1 receptor (IGF-1R) inhibitor, in thyroid eye disease (TED) patients who had failed glucocorticoids.

● **METHODS:** In this pilot case series study, patients with TED failing intravenous or oral glucocorticoid treatments were treated with teprotumumab N01 (10 mg/kg for the first infusion then 20 mg/kg every 3wk for subsequent 3 infusions). Proptosis, clinical activity score (CAS), Gorman diplopia score, magnetic resonance imaging (MRI), adverse events and laboratory tests were evaluated during the treatment.

● **RESULTS:** The patients' mean age was 38.7y, 6 of 10 were female, and TED duration of these patients ranged from 0.8 to 5y. At week 12, 7 patients had proptosis response, 6 achieved a CAS of 0 or 1 and 5 achieved an overall response. For patients with proptosis improvement, MRI also showed consistent changes including volume decrease of extraocular muscles and orbital fat tissues. The incidence of adverse events was low.

● **CONCLUSION:** Teprotumumab N01 infusions result in proptosis response and clinical activity improvements accompanied with favorable safety profile in TED patients who had failed glucocorticoids. Randomized controlled trials will be conducted to further assess the efficacy and safety of teprotumumab N01 in TED patients.

● **KEYWORDS:** thyroid eye disease; glucocorticoids; insulin-like growth factor-1 receptor; teprotumumab N01; IBI311

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INTRODUCTION

Thyroid eye disease (TED) is a disfiguring and potentially sight-threatening autoimmune inflammatory disorder commonly associated with Graves hyperthyroidism. Clinical manifestations vary among patients, ranging from mild dry eye symptoms to sight-threatening exposure keratopathy or optic neuropathy[1]. Exophthalmos is the hallmark of TED and is difficult to treat with medication[2].

For a long period of time, glucocorticoids have been the first-line treatment for patients with active moderate-to-severe TED[3-4]. However, the effectiveness of glucocorticoids on proptosis was limited, ranging from 0 to 46%[4-6]. Moreover, glucocorticoids may result in a series of unwanted side effects, including weight gain, mood alterations, glucose intolerance, osteopenia, infections, gastric distress, and even some rare but fatal complications, including fulminant hepatic failure, cardiac arrhythmias, and myocardial infarction[7-8]. Given limitations to the effectiveness and safety profile of glucocorticoid therapy

for TED, there has been ongoing research on alternative therapies.

In the last few decades, better understanding of the pathophysiology of TED indicated that insulin-like growth factor 1 receptor (IGF-1R), together with thyrotropin receptors, form physical and functional complexes on orbital fibroblasts and immune cells and cause TED[9]. Teprotumumab, a monoclonal antibody targeting IGF-1R, interrupts the progress of TED[10]. The transformative phase 2 and phase 3 trials of teprotumumab have demonstrated marked improvements in proptosis, clinical activity score (CAS), diplopia, as well as patient-reported outcomes, representing a major contribution to the advancement of TED treatment[11-12]. Although teprotumumab received its initial United States Food and Drug Administration (US FDA) approval for the treatment of TED in January 2020, followed by regulatory approval in a number of countries and regions, it is still not available in China. Therefore, glucocorticoids still remain as the first-line treatment for TED in many countries, including China, despite their safety concerns and limited efficacy.

Teprotumumab N01 (IBI311) is a recombinant fully human anti-IGF-1R monoclonal antibody developed in China for the treatment of moderate-to-severe TED. Although it has the same amino acid sequence as teprotumumab, teprotumumab N01 differs in its modified dosage form (change from lyophilized powder to solution), which is designed to facilitate administration. A phase II trial of teprotumumab N01 demonstrated its superiority over placebo in proptosis response at week 12 in patients with moderate-to-severe active TED[13], and a phase III trial of teprotumumab N01 has evaluated its efficacy and safety[14]. In the phase II and III studies of teprotumumab N01 and teprotumumab, patients who had previously received high-dose glucocorticoids for TED were excluded. Therefore, the efficacy of IGF-1R inhibitor in TED patients who do not respond to glucocorticoids remains unclear. Therefore, the purpose of this case series was to study the efficacy of teprotumumab N01 in patients who do not respond to glucocorticoids (defined as a reduction in CAS of less than 2 points following a 3-month treatment of intravenous methylprednisolone (4.5–8.0 g) or 3–6mo of oral glucocorticoids).

