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RESEARCH ARTICLE

A comparison of proptosis reduction with teprotumumab versus surgical decompression based on fat-to-muscle ratio in thyroid eye disease

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ABSTRACT

Purpose: To explore if orbital fat-to-muscle ratio (FMR) is predictive of whether surgical decompression or teprotumumab leads to greater proptosis reduction in thyroid eye disease (TED).

Methods: A single-center retrospective cohort study comparing surgical decompression with teprotumumab according to FMR. All TED patients completing an 8-dose course of teprotumumab between January 2020 and September 2022 and all patients undergoing bony orbital decompression from January 2017 to December 2019 were included. Subjects were excluded if they were <18 years, received both surgical decompression and teprotumumab, or lacked orbital imaging. The primary exposure variable was teprotumumab or surgical decompression. The secondary exposure variable was baseline FMR. The primary outcome measure was change in proptosis (mm).

Results: Thirty-eight patients, mean age 53.5 years (±11.4), were included in the teprotumumab group and 160 patients, mean age 48 years (±11.1), in the surgical group. Average proptosis reduction after teprotumumab and surgical decompression was 3 mm (±1.44) and 5 mm (±1.75), respectively. The FMR was stratified at the median of 1.80. In subjects with FMR < 1.80, teprotumumab showed equivalent proptosis reduction compared to surgical decompression, −0.33 mm (SE 1.32) $p = .802$. In subjects with FMR ≥ 1.80, surgical decompression led to significantly more proptosis reduction than teprotumumab, 3.01 mm (SE 0.54), $p < .001$.

Conclusions: Baseline FMR can be used to counsel patients as to proptosis reduction with teprotumumab versus surgery. Subjects with low FMR obtain comparable proptosis reduction with teprotumumab or surgery, whereas high FMR is associated with more significant proptosis reduction following surgery over teprotumumab.

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Thyroid eye disease (TED), an often debilitating and disfiguring condition, is characterized by autoimmune orbital inflammation, orbital fat expansion, and extraocular muscle enlargement. These changes result in proptosis, which can be present in up to 75% of dysthyroid patients presenting to an ophthalmologist.[1] Other manifestations include restrictive strabismus, lid retraction, and in severe cases dysthyroid optic neuropathy or corneal ulceration. Historically, the only treatment for thyroid-related proptosis has been surgical decompression of the orbit, typically performed during the "inactive" phase of the disease.[2,3] However, since publication of the OPTIC study (NCT03298867), a phase 3 randomised double-masked clinical trial demonstrating the ability of teprotumumab (Tepezza, Horizon Therapeutics, Dublin, Ireland) to reduce proptosis,[4] and the subsequent FDA approval of teprotumumab in January 2020, patients have had the option of teprotumumab infusions or surgical decompression as first-line treatment to reduce proptosis. Teprotumumab, a monoclonal insulin-like growth factor-1 receptor antagonist, is the first potentially approved disease-modifying treatment for TED; its introduction has altered practice patterns within the United States. One study looking at patients diagnosed with moderate to severe TED found that orbital decompression rates significantly decreased for patients treated with teprotumumab (20%) compared with a control population of patients (85%) who were treated before FDA approval. However, whether teprotumumab is as effective as surgical decompression is unknown; no studies comparing the efficacy of teprotumumab compared to surgical decompression have been published.

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While the phenotypic presentation of TED is undoubtedly varied,[5] it was traditionally dichotomised into two groups: those patients with primarily orbital fat expansion, classically termed "type 1 disease" and others with predominantly extraocular muscle expansion, termed "type 2 disease."[6–8] However, TED likely falls along a continuum, resulting in a variety of phenotypes.[5,9] It has been observed that fat-to-muscle ratio (FMR) can be used to differentiate TED patients with primarily orbital fat expansion with a high orbital fat-to-muscle ratio (FMR) from patients with predominantly extraocular muscle expansion with a low FMR. A recent study has shown that FMR distribution is not bimodal but unimodally distributed across the study group, suggesting that FMR represents a continuum of disease.[9] The results of that study showed an inverse graded relationship between pre-treatment FMR and therapeutic response to teprotumumab: the lower the FMR, the stronger proptosis reduction from teprotumumab, even after adjusting for age and sex.[9]

Given that not all patients respond equally to teprotumumab and hypothesising that FMR may have utility as a prognostic indicator, our objective was to explore if FMR could be used to identify whether surgical decompression or teprotumumab might lead to a greater reduction in thyroid-related proptosis.

