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Outcomes of Patients With Thyroid Eye Disease Partially Treated With Teprotumumab

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Abstract

Purpose: In response to the coronavirus (COVID-19) pandemic, teprotumumab production was temporarily halted with resources diverted toward vaccine production. Many patients who initiated treatment with teprotumumab for thyroid eye disease were forced to deviate from the standard protocol. This study investigates the response of teprotumumab when patients receive fewer than the standard 8-dose regimen.

Methods: This observational cross-sectional cohort study included patients from 15 institutions with active or minimal to no clinical activity thyroid eye disease treated with the standard teprotumumab infusion protocol. Patients were included if they had completed at least 1 teprotumumab infusion and had not yet completed all 8 planned infusions. Data were collected before teprotumumab initiation, within 3 weeks of last dose before interruption, and at the visit before teprotumumab reinitiation. The primary outcome measure was reduction in proptosis more than 2 mm. Secondary outcome measures included change in clinical activity score (CAS), extraocular motility restriction, margin reflex distance-1 (MRD1), and reported adverse events.

Results: The study included 74 patients. Mean age was 57.8 years, and 77% were female. There were 62 active and 12 minimal to no clinical activity patients. Patients completed an average of 4.2 teprotumumab infusions before interruption. A significant mean reduction in proptosis (−2.9 mm in active and −2.8 mm in minimal to no clinical activity patients, $P < 0.01$) was noted and maintained during interruption. For active patients, a 3.4-point reduction in CAS ($P < 0.01$) and reduction in ocular motility restriction ($P < 0.01$) were maintained during interruption.

Conclusions: Patients partially treated with teprotumumab achieve significant reduction in proptosis, CAS, and extraocular muscle restriction and maintain these improvements through the period of interruption.

Thyroid eye disease (TED) is the most common orbital disorder in adults.[1] Based on the findings of 2 randomized placebo controlled clinical trials, teprotumumab became the first and only Food and Drug Administration (FDA) approved medication for TED.[2,3] These studies have shown significant improvement in proptosis, clinical activity score (CAS), subjective diplopia, and quality of life in patients with active, moderate to severe TED.

As a response to the coronavirus (COVID-19) pandemic, teprotumumab production was temporarily halted in December 2020 with resources diverted toward government mandated

COVID-19 vaccine production orders.[4] The FDA allowed manufacturing to resume in April 2021.[5] As a result of this disruption, teprotumumab was widely unavailable during the first quarter of 2021, resulting in a treatment protocol deviation for many patients who could not receive intravenous infusions every 3 weeks for a total of 8 doses.

Disease control and patient outcomes depend on medication adherence and drug availability. Although drug supply shortages have generally been linked to adverse patient outcomes in other areas,[6,7] the ramifications in the treatment of TED are unknown particularly since the optimal dosing regimen for teprotumumab had never been ascertained through a randomized control trial with the current regimen reflecting an empiric extrapolation of oncologic protocols. Therefore, this disruption presented a unique opportunity to evaluate the treatment response of teprotumumab when patients receive a shorter than 8-dose regimen.

MATERIALS AND METHODS

The study was approved by the institutional review boards at each participating site and coordinated through the institutional review board at the Washington University School of Medicine in St. Louis. This study is compliant with the Health Insurance Portability and Accountability Act and the Helsinki Declaration.

In this observational cross-sectional cohort study, data from 15 institutions were included. Participants were adult patients greater than 18 years old with active or minimal to no clinical activity TED treated with a standard teprotumumab infusion protocol that was interrupted by the national drug shortage. Standard protocol dosing was planned for each case. This consisted of initial infusion of 10 mg/kg followed by subsequent infusions of 20 mg/kg given every 3 weeks for a total of 8 doses.[2] Patients were included if they had completed at least 1 infusion of teprotumumab before treatment interruption and had not yet completed all 8 planned infusions. Exclusion criteria included patients who were interrupted for reasons other than national drug shortage and patients with insufficient follow-up data. In addition to assessing pre- and post-treatment characteristics, we further extended the study to potentially differentiate between active and minimal to no clinical activity TED at time of treatment initiation. Active TED was defined as a CAS of 4 or more on a 7-point scale regardless of duration of TED symptoms.[8] Minimal to no clinical activity TED was defined as CAS less than 4 and TED symptoms longer than 9 months.[9] These minimal to no clinical activity criteria were selected as patients in this group were excluded from the active TED teprotumumab clinical trials.

