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Effects of Smoking on Outcomes of Thyroid Eye Disease Treated with Teprotumumab: A Retrospective Cohort Study

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ABSTRACT

Introduction. Smoking has been demonstrated to worsen the disease process and conventional treatment outcomes of thyroid eye disease. However, the effects of smoking on outcomes of thyroid eye disease treated with the novel therapeutic teprotumumab are currently unknown. Our study compares response to teprotumumab treatment between smokers and non-smokers with thyroid eye disease.

Methods. A single-center, retrospective cohort study was conducted. Inclusion criteria were patients diagnosed with thyroid eye disease who had started or completed therapy with teprotumumab at the time of our data collection. Main outcome measures included reduction in clinical activity score, diplopia, and proptosis.

Results. All smokers had type 2 thyroid eye disease prior to treatment and demonstrated less improvement in diplopia, proptosis, and overall clinical activity score compared to non-smokers with thyroid eye disease. There was no significant difference between smokers and non-smokers in baseline variables (sex, thyroid stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), number of infusions completed). Data analysis revealed a statistically significant difference in proptosis reduction between non-smokers and smokers.

Conclusions. Smoking is a modifiable risk factor which portends a worse response to treatment of thyroid eye disease with teprotumumab.

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INTRODUCTION

Thyroid eye disease (TED) is a common manifestation of Graves' hyperthyroidism. Up to 50% of patients with hyperthyroidism will develop TED, of whom 3-5% will develop severe disease.[1-3] The precise pathophysiology is not understood fully, but TED is thought to occur due to activation of orbital fibroblasts by autoantibodies leading to subsequent orbital inflammation and connective tissue remodeling.[3] Clinical signs and symptoms of TED include lid retraction (present in up to 90%), exophthalmos, eye pain, diplopia, extraocular muscle myopathy, and vision loss in severe cases.[3,4] TED can be classified as type 1 disease which affects orbital fat without diplopia, or type 2 disease which is defined as diplopia within 20 degrees of fixation with restrictive myopathy.[5] TED severity can be graded using the Mourits Clinical Activity score (CAS) to guide management decisions.[6] Risk factors for TED include both genetic predisposition and environmental influences. Risk for developing TED is increased in women, patients with high serum cholesterol, those exposed to radioactive iodine therapy, and those who smoke.[1,7,8]

Smoking is a risk factor which consistently has been linked to development and worsening of TED.[2,3] It is the strongest modifiable risk factor, shown to both increase the severity of TED symptoms and decrease treatment response.[1,2] Patients with TED who smoke have been shown to have poorer response to treatments such as corticosteroids in comparison to non-smokers.[6]

Current management of TED has evolved over recent years to include use of immunomodulators with growing promise. Teprotumumab, a monoclonal antibody directed against insulin-like growth factor 1 receptor (IGF-1R), has demonstrated significant improvement in proptosis, CAS, diplopia, and quality of life compared to placebo for treatment of TED.[1,3,4,9] Teprotumumab can be used alone or in combination with corticosteroid therapy.[4,9] The effectiveness of teprotumumab treatment in smokers with TED has yet to be established. We hypothesized that the efficacy of teprotumumab will be reduced in TED patients who smoke compared to TED patients who do not smoke, similar to the reduced efficacy of other treatments seen in TED patients who smoke.

METHODS

A single-center, retrospective review of patients with TED treated with teprotumumab was conducted. Institutional Review Board approval was obtained and patients who had started or completed treatment with teprotumumab during the study were included. Data were analyzed using STATA (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC; USA). The differences between smokers and non-smokers in baseline characteristics as well as clinical response were assessed using Fisher's exact test for categorical variables and Wilcoxon rank-sum (Mann-Whitney) test for continuous variables. Statistically significant results were defined as $p < 0.05$.

RESULTS

A total of 34 patients with TED who were scheduled to begin teprotumumab were reviewed. Sixteen patients who began or completed treatment during the study were included in the initial comparisons. However, one patient did not have sufficient documentation, thus 15 were included in the statistical analysis (Tables 1 and 2). Six of the included 15 (40%) patients were current or former smokers. All the smokers in the study had type 2 disease, whereas all the non-smokers had type 1 disease (Figure 1).

The primary outcome assessed was change in CAS. Mean reduction in CAS was 3.7±2 in smokers, compared to 4.9±2.2 in non-smokers. Other variables assessed were change in visual acuity (VA), proptosis, and diplopia. VA outcomes were not significantly different between smokers versus non-smokers. All smokers had VA of 20/25 or better after receiving treatment with teprotumumab, except one patient who had a long-standing history of nystagmus and decreased visual potential whose vision remained stable and fluctuated between 20/30 and 20/40 OU.

Proptosis was reduced by 1.2±1.2 in the right eye and by 1.75±0.5 in the left eye in smokers versus by 4±1.4 in the right eye and 4.2±1.8 in the left eye in non-smokers. This reduction was found to be statistically

significant, as seen in Table 2.