Materials and methods

Study design

This was a retrospective cohort study comparing surgical decompression with teprotumumab for proptosis reduction according to pre-treatment FMR at a single tertiary ophthalmic center. The primary exposure variable was teprotumumab or surgical decompression. The secondary exposure variable was baseline FMR. The primary outcome measure was change in clinical proptosis (mm) after intervention. This study adhered to the tenets of the Declaration of Helsinki, was performed in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and was approved by the site's institutional review board.

Patients

All adult patients completing an 8-dose course of teprotumumab (10 mg per kg body weight for the first infusion, 20 mg per kg body weight for subsequent infusions) between January 2020 and September 2022 were included in the teprotumumab group. All patients undergoing bony orbital decompression from January 2017 to December 2019 were included in the surgical decompression group. Subjects were excluded from either group if they were aged <18 years, had received both surgical decompression and teprotumumab, or lacked baseline orbital imaging. Subjects were excluded from the surgery group if they had <3 months of post-operative follow-up.

Data collection

Data were collected retrospectively by chart review in EPIC and also review of paper charts. Data collected for all patients included age, sex, smoking status, euthyroid status, duration between disease onset and intervention, pre-treatment clinical activity score (CAS), and baseline clinical proptosis measurements using exophthalmometry prior to intervention (<30 days prior to teprotumumab or surgery). For the teprotumumab group, post-treatment proptosis was measured within 30 days following the completion of the final dose of teprotumumab, as well as the total number of teprotumumab infusions, and any reported side effects. For the surgical group, post-treatment proptosis was measured within 3–6 months post-operatively and the number of walls surgically decompressed was recorded.

Measuring fat-to-muscle ratio (FMR)

Quantitative analysis of FMR on patients' orbital imaging was performed by manual segmentation using OsiriX software. A single reformatted oblique coronal slice of orbital CT or MRI, created perpendicular to the optic nerve, was exported in DICOM format to Osirix software. Orbital imaging slices for CT or MRI were 2 mm thick. In all patients, the chosen coronal image was the slice positioned immediately posterior to the globe. Manual segmentation of the intraorbital contents was performed by two investigators. The segmented structures included the bony margins of the orbit, the superior (SR), medial (MR), lateral (LR), and inferior rectus (IR) muscles, the superior oblique (SO), and the optic nerve (Figure 1). The cross-sectional areas of the SR, MR, LR, IR, and SO were added together to give the total muscle area. Given the small caliber of other neurovascular structures within the orbit, the remaining area within the bony orbit was presumed to be composed primarily of fat. Therefore, the area of fat was calculated by subtracting the total muscle area and the optic nerve area from the area confined by the bony walls of the orbit. This was performed for the right and left orbit of each patient. To assess whether a single coronal slice was representative of the overall fat-to-muscle ratio volumetrically within the posterior orbit, we

