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CASE REPORT
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The Effect of Teprotumumab on Eyelid Position in Patients with Thyroid Eye Disease

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Summary: Teprotumumab has been shown to improve proptosis and clinical activity scores (CAS) in patients with thyroid eye disease, but little has been published regarding its effects on eyelid retraction. The purpose of this work was to evaluate changes in eyelid position in thyroid eye disease patients after teprotumumab. Eight patients completed eight cycles of teprotumumab. Data collected included exophthalmometry; clinical activity scores; margin reflex distance (MRD) 1; MRD2; and pre-, during, and posttreatment photographs. ImageJ analysis was also used to evaluate eyelid position in photographs. Proptosis significantly improved in 15 of 16 orbits [mean 4.75 ± 2.07 mm reduction ($P = 0.0001$) in study orbits and mean 3.00 ± 2.14 mm reduction ($P = 0.0048$) in nonstudy orbits]. CAS was significantly reduced (pretreatment mean 4.88 mm and posttreatment mean 1.88 mm, $P = 0.006$). MRD1 decreased in 11 of 16 orbits and increased in five orbits ($P = 0.18$ in study orbits and $P = 0.22$ in nonstudy orbits). MRD2 decreased in six of 16 orbits and increased in eight orbits ($P = 0.49$ in study orbits and $P = 0.43$ in nonstudy orbits). Patients exhibited variable changes in eyelid position with teprotumumab. There was a statistically insignificant decrease in MRD1 after teprotumumab. Proptosis reduction led to unpredictable changes in MRD1 and MRD2. Severity of eyelid retraction did not correlate with clinical activity score response to teprotumumab. There are inherent difficulties in evaluating eyelid position in thyroid eye disease, which may necessitate a paradigm shift in how patients are examined, measured, and photographed. *(Plast Reconstr Surg Glob Open 2022;10:e4287; doi: 10.1097/GOX.0000000000004287; Published online 22 April 2022.)*

INTRODUCTION

Teprotumumab is a monoclonal antibody that inhibits a key receptor in thyroid eye disease (TED), insulin-like growth factor-1 receptor.[1] Although teprotumumab improves proptosis in TED,[1,2] conflicting reports exist regarding teprotumumab's effect on eyelid position. One study of nine patients noted insignificant changes in eyelid position after teprotumumab,[3] whereas a more recent series of 23 patients reported a statistically significant improvement in eyelid position after six to eight infusions over 18–24 weeks.[4] However, this latter study did not evaluate patients beyond the treatment period. The current work summarizes the authors' experience evaluating changes in eyelid position with teprotumumab before, during, and after therapy. Given the general purview of plastic surgery, and the functional and cosmetic concerns of TED patients, the authors feel these findings have significant applicability to the plastic surgery community. This work is IRB-approved, HIPAA compliant, and adheres to the tenets of the Declaration of Helsinki.

METHODS

This was a retrospective consecutive case series of patients with TED who completed teprotumumab infusions every 3 weeks for a total of eight cycles at a single academic institution.[2] There were no exclusion criteria.

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Clinical data collected by the physician pre-, during, and 2–4 weeks posttreatment included Hertel exophthalmometry, standard eyelid measurements of MRD1 and MRD2, and CAS. Standardized external photographs in primary gaze were obtained during those same visits. The orbit with greater proptosis was designated the study orbit, and the less proptotic was the nonstudy orbit.[2] If MRD measurements were not recorded, representative external photographs from the visit were independently selected for analysis (BAS, CT, EMS). Images were analyzed with NIH ImageJ software (version 1.5) to obtain image-derived MRD1 and MRD2.[5]

RESULTS

Eight patients (4 men, 4 women) met inclusion criteria. Proptosis significantly improved after treatment in 15 of 16 orbits [mean 4.75 ± 2.07 mm reduction ($P = 0.0001$) in study orbits and mean 3.00 ± 2.14 mm reduction ($P = 0.0048$) in nonstudy orbits]. Proptosis reduction led to unpredictable changes in MRD1 and MRD2. MRD1 decreased in 11 of 16 orbits and increased in five orbits [mean 0.84 mm reduction ($P = 0.18$) in study orbits and mean 0.65 mm reduction ($P = 0.22$) in nonstudy orbits]. MRD2 decreased in six of 16 orbits and increased in eight orbits [mean 0.23 mm decrease ($P = 0.49$) in study orbits and mean 0.25 mm increase ($P = 0.43$) in nonstudy orbits]. The majority of patients experienced a significant reduction in CAS (pretreatment mean 4.88 and posttreatment mean 1.88, $P = 0.006$). (**see Supplemental Table 1,** which shows changes in eyelid position, proptosis, and CAS pre- and 2–4 weeks postteprotumumab infusions. A negative change in MRD1 value indicates a lower MRD1 height, whereas a negative change in MRD2 value indicates a more elevated lower eyelid. Proptosis was measured by Hertel exophthalmometry. A negative proptosis reduction value indicates worse exophthalmos. **http://links.lww.com/PRSGO/C13**.)

DISCUSSION

While the effects of teprotumumab on proptosis in TED are well documented,[1,2] several small studies present conflicting results regarding eyelid changes after teprotumumab.[3,4] While this case series showed no statistically significant changes in eyelid position, it revealed difficulties evaluating eyelids in TED patients that may explain the dearth of published literature and the conflicting results previously published.