Patient data collection occurred at 3 time points. First, patients were evaluated before the teprotumumab initiation. Following this visit, patients received standard protocol dosing every 3 weeks. The second time point was the partial-treatment baseline examination and occurred within 3 weeks following the last dose of teprotumumab before interruption. The third time point was the latest visit before teprotumumab reinitiation (final follow-up visit) at least 4 weeks following the postinterruption baseline examination.

Clinical information was extracted from patient records. Patient demographics and clinical history were analyzed including age, gender, thyroid history, smoking status, and prior treatment modalities.

The primary outcome measure was reduction of more than 2 mm in proptosis. Analysis was performed on the more proptotic (study eye). In patients with equal exophthalmometry measurements, 1 eye was selected randomly to be the study eye. Maintained responders were those patients who continued to meet the response definition of more than 2 mm in proptosis reduction at the final follow-up visit. Secondary measures included CAS, diplopia, extraocular motility restriction, MRD1, and medication-related adverse events. Maintenance of secondary measures includes those patients who continued to have a statistically significant response at final follow-up visit compared with before teprotumumab initiation.

Proptosis measurements were made using a Hertel exophthalmometer. The 7-point CAS scale was used to quantify activity. CAS of 0 or 1 was indicative of disease inactivity.[8] Diplopia was assessed in primary gaze as present or absent. Ocular ductions were assessed using a standard 4-point scale with zero indicating full motility and −4 indicating no motility past midline.[10] Restriction was summated in the horizontal and vertical directions for each eye.[11] MRD1 measurements were obtained for each eye individually. Adverse events were documented at each patient visit.

For comparison of categorical variables between 2 cohorts, the 2-tailed paired t-test and Fisher's exact test were employed. Linear regression was performed to assess correlation between number of infusions and change in proptosis. Multivariate modeling was performed to assess effects of number of infusions and interruption time on the change in proptosis during the interruption period. A P value of less than 0.05 was considered statistically significant. All analysis was conducted using IBM IPSS (version 26, IBM Corporation, Armonk, NY).

RESULTS

The study population included 74 patients from 15 institutions. The mean age before initiation of teprotumumab was 57.8 years (median 58 years, range 21–92 years). There were 62 active and 12 minimal to no clinical activity patients. There were 57 females (77.0%) and 17 males (23.0%). All patients had Graves' disease, which was diagnosed an average of 5.3 years (median 2 years, range 2 months–38 years) before teprotumumab initiation. The average duration of TED symptoms was 23.4 months (median 12 months, range 3 weeks–360 months) at the first visit when teprotumumab was prescribed.

Prior treatments for Graves' disease include methimazole (41/74), levothyroxine (9/74), radioactive iodine (17/74), thyroidectomy (19/74), and combination of these treatments. Thirty-1 patients had previously received treatments for TED including oral steroids (17), intravenous steroids (11), surgery (7), orbital radiation (3), and rituximab (2). All patients with history of surgery were active patients. Six patients had prior orbital decompression, 2

patients had prior eyelid retraction repair, and 1 patient had strabismus surgeries. No patients had active TED-related optic neuropathy at the time of teprotumumab initiation.

Patients underwent a mean of 4.2 teprotumumab infusions before interruption (median 4, range 1–7). The average follow-up period was 13.2 weeks (median 11.7 weeks, range 7–23 weeks) after the postinterruption examination. Baseline characteristics are summarized in Table 1.

Primary Outcome.

The primary outcome of more than 2 mm proptosis reduction was achieved by 73% of patients (45 active and 9 minimal to no clinical activity) before interruption. Both active and minimal to no clinical activity patients showed a significant decrease in proptosis while on teprotumumab. Active patients demonstrated 2.9mm in mean proptosis reduction ($P < 0.01$) while the minimal to no clinical activity patients achieved an average 2.8 mm proptosis reduction ($P < 0.01$). Further statistical analysis revealed a weak but significant correlation between number of infusions and increasing amount of proptosis reduction (r = 0.406 and $P < 0.01$) (Figure 1).