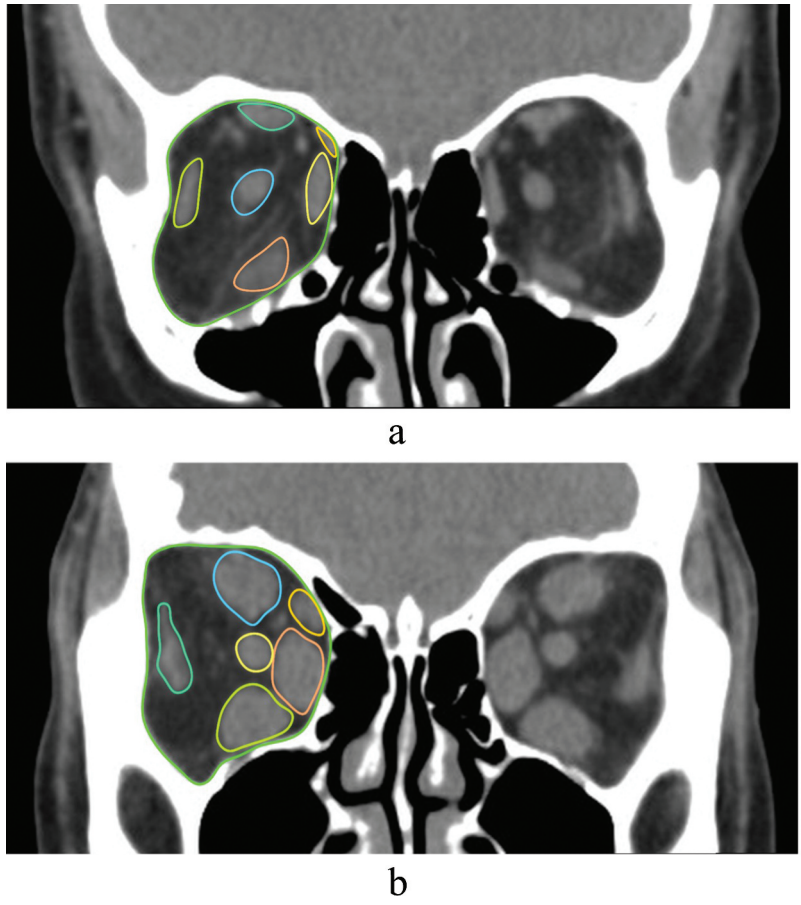

Figure 1. (a) Coronal CT of a patient with a high FMR showing manual segmentation of the right intraorbital contents. (b) Coronal CT of a patient with a low FMR showing manual segmentation of the right intraorbital contents.

manually segmented all orbital slices posterior to the globe for the first 10 consecutive participants. For each of these participants, we then examined the level of agreement between the chosen slice and the average of all slices, using two-way consistency intraclass correlation coefficient.

Surgical technique

All orbital decompression operations were performed by one of two surgeons. Walls were decompressed in cumulative sequential order: lateral wall for single wall surgery, lateral and medial wall for balanced, or two-wall decompression, and lateral, medial, and floor for three-wall decompression. An *ab interno* technique via an upper lid skin crease incision was used to decompress the lateral wall. A retrocaruncular approach was taken to access the medial wall in isolation, and a swinging eyelid approach was taken when also accessing the orbital floor. The posterior strut was preserved in all cases of orbital floor decompression. In all cases, the periosteum was opened and 2–4 cubic centimeters of intraconal fat was excised.

Statistical analysis

Analysis was carried out per patient with a single eye from each patient selected for the study. In the surgical group, in patients who had undergone unilateral decompression the operated eye was analyzed – in all unilateral surgical cases, this was the more proptotic eye. Therefore, in patients who had undergone bilateral decompression, the more proptotic eye was also selected for analysis. In the teprotumumab group, the clinically more proptotic eye was designated the study eye in accordance with the original clinical trial protocols[4] and to mirror the selection process within the surgical group.