PARTICIPANTS AND METHODS

Ethical Approval The authors state that the study was approved by the institutional review board/ethics committee at Peking University People's Hospital (approval number: RD2022-417) and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

This was an investigator-initiated prospective pilot case series study, and was a separate part of a clinical study which included a second part of randomized clinical trial (registered on https://www.medicalresearch.org.cn). Patients who have been exposed to glucocorticoids and have failed the treatment, defined as less than 2 points of CAS reduction or less than 2 mm decrease in proptosis after 3-month treatment of methylprednisolone (4.5 to 8.0 g) or 3–6mo of oral glucocorticoids, prednisone (start at 30 mg, taper and discontinue), or methylprednisolone (start at 24 mg, taper and discontinue), were treated with teprotumumab N01 (10 mg/kg for the first infusion then 20 mg/kg for subsequent infusions) every 3wk for a total of 4 infusions. The last follow-up occurred at 3wk after the last infusion (week 12).

Proptosis response (defined as a reduction in proptosis ≥2 mm without a corresponding deterioration of ≥2 mm in the fellow eye), percentage of patients achieved a CAS of 0 or 1, overall response (defined as a reduction of ≥2 points in the CAS and a reduction in proptosis of ≥2 mm without a corresponding deterioration of ≥2 points or ≥2 mm in the fellow eye), change from baseline to week 12 in diplopia response (defined as reduction in diplopia ≥1 grade from baseline) and adverse events were assessed during teprotumumab N01 treatment. Patients also received orbital magnetic resonance imaging (MRI) before and after the treatment.

RESULTS

Patients included 6 women and 4 men, aged between 21 and 57y (mean age 38.7y). All of them were Chinese with a TED duration ranging from 0.8 to 5y (Table 1). The average proptosis at baseline was 21.5 mm [standard deviation (SD) 4.94 mm], 2 of 10 patients had a baseline CAS score of 5, and 4 of 10 patients presented diplopia at baseline. Three patients were prior smokers and 1 patient was a current smoker. Eight of 10 patients failed 3-month treatment of intravenous methylprednisolone. Three patients received oral glucocorticoids and two underwent local injection of steroids, whereas clinical manifestations including proptosis and diplopia were exacerbated after these treatments. All patients completed 4 infusions of teprotumumab N01 at week 0, 3, 6, and 9, but 2 patients lost to the last follow-up at week 12, resulting in a study completion rate of 80%.

Table 2 presents the baseline and week 12 measurements of proptosis, CAS and diplopia for these 8 patients. At week 12, of the 10 patients, 7 patients (70%) achieved a proptosis response, 6 patients (60%) achieved a CAS of 0 or 1 and 5 patients (50%) achieved an overall response. In addition, results of MRI supported the improvement of proptosis and CAS in these patients, as mean changes of fat tissue volume and extraocular muscles were -0.92 cm^3 (SD 1.42) and -1.32 cm^3 (0.91). Treatment-emergent adverse events (Table 3) were all mild or moderate. No serious adverse events were observed. Muscle spasm, irregular menstruation, hyperuricemia, and