During interruption, all proptosis responding patients (45 active and 9 minimal to no clinical activity) maintained the significant decrease, and 3 additional active patients met primary outcome for proptosis reduction (Table 2). Six active patients (8.1%) had additional more than 2 mm proptosis reduction during the interruption period. One active patient had 2.5 mm worsening in proptosis at final follow up but still met proptosis responder criteria. A multivariate regression revealed no significant correlation between number of infusions ($P = 0.78$) or time of interruption ($P = 0.98$) on change in proptosis measurement during interruption.

Secondary Outcomes.

In our cohort of 62 active patients, there was a significant 3.4-point reduction in CAS while on teprotumumab ($P < 0.01$), which was maintained during interruption (Table 2). In these patients, 48.3% (30/62) achieved CAS of 0 or 1, while on teprotumumab. By the last follow-up visit, 61.2% (38/62) had a CAS of 0 or 1. Four patients (6.5%) had an increase in CAS greater than 2 from the partial-treatment baseline examination to the final follow-up visit.

Sixty-two patients reported diplopia in primary gaze before initiation of teprotumumab. Subjective diplopia resolved in 11 patients (17.7%) while on teprotumumab. Two patients (3.2%) reported a return of diplopia during the interruption period. For active patients, there were a significant decrease in the total extraocular muscle restriction on teprotumumab ($P < 0.01$) that was maintained during interruption. For minimal to no clinical activity patients, there was no significant change in extraocular motility restriction while on teprotumumab or during the interruption period. There was no significant change in MRD1 for both active and minimal to no clinical activity patients while on teprotumumab or during interruption.

During the interruption period, no patients developed new TED-related optic neuropathy. One patient who was status-post left medial and lateral orbital decompression underwent

left floor decompression for symmetry and worsening exposure symptoms. No other patients required additional therapy such as pulsed intravenous or oral corticosteroids for worsening TED during the interruption period.

Adverse Events.

At the first postinterruption visit (second timepoint), 45 patients (66%) reported at least 1 or more adverse events (range 1–7 adverse events). The most commonly reported adverse event included muscle cramps 27% (20/74) followed by hair loss 17.5% (13/74), hyperglycemia 13.5% (10/74), hearing changes 10.8% (8/74), fatigue 9.4% (7/74), and gastrointestinal upset 8.1% (6/74).

At the postinterruption examination, 22 (29%) patients continued to report at least 1 adverse event. Of those who reported adverse events, the most common adverse events at the last visit were hyperglycemia 36% (8/22), muscle cramps 32% (7/22), and hearing changes 23% (5/22). Three patients (4%) who did not have a diabetes mellitus diagnosis before initiation of teprotumumab were started on oral hypoglycemic agents. One patient had persistently high blood glucose (>700) during the interruption, and the decision was made to discontinue future infusions. During postinterruption examination, no patient developed new safety concerns that were not present while receiving teprotumumab infusions.

DISCUSSION

Drug supply shortages are a growing global problem, but there is limited literature on their effects on patient safety.[6,7,12,13] Since noncompliance can be a factor for poor clinical outcomes, advisory panels have recommended strict adherence to standard treatment regimens including for teprotumumab.[14] Hence, when the disruption in teprotumumab production was first announced, there was substantial concern regarding the potential negative impact on disease progression, adverse event profile, and efficacy of teprotumumab therapy for TED.[15]

All randomized controlled trials utilizing teprotumumab have been conducted with a standard 8-dose regimen. Based on pharmacokinetic modeling, this regimen was selected to sustain greater than 20 μg/mL trough concentration to maintain greater than 90% saturation of insulin-like growth factor 1 receptor (IGF-1R) during the dosing intervals[16] and for total treatment duration of 6 months. Studies have yet to be conducted on the optimal dosing regimen for teprotumumab for different phases, phenotypes, and clinical presentations of TED. It is conceivable that shorter dose intervals are required for sustained improvement in some presentations and longer dosing intervals would be required in others. Additionally, requirements for an 8-dose protocol are not strictly based on specific clinical studies. Decreasing the total doses could be a useful strategy for some patients to optimize outcomes while reducing the incidence of dose dependent adverse events.