Continuous variables were summarized as median ± interquartile range (IQR) and categorical variables as frequency and percentages. We used the Mann-Whitney U test and U statistic of permutation (a variant of the Pearson chi-squared statistic) for comparison of continuous and categorical variables between groups. The Shapiro Wilk test for normality was used to assess the distribution of FMR across the study population. To test whether FMR was an effect modifier, FMR was

stratified into two groups based on the median FMR, with those at and above the median being classified as "high FMR" and those below the median being labelled as "low FMR." Linear regression was used to model reduction in proptosis as the outcome variable with an interaction effect between FMR and intervention (teprotumumab or surgical decompression). The Wald test was used to assess the significance of interaction variables. Significance was set at a level of $p < .05$. All analyses were performed, and visualisations generated in R, version 4.1.0 (R Core Team, 2021. R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

Thirty-eight patients (32 female) with a mean (SD) age of 53.5 years (±11.4) were included in the teprotumumab group and 160 patients (125 female) with a mean age of 48 years (±11.1) were included in the surgical decompression group. There was one smoker in the teprotumumab group (2.6%) and 7 smokers in the surgical group (4.4%). In both groups, all patients were biochemically euthyroid prior to intervention. In the teprotumumab group, the mean (SD) pre-treatment CAS was 2.85 (1.70). In the surgical group, the mean (SD) pre-treatment CAS was 1.93 (1.48). In the teprotumumab group, the median duration between TED onset and first infusion was 18 months (IQR 6–45 months). In the surgical group, the median duration between TED onset and surgery was 19 months (IQR 15–36 months).

Table 1 summarises the baseline characteristics of the two groups.

Intervention

In the teprotumumab group, all patients received 8 doses of teprotumumab (10 mg per kg body weight for the first infusion, 20 mg per kg body weight for subsequent infusions). One patient developed a transient skin rash that resolved after the completion of teprotumumab treatment. Another patient reported menorrhagia after infusions 3 and 4, after which her menstrual pattern returned to normal. No other side effects were reported.

In the surgery group, 12 patients underwent single wall decompression, 71 patients underwent two-wall decompression, and 77 patients had three walls decompressed.

Fat-to-muscle ratio

In the teprotumumab group, 38 baseline orbital scans were exported (11 CT, 27 MRI), yielding 38 orbits for analysis. In the surgery group, 160 baseline orbital scans were exported (126 CT, 34 MRI), yielding 160 orbits for analysis. The median FMR in the teprotumumab group was higher than in the surgical group, 2.95 (±0.98) vs 1.45 (±0.55), $p < .00001$. The overall spread of FMR was unimodal with a right positive skew (Shapiro Wilk test for normality, $W = .873$, $p < .001$), Figure 2. The intraclass correlation between single slice FMR and the average FMR of all slices posterior to the globe for the first 10 consecutive patients was 0.94 (CI 0.70–0.99, $p < .001$).

Proptosis

In the teprotumumab group, mean (SD) baseline proptosis was 22.59 (±3.18) mm. In the surgical group, mean (SD) baseline proptosis was 24.10 (±3.55) mm. Average proptosis reduction after teprotumumab was 3 mm (±1.44) (percent proptosis reduction of 12.4%). Average proptosis reduction after surgical decompression was 5 mm (±1.75) (percent proptosis reduction of 20.7%).

Comparison of proptosis reduction according to FMR

The FMR was stratified at the median of 1.80. In subjects with a low FMR (<1.80), there was no difference in proptosis reduction between teprotumumab (mean (SD) 4.71 (1.50) mm) and surgical decompression (mean (SD) 5.04 (2.87) mm), −0.33 mm (SE 1.32)

Table 1. The baseline characteristics of the teprotumumab and surgery groups.

Group characteristics	Teprotumumab group	Surgical decompression group
Total number of patients	38	160
No. of female patients	32 (84.2%)	125 (78.1%)
Age in years	53.5 (±11.4)	48 (±11.1)
Smokers	1 (2.6%)	7 (4.4%)
No. of patients achieving euthyroid status prior to intervention	38 (100%)	160 (100%)
CAS	2.85 (±1.70)	1.93 (±1.48)
Duration of disease prior to treatment, months	18 (IQR 6–45)	19 (IQR 15–36)
Baseline proptosis in mm	22.59 (±3.18)	24.10 (±3.55)