Table 1 Demographics and clinical characteristics

Case	Age (y)	Sex	Smoker	TED duration (y)	Prior treatment	Prior steroids course	Cumulative steroids dose	TSH (mIU/L)	TRAb (IU/L)
1	47	Male	Prior	0.9	IV steroids	3mo	5.75 g	1.63	1.20
2	27	Female	Never	1.0	IV steroids	3mo	4.5 g	0.11	15.20
3	21	Female	Never	1.5	IV steroids	3mo	4.5 g	3.86	9.76
4	33	Male	Prior	1.3	Oral steroids	3mo	1.2 g	1.00	10.29
5	45	Female	Never	0.8	IV steroids	3mo	4.5 g	2.54	2.11
6	45	Female	Never	1.2	IV and oral steroids	6mo	IV: 1 g; oral: 4 g	<0.01	1.93
7	25	Female	Never	1.3	Local steroids injection	4 injections	N/A	6.73	13.42
8	57	Male	Current	1.2	IV and oral steroids	3mo	IV: 7.5 g; oral: N/A	2.60	7.52
9	32	Male	Prior	1.1	IV and local injection of steroids	3mo	4.5 g	1.06	4.06
10	55	Female	Never	5.0	IV steroids	3mo	4.5 g	0.01	31.90

IV: Intravenous; N/A: Not applicable; TED: Thyroid eye disease; TRAb: Thyrotropin receptor antibodies; TSH: Thyrotropin.

Table 2 Therapeutic response

Case	Baseline proptosis (mm)	Proptosis after teprotumumab N01 treatment (mm)	Proptosis reduction (mm)	Baseline CAS	CAS after teprotumumab N01 treatment	CAS improvement	CAS 0/1	Diplopia score at baseline	Diplopia score at week 12	Diplopia response
1	24	21	3	4	2	2	No	3	3	No
2	22	19	3	5	1	4	Yes	0	0	N/A
4	20	18	2	2	1	1	Yes	0	0	N/A
5	20.5	19	1.5	3	1	2	Yes	0	0	N/A
7	24	21	3	3	0	3	Yes	1	0	Yes
8	28	25	3	5	0	5	Yes	0	0	N/A
9	23	20	3	3	0	3	Yes	3	0	Yes
10	24	22	2	3	2	1	No	2	2	No

Case 3 and Case 6 were lost at the last follow-up, hence no efficacy data. CAS: Clinical activity score; N/A: Not applicable (these patients were of no diplopia at baseline).

Table 3 Summary of adverse events

Adverse events	1	2	3	4	5	6	7	8	9	10	Total, *n* (%)
Abdominal distension		√									1 (10)
Asthenia	√										1 (10)
Blood uric acid increased	√										1 (10)
Diarrhea	√	√					√				3 (30)
Dizziness	√										1 (10)
Hearing impairment				√							1 (10)
Heart rate decreased	√			√							2 (20)
Menstrual disorder							√				1 (10)
Muscle spasm			√								1 (10)
Nasal dryness							√				1 (10)
Nausea							√				1 (10)
Taste disorder							√				1 (10)
Weight decreased							√				1 (10)

hearing impairment were each reported in one case during the treatment period, all were in the process of recovering at the last follow-up.

Audiometry and blood sugar were also monitored throughout the study. The mean change in hearing threshold was modest across frequencies, with increases of 5.00, 6.43, 7.14, and 3.57 dB at 0.5, 1, 2, and 4 kHz, respectively, resulting in an overall mean change of 5.54 dB. Mean fasting blood glucose (FBG) remained stable, with values of 5.21 mmol/L at baseline and 5.20 mmol/L post-treatment. Mean HbA1c showed a slight increase from 5.61% to 5.70%.

One patient who failed highest dose of methylprednisolone pulse infusion (7.5 g) and oral steroids demonstrated proptosis decrease by 3 mm and CAS score decrease from

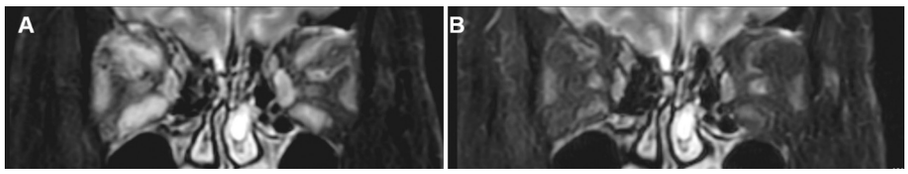


Figure 1 MRI manifestations of Case 8 A: Pretreatment coronal MRI findings, revealing apical crowding accompanied by extraocular muscle hypertrophy; B: Post-treatment imaging following a 12-week therapeutic regimen, showing resolution of apical crowding with concomitant reduction in extraocular muscle dimensions.