When examining the proptosis response curve over time from the phase 2 and 3 clinical trials, more than 75% of active patients met the benchmark of 2 mm proptosis reduction by 12 weeks (after 4 infusions), and the response rate plateaued at more than 80% after 16 weeks.[2,3] When pooling the clinical trials data set, Kahaly et al.[17] found that 65

(77%) of patients in the teprotumumab group achieved a proptosis reduction of more than 2 mm after completion of teprotumumab 8-dose treatment regimen. This current study identified proptosis reduction (>2 mm) in 72.5% active and 75% minimal to no clinical activity patients after an average of 4.2 teprotumumab infusions. Our findings support prior studies that the onset of significant clinical response occurs early in the treatment course. However, increasing teprotumumab doses correlates with increased proptosis reduction. This highlights the importance of dose-ranging studies to determine the optimal frequency, duration, and number of teprotumumab infusions for achieving optimal efficacy and safety outomes. A randomized controlled trial evaluating the safety and efficacy of 4, 8, and 16 teprotumumab infusions is currently ongoing.

In this study, we evaluated the short-term ramifications of interrupted treatment regimens in a cohort of 74 patients partially treated with teprotumumab. At the final follow-up visit after an average of 13.2 weeks of teprotumumab interruption, 77% of patients met proptosis response criteria with 3 initial nonresponders achieving the primary outcome. These initial nonresponders received between 2 and 4 infusions before interruption. Given teprotumumab's long half-life of 19.9 days[16] and slow systemic clearance,[16] residual drug activity may contribute to additional proptosis improvement during drug cessation. These findings also concur with the OPTIC-X study in which 90% of proptosis responders at week 24 maintained their proptosis response 3 months after final teprotumumab dose.[18] At 27 weeks after final teprotumumab dose, the response remained high (89%). Long-term efficacy for treatment with teprotumumab is still an open question, and studies on the matter are ongoing.

Secondary outcomes in this study followed a similar pattern with significant reduction of CAS, proptosis, and motility restriction on teprotumumab. These changes were maintained during the interruption period. Similar to previously published clinical trials results at 12 weeks,[2,3,17] the observations of the present study included proptosis reduction (2.9 mm in active patients) and CAS reduction (3.4 points), with 49% of patients demonstrating a CAS of 0–1 points at the final study follow-up visit. Our study suggests that a delay of several weeks to months between teprotumumab infusions does not appear to have clinically deleterious effects with regard to most measured data points. Patients overwhelmingly maintained the gains achieved with prior teprotumumab doses and did not require adjunctive medical treatments for worsening disease in the short-term.

Although the clinical trials were conducted on patients with active TED, recent reports on the effectiveness of teprotumumab on minimal to no clinical activity TED patients have highlighted improvements in proptosis, diplopia, and orbital soft tissue volume.[9,19,20] Inclusion of patients with minimal to no clinical activity TED in this study may capture a subset of active patients with low CAS who have classically been described by Nunery as Type 1 patients.[21–23] These patients typically have proptosis, minimal diplopia, and low CAS and have been excluded from prior clinical trials. Given the significant improvement observed in the present study following a mean of 4.2 infusions, patients with minimal to no clinical activity TED may also demonstrate an early response to teprotumumab, similar to active patients. Additional studies investigating how TED patients with minimal to no clinical activity and whose disease process is later in its time course respond to

teprotumumab treatment will help elucidate the medication's efficacy and safety. A phase 4 randomized controlled trial investigating the treatment of TED patients with CAS < 1 and disease duration over 2 years with teprotumumab is currently in the recruitment process.[24,25]

In our study, there was no significant change in MRD1 for patients on teprotumumab. Prior studies have demonstrated similar results in active[11] and minimal to no clinical activity patients.[9] A variety of factors contribute to the etiology of upper eyelid retraction including Müller's muscle hyperactivity mediated by thyroid hormones and the cicatricial changes within Müller's and levator muscle.[26–28] Although teprotumumab targets the overexpression of IGF-1R on orbital fibroblasts,[29] this signaling pathway may not modify the fibrosis and inflammation contributing to upper eyelid retraction. Additional studies are needed to elucidate the role of IGF-1R on eyelid tissue and the long-term effects of teprotumumab on upper eyelid retraction.