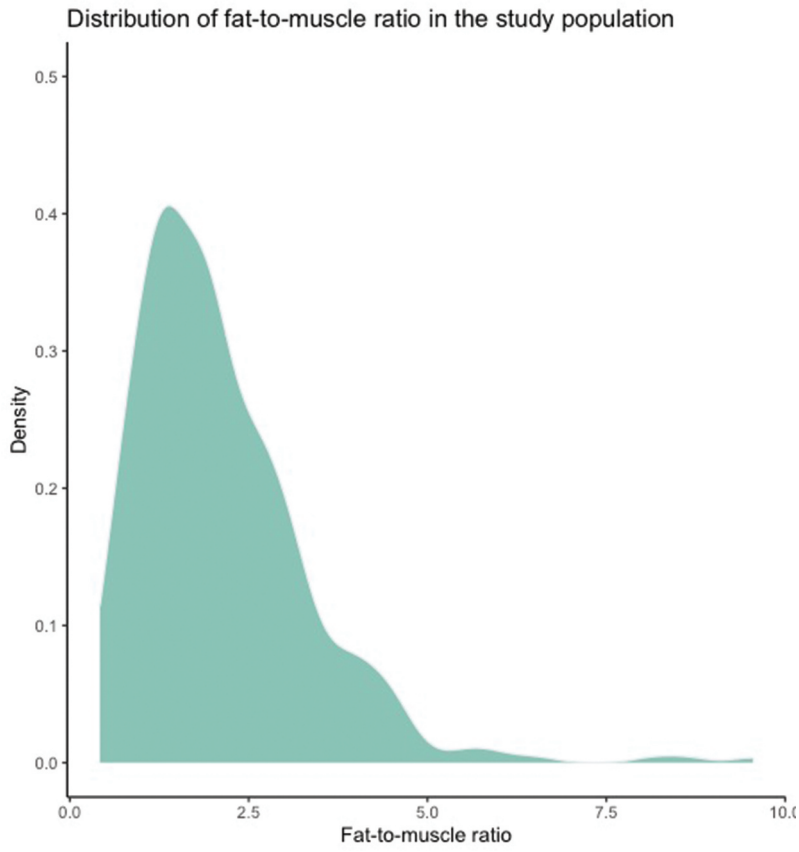

Figure 2. Unimodal distribution of FMR in the study population, showing a positive skew.

$p = .802$. In patients with a high FMR (≥1.80), surgical decompression led to significantly more proptosis reduction (4.94 (2.35) mm) than teprotumumab (1.93 (1.22) mm), 3.01 mm (SE 0.54), $p < .001$, (Figure 3).

Comparing the low and high FMR groups, the average proptosis reduction following surgical decompression was not significantly different (5.04 vs 4.94 mm), $p = .25$. In contrast, there was a significant difference in teprotumumab response between the low vs high FMR groups (1.93 vs 4.94 mm), $p = .01$.

Discussion

In this single-center cohort, we found baseline FMR value to be associated with whether teprotumumab or surgical decompression led to a greater proptosis reduction in TED. In patients with low FMR (<1.80) teprotumumab compared to surgical decompression led to equivalent proptosis reduction. However, in patients with high FMR (≥1.80), orbital decompression was associated with a greater level of reduction in proptosis than teprotumumab. Given that the average proptosis reduction following surgical decompression was not significantly different between the low and high FMR groups, the differential effect noted in this study can be attributed to the significant difference in teprotumumab response between the low vs high FMR groups. This is in keeping with previous observations that show a differential effect of teprotumumab based on FMR.[9] It is also supported by the lack of relationship found between FMR and response to surgery (Figure 4). Our overall conclusion is that surgical decompression should still be considered as an option for proptosis reduction in TED patients with high FMR. In patients with a low FMR, surgical decompression appears to be equally as effective as teprotumumab, therefore the choice between the two as a first-line therapy should be guided by other factors such as patient input, potential side effect profile, and fitness for surgery.