Change in diplopia was not significant between the groups, but was more likely to be present initially in smokers compared to non-smokers (Figure 1). Of the 16 initially included, six of seven (85.7%) smokers had diplopia prior to treatment, whereas six of nine (66.6%) non-smokers had diplopia prior to treatment. One smoker and one non-smoker had resolution of diplopia with treatment. One smoker without diplopia prior to treatment developed complaints of diplopia after treatment.

Table 1. Baseline characteristics of 15 thyroid eye disease patients treated with teprotumumab, in terms of smoking status.

Variable	Categories	Total (%)	Non-Smokers	Smokers	p Value
Total		15 (100)	9 (60)	6 (40)	
Sex					0.10
	Females	13 (86.7)	8 (61.5)	5 (38.5)	
	Males	2 (13.3)	1 (50)	1 (50)	
Thyroid Stimulating Hormone TSH**		5.1 ± 12.7	6.2 ± 16.2	3.5 ± 5.2	0.80
Free Thyroxine T4**		1.9 ± 2.2	1.3 ± 0.7	2.7 ± 3.4	0.70
Free Triiodothyronine T3**		108 ± 136.8	131 ± 163.7	67.8 ± 73.6	1.00
Number of infusions**		5.7 ± 2.6	6.4 ± 2.4	4.5 ± 2.7	0.10

**Presented as mean ± Standard Deviation (SD).

Table 2. Differences in clinical response between the 15 patients based on smoking status.

Variable	Categories	Mean ± SD	Non-Smokers	Smokers	p Value
Total					
Reduction in CAS		4.4 ± 2.2	4.9 ± 2.2	3.7 ± 2	0.30
Diplopia**					
	Diplopia prior initiation of treatment	11 (73.3)	6 (54.6)	5 (45.4)	0.50
	Diplopia after initiation of treatment	5 (50)	3 (60)	2 (40)	0.50
Proptosis					
	Right proptosis prior	23.3 ± 2.4	24±2	22 ± 2.5	0.20
	Right proptosis after	19.9 ± 2.7	19.7 ± 3.2	20.3 ± 2	0.70
	Change in right eye proptosis	2.3 ± 2	4 ± 1.4	1.2 ± 1.2	0.02
	Left proptosis prior	24 ± 2.4	24.4 ± 2.2	23.4 ± 3	0.50
	Left proptosis after	20.4 ± 2.6	20.3 ± 3.3	20.5 ± 1.7	0.50
	Change in left eye proptosis	3.2 ± 1.9	4.2 ± 1.8	1.75 ± 0.5	0.04

**Presented as Total (%).

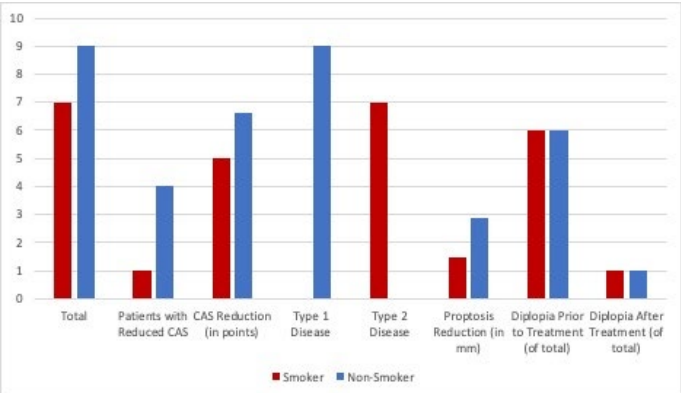

Figure 1. Patient characteristics in smokers and non-smokers.

DISCUSSION

Smoking is a modifiable risk factor known to be a causal factor increasing the risk and severity of thyroid eye disease. It is hypothesized that the causal association between smoking and TED may involve altered gene expression, cytokine production, and tissue hypoxia as well as other unknown components.[1,2] Aligned with our hypothesis, smokers demonstrated poorer response to teprotumumab treatment with regards to reduction of proptosis.

While our study agreed with the current literature regarding the effect of smoking on various treatments of TED, it was not without limitation. This was a single-center study with a small sample size which limited statistical power and generalizability to larger populations.

Additionally, only a small percentage of patients in our study completed the treatment course of eight infusions of teprotumumab. It will remain important to analyze the difference in treatment outcomes between smokers and non-smokers at the completion of treatment. Our patients were not stratified based on status as current smoker or ever smoker, and this too may alter the results, as smoking may have a dose-dependent effect on teprotumumab outcomes. More extensive research is needed to assess the long-term impact of smoking on teprotumumab efficacy. Despite these limitations, smoking cessation resources and counseling are crucial for those diagnosed with TED to prevent further disease progression and to prevent development of TED in those with thyroid dysfunction.[1,2]

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