Adverse events were common in this study with 60% of all patients experiencing at least 1 adverse event. Higher rates of adverse events were previously reported in a review analysis.[17] Although most adverse events were mild and resolved with drug cessation, serious adverse events such as hyperglycemia and hearing changes appear to persist during short-term interruption and after 72 weeks follow-up.[17] Further investigations are needed to analyze the duration of these adverse events.

This study has several limitations. The patient population included a heterogenous population including patients from several institutions who had received a range of medical and surgical treatments before the initiation of teprotumumab. However, this diverse patient population does appropriately reflect the different ways in which physicians incorporate teprotumumab in their clinical practice. Further limitations include the small number of minimal to no clinical activity TED patients. Finally, the patients in this cohort were not followed long enough to comment on the durability of teprotumumab treatment or determine the recurrence rate. Long-term follow up to review the outcomes of these patients impacted by interruption was not available and will be the subject of ongoing work.

In summary, this study found that patients partially treated with teprotumumab achieve significant reduction in proptosis, CAS, and extraocular muscle restriction and maintain these improvements during short-term interruption.

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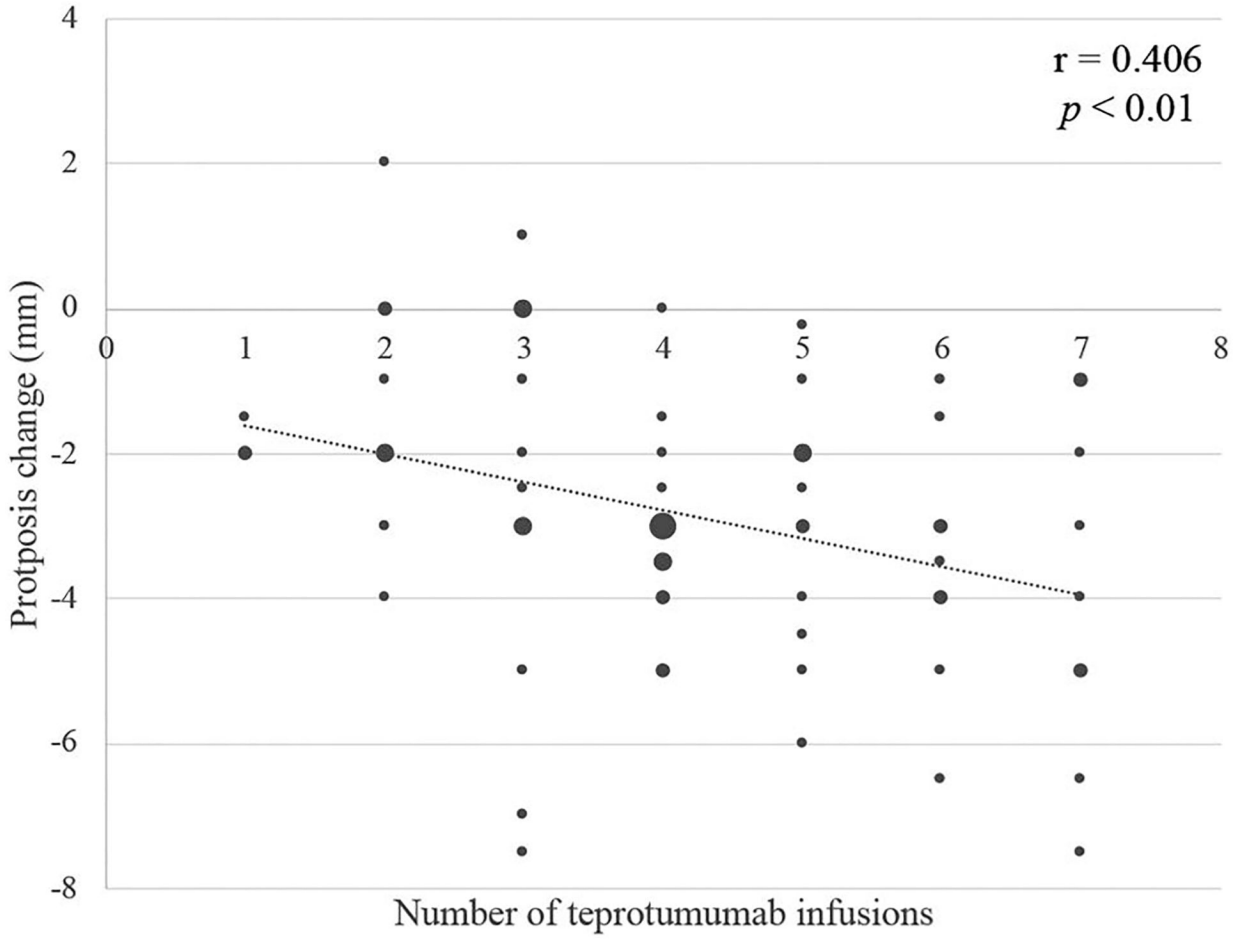