While practice patterns since the introduction of teprotumumab have shown a significant reduction in the amount of orbital decompression surgery performed for TED, this study highlights the continued relevance of surgery. Our current understanding of the scope of the use and efficacy of teprotumumab is continually being defined. Although teprotumumab has reduced the number of patients requiring surgical decompression, some patients still undergo surgical decompression for further proptosis reduction despite treatment with a full course of teprotumumab. By identifying which

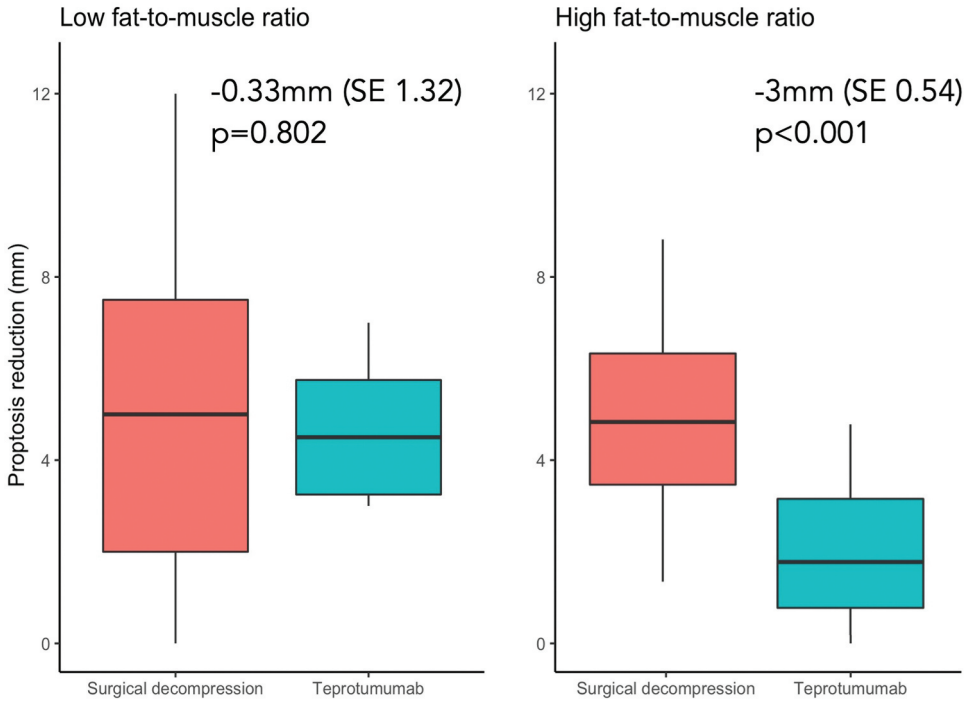

Figure 3. In the low FMR group (left), teprotumumab and surgical decompression were associated with similar levels of proptosis reduction. In the high FMR group (right), teprotumumab was associated with less proptosis reduction than surgical decompression.