5 to 0, indicating a significant response after treatment of teprotumumab N01. Detailed information was summarized as following.

Case Presentation A 57-year-old male patient presented with eyelid edema, proptosis, photophobia, and increased lacrimation in June 2022. Initial tests showed normal thyroid function but positive TRAb, leading to a suspected diagnosis of TED. He was treated with prednisone for 6mo, but failed to respond. The patient had a history of smoking with no family history of hyperthyroidism or TED. Six months later, his symptoms worsened, with the addition of intermittent diplopia. Further tests revealed positive TRAb and thyroid stimulating immunoglobin and MRI showed thickened extraocular muscles and orbital fat edema. After formally diagnosed with active TED, the patient underwent methylprednisolone pulse therapy totaling 7.5 g. This treatment reduced inflammatory symptoms and orbital fat edema but showed limited effect on proptosis. The baseline proptosis of the study eye was 28 mm accompanied with a CAS of 5. In September 2023, the patient began teprotumumab N01 treatment (initial dose of 10 mg/kg followed by 20 mg/kg 3 doses every 3wk). At week 12, the patient's condition had markedly improved: CAS score reduced to 0, proptosis decreased by 3 mm, and MRI showed significant improvements in proptosis and muscle inflammation of the study eye (Figure 1) without any adverse events. The patient's TED maintained stable during follow-up. This patient achieved high response (defined as a reduction of 3 mm or more in proptosis and a decrease of at least 3 points in CAS[11]).

DISCUSSION

Glucocorticoids have long been the first-line treatment for TED. Although glucocorticoids may provide benefits in mitigating inflammatory symptoms during the acute phase of TED, their impact on reducing proptosis and alleviating diplopia is limited[15]. Furthermore, glucocorticoids, especially high-dose glucocorticoids, are associated with significant adverse events, including but not limited to hypertension, hyperglycemia, osteoporosis, gastrointestinal bleeding, and liver function impairment[16-17]. Teprotumumab, an IGF-1R antibody, has demonstrated significant proptosis response in patients with TED and has been recommended by American and European guidelines for patients with moderate-to-severe and active TED[3-4]. In China, teprotumumab is still not available, and teprotumumab N01, as a modified form of teprotumumab, has proved its efficacy and safety in randomized controlled trials[13-14]. Patients with prior use of glucocorticoids were excluded in trials for both teprotumumab and teprotumumab N01[11-14]. Therefore, the therapeutic response to IGF-1R inhibitors in individuals previously treated with glucocorticoids remains unevaluated in those studies. An indirect comparison showed that teprotumumab is also associated with greater improvements in proptosis and diplopia compared with intravenous methylprednisolone[18]. However, whether patients failing glucocorticoid treatment can benefit from anti-IGF-1R agents is still unclear.

In this study, 10 active TED patients who failed glucocorticoids were treated with teprotumumab N01 for a total of 4 infusions. At week 12, 70% of patients (7 of 10) showed a proptosis response, with a mean reduction of 2.50 mm from baseline. This is comparable to the results of the phase 3 trial of teprotumumab, which reported a 76% proptosis response rate and a 2.70 mm mean reduction at the same time point[12]. It is worthwhile to point out that patients in the phase 3 trial of teprotumumab were treatment-naïve patients. In clinical practice, patients whose disease was refractory to intravenous or oral steroid therapy showed rapid response following teprotumumab administration[19-20]. Furthermore, two retrospective studies, one evaluating teprotumumab for patients failing conventional therapies including corticosteroids and one evaluating teprotumumab or tocilizumab for patients failing steroids, have demonstrated 85.9% and 81% proptosis response in patients after at least 4 infusions of teprotumumab, respectively[21-22]. These findings align closely with the outcomes observed in our prospective case series, which substantiate that patients who fail to respond to glucocorticoid therapy can derive clinical benefit from teprotumumab N01 treatment.