FIG. 1.
Scatterplot of number of teprotumumab infusions against proptosis change. Larger data points indicate more than 1 patient represented.

TABLE 1.

Baseline patient demographics, clinical history, and thyroid treatment characteristics

	Total patients	Active TED patients	Minimal to low activity TED patients
Age, mean (range)	58 (21–92)	58 (22–92)	51 (21–77)
Sex, n (%)			
Female	57 (77%)	48 (77%)	9 (75%)
Male	17 (23%)	14 (23%)	3 (25%)
Tobacco use history, n (%)			
Nonsmoker	55 (74%)	45 (73%)	10 (83%)
Smoker	19 (26%)	17 (27%)	2 (17%)
Years since diagnosis of Graves' Disease, Median (range)	2	2 (0.2–31)	4.5 (2–38)
Months since diagnosis of TED, Median (range)	12	10 (0.75–360)	22 (10–20)
History of radioactive iodine, n (%)	17 (23%)	14 (23%)	3 (25%)
History of thyroidectomy, n (%)	19 (26%)	17 (27%)	2 (17%)
Concomitant medications at baseline, n (%)			
Methimazole	41 (55%)	32 (52%)	9 (75%)
Levothyroxine	9 (12%)	7 (11%)	2 (17%)
Prior TED treatments, n (%)			
Oral steroids	17 (23%)	16 (26%)	1 (8%)
Intravenous steroids	11 (15%)	6 (10%)	5 (42%)
Orbital radiation	3 (4%)	3 (5%)	0
Rituximab	2 (3%)	2 (3%)	0
Surgery	7 (9)	7 (11%)	0

TED, thyroid eye disease.

TABLE 2.

Clinical examination data for active and minimal to low activity TED patients at baseline, partial teprotumumab treatment course, and following treatment interruption

	Active TED patients					Minimal to low activity TED patients				
	Pretreatment exam	Partial-treatment exam	*P*	Final follow-up exam	*P*	Pretreatment exam	Partial-treatment exam	*P*	Final follow-up exam	*P*
Proptosis (mm)	23.4 ± 4.1	20.4 ± 3.0	<0.01	20.2 ± 3.0	<0.01	22.9 ± 1.7	20.3 ± 2.1	<0.01	20.1 ± 2.5	<0.01
CAS (points)	4.9 ± 1.2	1.5 ± 1.4	<0.01	1.6 ± 1.6	<0.01	1.7 ± 1.0	1.3 ± 1.5	0.14	1.0 ± 1.3	0.05
Total extraocular restriction	−2.6 ± 2.8	−1.5 ± 1.9	<0.01	−1.3 ± 1.8	<0.01	−0.3 ± 0.7	−0.1 ± 0.2	0.96	−0.2 ± 0.5	0.17
MRD1 (mm)	5.4 ± 1.9	5.4 ± 1.8	0.89	5.4 ± 1.9	0.87	4.9 ± 1.4	4.8 ± 1.2	0.25	4.7 ± 1.1	0.48

P compares partial-treatment exam and follow-up exam during interruption to pretreatment exam.

TED, thyroid eye disease.