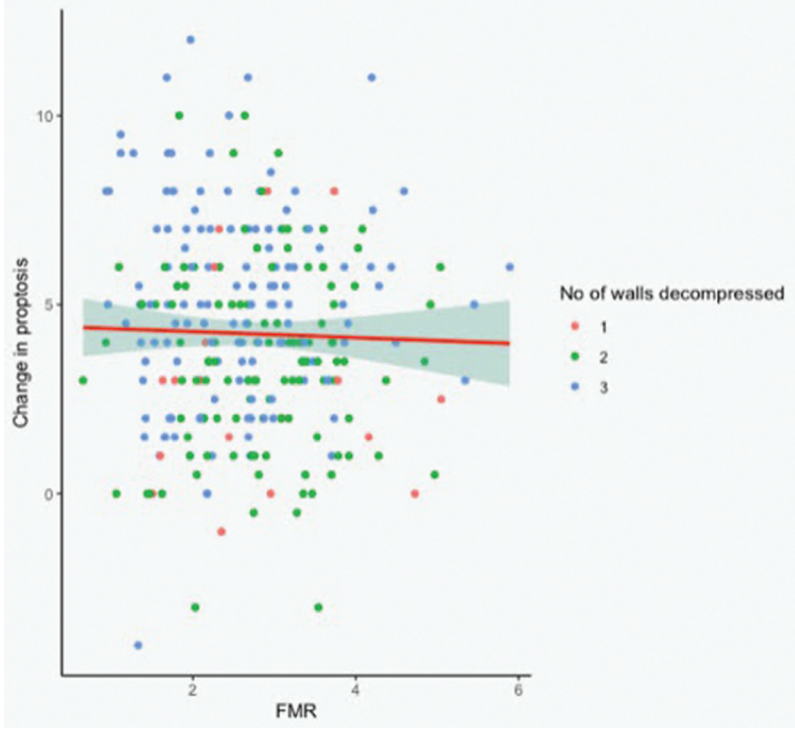

Figure 4. Univariable linear regression of patients undergoing surgical decompression, showing absence of correlation between baseline FMR and reduction in proptosis.

subset of patients might benefit from surgery over teprotumumab and vice versa, this study contributes to the growing framework of our understanding of when and how teprotumumab can best be utilised. This is important given treatment burden and duration, as well as the potential side effects of teprotumumab.[10–12]

Several points should be considered before applying the findings of this study to clinical practice. Firstly, there is unlikely to be a precise FMR value threshold at which the likelihood of surgical success exceeds the likelihood of a clinically significant response to teprotumumab for all patients. Rather, the findings in this study point towards overall trends, namely that those with a high FMR may trend towards a better response with surgery and those with a low FMR tend towards a good response with either teprotumumab or surgery. In this study, we chose to split the two FMR groups at the median FMR value of 1.80, because our current and previous studies show that FMR follows a unimodal distribution.[9] Further segmentation into smaller groups was limited by the number of subjects in the teprotumumab group, which was not high enough to power a more granular analysis in this instance. At this point, we cannot propose that 1.80 or a specific FMR value is an absolute threshold for choosing one treatment modality over the other until greater statistical power can be reached. Rather, we suggest that the clinician consider FMR as one factor to inform their recommendation of treatment choice.

Clinicians should also remember that FMR is just one factor influencing the overall treatment choice. Other factors to consider include relative and absolute contraindications to teprotumumab, the patient's fitness for surgery, surgeon experience, and the phase of disease at that given point in time. With regards to the latter, teprotumumab has been shown to be effective in active as well as chronic disease,[13] whereas surgery has traditionally been only an option in the "inactive" phase, typically after at least a 6-month period of stable inactivity.

Another important consideration is the differing potential side effect/complication profile between a medical and surgical therapy. Beyond a simple weighing up of efficacies, the side effect/complication risk may alter the patient willingness to receive either treatment. As an example, a patient with high FMR may be willing to accept the potential side effects associated with teprotumumab but not those associated with surgery. Yet even in such a case, the predictive value of the patient's high FMR would still be useful to inform the clinician and patient potential outcome with teprotumumab, thus, to manage the patient's expectations by discussing the possible need for surgery in future. Pretreatment FMR is an informative piece of data when taken in the context of the other factors mentioned above, to help guide the clinician towards the most efficacious treatment, thus, to customize the treatment plan according to the individual patient.