In this case series study, five patients (62.5%) achieved high response according to the definition in phase 2 study of teprotumumab[11], even in the patient whose baseline proptosis and CAS indicating a severe disease status. These results support the use of teprotumumab N01 in patients who failed prior glucocorticoid treatment. IGF-1R inhibition can

prevent extraocular muscle and fat tissue proliferation and remodeling, reducing tissue swelling. The preliminary effect of teprotumumab N01 on TED patients failing glucocorticoids warrants further validation in randomized, placebo-controlled trials.

Proptosis response of these patients was further assessed by MRI. Patients who achieved a proptosis response in this study exhibited varying degrees of reduction in ocular fat tissue and extraocular muscles on MRI. These findings are generally consistent with clinical measurements in this study. No specific tendency was observed regarding which muscle was most affected, whereas inferior rectus muscle volume exhibited the largest reduction in most evaluable patients in phase 3 trial of teprotumumab[12]. Small sample size may cause such difference; with respect to the most affected muscle, 35% mean percentage decrease in volume from this study is slightly lower than results in phase 3 trial of teprotumumab. Meanwhile, patients with greater volume of extraocular muscles at baseline tend to present more decrease after teprotumumab N01 treatment. A systematic review has suggested the signal intensity ratio on T1 weighted MRI of extraocular muscles as an imaging parameter for management of TED[23]. MRI imaging is a promising method for TED diagnosis and activity assessment, whereas the investigation of robust criteria is necessary.

All patients tolerated teprotumumab N01 treatment and no patients experienced serious adverse events. Only one patient experienced hearing impairment with abnormal audiometry test after teprotumumab N01 treatment. Multiple post marketing studies of teprotumumab have indicated high percentage of patients with otologic symptoms[24-28]. Although rate of hearing impairment is low in this case series, it should be investigated in further randomized trials. Notably, hyperglycemia is an important adverse reaction of teprotumumab, with multiple case reports and real-world studies indicating the relationship between teprotumumab and hyperglycemia[29-32]. Although no hyperglycemia was reported in this case series study, this adverse event should be further investigated in the future studies of teprotumumab N01. The incidence of other important adverse events in the trials of teprotumumab including menstrual disorder, muscle spasm, and injection reaction was low or not reported in this case series. Collectively, teprotumumab N01 demonstrated a favorable safety profile. Our findings suggest that teprotumumab N01 exhibits an efficacy and safety profile comparable to teprotumumab in patients who had failed glucocorticoids. Further evaluation of teprotumumab N01 in this population will be conducted in a randomized controlled trial.

This study has several limitations. Sample size of this study is small. With only 10 patients, this case series provides limited statistical power and may not be representative of the broader TED population who fail glucocorticoids. The absence of a control group makes it difficult to definitively attribute improvements to teprotumumab N01 rather than natural disease course or delayed effects of previous treatments. In addition, given that 70% of TED patients achieved a proptosis response by week 12 in the phase 3 trial of teprotumumab N01[14], this study only utilized a 12-week treatment period to preliminarily evaluate efficacy. This follow-up period may not be sufficient to assess the long-term efficacy and safety of teprotumumab N01 in patients who failed prior glucocorticoids. Despite these limitations, this case series provides important preliminary evidence for the potential efficacy of teprotumumab N01 in TED patients who failed to respond to glucocorticoid. Based on the results in this study, a randomized, double-masked, placebo-controlled clinical trial has been designed to evaluate the efficacy and safety of teprotumumab N01 in patients with TED who had failed glucocorticoids (ClinicalTrials.gov, NCT06269393).

In conclusion, this pilot case series of 10 TED patients who failed prior glucocorticoid treatment provides preliminary evidence for the efficacy and safety of teprotumumab N01. The study demonstrated notable improvements in proptosis, CAS and diplopia supported by MRI findings, and the safety profile was favorable. Teprotumumab N01 can serve as a novel treatment option for TED patients failing glucocorticoids.

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