While there was a trend toward decreasing MRD1 in the current study after teprotumumab, this was statistically insignificant, and patients exhibited variable changes in eyelid position. Severity of eyelid retraction did not correlate with CAS: posttreatment, some patients had decreased CAS scores with increased eyelid retraction. These findings may be due to multiple factors affecting the eyelid position in TED: scarring of eyelid tissues including the levator palpebrae superioris, Mueller's muscle, and the capsulopalpebral fascia-inferior rectus-inferior oblique complex; overaction of the levator against a tight inferior rectus; and increased stimulation of Mueller's muscle or the inferior tarsal muscle. Fluctuating sympathetic tone, changes in periorbital edema, and strabismus with an altered corneal light reflex create difficulty obtaining reproducible, accurate eyelid measurements. One of the upper eyelid retractors, Mueller's muscle, does not show increased expression of insulin-like growth factor-1 receptor[6]; so eyelid response to teprotumumab would rely on some unidentified pathway. Altogether, the eyelid retraction seen in TED not only does not predictably respond to teprotumumab, but also makes evaluation of eyelid position in these patients inherently challenging.

It proved surprisingly difficult to obtain accurate, consistent photographs and eyelid measurements. On clinical examination, eyelid height appeared more variable with TED than in patients with eyelid malposition from other etiologies. The unmasked authors recognized—and actively worked to counteract—bias initially felt to be

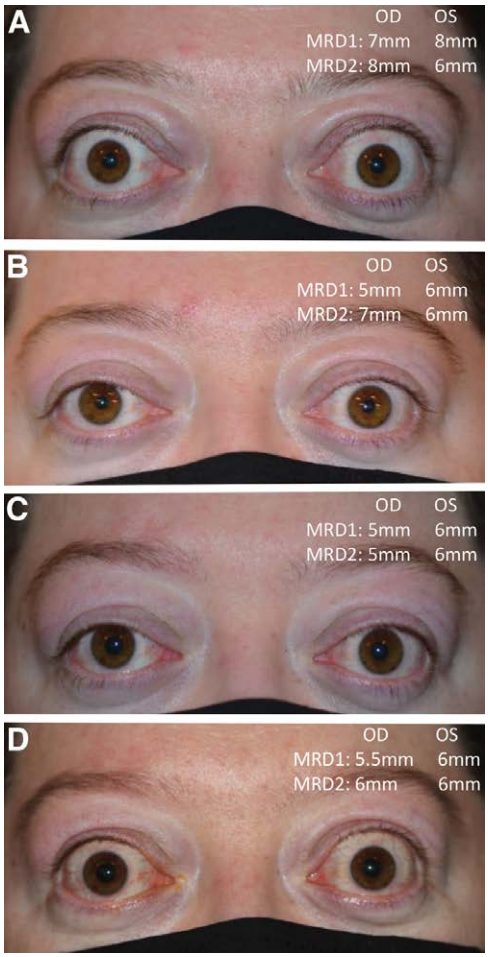

Fig. 1. External photographs of a single patient (A) at pretreatment, (B) after three infusions, (C) after four infusions, and (D) 3 weeks after completion of eight infusions of teprotumumab therapy. MRD1 and MRD2 values from each visit are provided in the top right corner. Note the discrepancy in external photographs and eyelid measurements, most notable in B and D, which illustrates the effect of increased sympathetic tone when taking a photograph compared with the clinical measurements obtained. Collectively, these photographs demonstrate the difficulty in obtaining reliable, reproducible photographs and measurements in TED patients.

influencing eyelid measurements. Even then, unmasking led to inherent bias when selecting representative photographs for analysis when no measurements were recorded. Despite using experienced ophthalmic technicians as photographers, same-day clinical photographs demonstrated marked variability in eyelid heights with discrepancies between the clinical photographs and recorded examination values. Measurements in clinic were typically recorded with encouragement for frontalis relaxation as is customary for similar measurements in ptotic patients. When photographs were taken, however, patients often had an increase in retraction (presumably from increased sympathetic tone as they sat "at attention" for photographs). Multiple factors and fluctuating eyelid position in TED led to difficulty in obtaining unbiased, accurate measurements and representative clinical photographs. (Fig. 1)

Of note, patients with prior eyelid surgery may benefit from teprotumumab. Despite presumed scarring after previous eyelid retraction repair in three of four eyelids, patient 5 showed appreciable improvement in MRD1 in study and nonstudy orbits, and MRD2 in the study orbit after teprotumumab.

A minority of patients displayed worsening eyelid position and CAS weeks after teprotumumab completion, raising questions about the durability of teprotumumab's effect. The lack of statistically significant changes in eyelid position in this study after teprotumumab treatment may be due in part to rebound of TED or its manifestations.

CONCLUSIONS

Eyelid retraction in TED is multifactorial and did not respond predictably to teprotumumab. There is a variability in eyelid retraction in TED patients at baseline, which presents challenges in evaluation. To minimize bias and capture the variability of eyelid position in TED patients, the authors recommend recording a range of measurements and obtaining multiple photographs. Further investigations would benefit from real-time verification of clinical photographs and eyelid measurements, evaluating variables of TED relating to chronicity and previous treatments, extending follow-up, and masking examiners. The authors look forward to larger studies critically evaluating eyelid position in an objective fashion, and hope the lessons identified in this short case series will help guide that evaluation.

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PATIENT CONSENT

The patient provided written consent for the use of the included images.

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