There are several potential mechanisms for the differential response to teprotumumab according to FMR, which we explored in our previous study.[9] Teprotumumab is a fully human monoclonal IgG1 antibody that binds with high selectivity and affinity to insulin-like growth factor 1 receptor (IGF-1 R), which is a ubiquitously expressed transmembrane tyrosine kinase receptor regulating cell growth and proliferation.[14] Increased IGF-1 R signalling has been proposed to contribute to orbital fibroblast activation in TED.[15] In response, orbital fibroblasts exhibit robust proliferative activity and extracellular matrix synthesizing capacity, differentiating into adipocytes and myofibroblasts with disease progression, thereby contributing to tissue expansion.[14,16–18] One possibility is that fat volume enlargement in TED relies on cellular proliferation[19] resulting in adipocyte hyperplasia, whereas extraocular muscle enlargement may be achieved through cellular hypertrophy and hyaluronan deposition as opposed to cell division.[20] Perhaps antagonism of IGF-1 R more quickly leads to reduction in cell size by reversing hypertrophy, but not to a reduction in cell number by apoptosis, thereby preferentially reducing the muscle volume over fat volume. One recent study analyzing post-treatment scans following teprotumumab has identified that both fat and muscle volume are reduced, with no difference between fat and muscle reduction seen. However, the relationship between baseline FMR and differential reduction in fat versus muscle was not examined.[21] Further basic science studies are required to improve our understanding of the response to teprotumumab.

Study limitations

Limitations of the dataset in this study include the small size of the teprotumumab group; in future studies a larger dataset would allow for a more granular analysis of the relationship between FMR and comparative response to intervention. The length of follow-up for the teprotumumab group was also limited at 30 days post-treatment, thus we cannot say whether the teprotumumab effect was permanent or whether some patients in the teprotumumab group subsequently regressed clinically with a recurrence in proptosis. Indeed, almost 30% of patients in the OPTIC trial experienced disease recurrence in the OPTIC-X follow-

up period, with the majority of these occurring at 5–6 months following the last dose.[22] A future study with longer real-world follow-up will help to answer this important question.

There were also differences in the baseline characteristics between the surgery and teprotumumab groups. These could not be controlled for statistically as the teprotumumab dataset was too small, and the retrospective nature of the study did not allow for prospectively balancing the two groups.

Additionally, as the dataset was derived from a single tertiary center, the external validity of the data is not clear. Lastly, this dataset was calculated from cross-sectional measurements and not volumetric analyses. However, the high level of intraclass correlation (0.94, $p < .001$) between single slice FMR and the average FMR of all slices posterior to the globe for the first 10 consecutive patients supports the use of cross-sectional FMR as a reliable surrogate for volumetric FMR.

A few sources of potential bias can be identified in this study. Firstly, there is a potential selection bias through the inclusion of only patients completing the full FDA approved 8 doses of teprotumumab. This could have resulted in inadvertent exclusion of patients who prematurely stopped receiving infusions, potentially in some patients due to lack of response. Clinical measurement of proptosis, although performed by an attending surgeon, can be subjective. In patients with less severe proptosis, patients may have treatment bias in electing medical therapy over surgery, leading to lower baseline entry proptosis in the teprotumumab group. Patients in this study were also investigated with either a CT or MRI scan, with a larger proportion of the teprotumumab group undergoing MRI and a larger proportion of the surgery group undergoing CT. Although both modalities were of sufficient resolution to determine FMR measurements, the mixture of imaging modalities within each group and between groups could potentially affect the reliability of FMR measurements between patients.

Future considerations

This study provides a comparison between two treatment modalities, intravenous teprotumumab and surgical decompression, for thyroid-related proptosis, according to baseline fat-to-muscle ratio. However, these two modalities are not necessarily exclusive of each other, we may find that some patients benefit from a combination of both teprotumumab and surgery. As more real-world data becomes available, future studies should ask: What is the efficacy of teprotumumab alone versus teprotumumab and surgery, versus surgery alone? Is there a beneficial effect of teprotumumab being administered prior to orbital decompression? In patients with disease recurrence after teprotumumab, is a second course of teprotumumab warranted, or would surgery be a better choice? Furthermore, if surgery is still required after teprotumumab, does prior treatment with teprotumumab reduce the total number of walls requiring surgical decompression? The answers to these important questions will help us to further define the role of teprotumumab in the management of this complex disease.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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