Monoclonal antibodies for the treatment of Graves' ophthalmopathy: A systematic review and meta-analysis

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Abstract:

PURPOSE: The traditional standard of care for Graves' ophthalmopathy (GO) is glucocorticoid therapy, which is associated with many long-term side effects. The aim of this systematic review and meta-analysis was to compare the traditional therapy to novel monoclonal antibodies (e.g. rituximab [RTX], teprotumumab, and tocilizumab [TCZ]).

METHODS: We searched the Medline, Embase, and Cochrane Central Register of Controlled Trials databases. We included randomized controlled trials (RCTs) that compared different monoclonal antibodies (e.g. RTX, teprotumumab, and TCZ) with glucocorticoids or placebo in patients with GO. We evaluated the clinical activity score (CAS), proptosis, subjective diplopia using the Gorman score, quality of life (QoT), adverse events, change in lid fissure, NOSPECS score, and TSH receptor antibody (TRAb) levels. The odds ratio (OR) was used to represent dichotomous outcomes. The continuous outcomes were represented as standardized mean difference (SMD). Data were pooled using the inverse variance weighting method. Risk of bias was assessed using the revised Cochrane risk-of-bias tool for randomized trials.

RESULTS: Six ($n = 571$) RCTs were deemed eligible. The different monoclonal antibodies were significantly more efficacious than glucocorticoid/placebo in terms of reduction in CAS (SMD = −1.44, 95% confidence interval (CI): −1.91–−0.97, $P < 0.00001$, $I^2 = 74\%$), change in proptosis (SMD = −4.96, 95% CI: −8.02–−1.89, $P = 0.002$, $I^2 = 99\%$), QoL (SMD = 2.64, 95% CI: 0.50–4.79, $P = 0.02$, $I^2 = 97\%$), and Gorman score for diplopia (OR = 3.42, 95% CI: 1.62–7.22, $P = 0.001$, $I^2 = 8\%$). However, monoclonal antibodies have shown higher rates of adverse events (OR = 2.91, 95% CI: 1.12–7.56, $P = 0.03$, $I^2 = 62\%$). No significant difference was found with respect to lid fissure, NOSPECS, and TRAb levels.

CONCLUSION: This meta-analysis demonstrated that monoclonal antibodies were associated with more favorable clinical outcomes than standard steroid therapy or placebo, especially with regard to CAS, change in proptosis, diplopia, and QoL, with teprotumumab being superior. In addition, only minor safety concerns were identified with monoclonal antibodies though less worrisome than using traditional steroids.

Keywords:

Graves' ophthalmopathy, Graves' orbitopathy, rituximab, teprotumumab, thyroid eye disease, tocilizumab

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Introduction

Graves' ophthalmopathy (GO), also known as thyroid eye disease (TED), is an autoimmune thyroid-related ocular manifestation characterized by pain, double or decreased vision, and exophthalmos.[1,2] It is also the most prevalent Graves' disease (GD) extrathyroidal manifestation. The incidence of GO in the general population is around 0.1%–0.3%; however, this proportion rises to 20%–40% in patients with GD.[2,3] The pathogenesis of GO is not fully understood, but cross-reactivity between thyroid and orbital tissue might be the mechanism behind the disease due to the presence of autoantibodies in the orbital tissues.[4,5] In patients with GD, these antibodies are not only present in the hyperthyroid state but also can persist in euthyroid or hypothyroid states when patients are under antithyroid treatments.[6] Changes in ocular performance and significant disfigurement such as lid retraction, periorbital

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tissue swelling, and fixed gaze are common adverse effects of GO that may disturb daily activities, thus negatively impacting the patients' quality of life (QoL).[3]

In clinical practice, the traditional standard of care for GO is glucocorticoid therapy. The benefits of systemic glucocorticoid treatment include the relief of acute GO symptoms, improved optical nerve function, and improved patient QoL.[3] Long-term use of corticosteroids, on the other hand, can cause steroid-related side effects that include weight gain, hyperglycemia, hypertension, osteoporosis, and liver damage.[7] In addition to these systemic adverse effects, steroids have many ocular side effects, including glaucoma, cataract formation, delayed wound healing, and an increased susceptibility to infections.[8] Furthermore, symptoms of GO may worsen when the amount of glucocorticoids is gradually reduced. Hence, additional studies into the pathophysiology of GO are required to develop a more commonly utilized therapy with fewer adverse effects.[3]

Recently, novel pharmaceutical agents have been widely evaluated for the management of GO. Monoclonal antibodies like tocilizumab (TCZ), rituximab(RTX), and teprotumumab are among the most important developments (TCZ). A recent meta-analysis, exploring the efficacy and safety of RTX, concluded that for individuals with moderate-to-severe GO, RTX is a generally safe and effective therapy that outperforms glucocorticoids and saline.[9] Two other randomized controlled trials (RCTs) showed that teprotumumab had superior results than placebo in terms of proptosis, clinical activity score (CAS), double vision, and QoL.[1,10] However, none of the published studies collectively determined the role of different monoclonal antibody drugs in the management of GO compared to steroids.

The aim of this systematic review and meta-analysis was to provide an exhaustive evaluation of the efficacy and safety of monoclonal antibodies (e.g. RTX, teprotumumab, and TCZ) compared to steroid therapy for the management of GO with respect to CAS, proptosis, and subjective diplopia using the Gorman score, QoL, lid fissure, NOSPECS score, TSH receptor antibody (TRAb) levels, and adverse events.

Methods

This systematic review was conducted in accordance with a prespecified protocol registered in PROSPERO (CRD42021266175). The report of this review was in the light of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist.[11]

Eligibility criteria

Population: Adult individuals with moderate-to-severe and active GO with CAS ≥3 out of 7. Intervention: Monoclonal antibody administered intravenously (IV) (i.e. RTX or teprotumumab or TCZ). Comparison: IV administered glucocorticoids or placebo. Placebo-controlled trials were included in order to reach a larger sample size as well as to include the most RCTs for the different monoclonal antibodies, as up to our knowledge, no studies compared teprotumumab or TCZ to glucocorticoids. Outcomes: CAS, proptosis, subjective diplopia score using the Gorman scale, QoT, adverse events, change in lid fissure, NOSPECS score, and TRAb levels. Study design: RCTs. We excluded trials that enrolled participants who received glucocorticoid therapy within the past month. We also excluded trials that included those who received radiotherapy.

Search strategy

The systematic search was performed on Medline, Embase, and the Cochrane Central Register of Controlled Trials from database inception to July 3, 2021, without any restriction on date or language. The complete search strategy is provided in the supplementary material. We manually searched the references of the included studies for potentially relevant RCTs missed during the systematic search.

Study selection and data extraction

Two reviewers performed title and abstract screening against the eligibility criteria, full-text assessment, and data extraction from eligible trials independently and in duplicate. Discrepancies were resolved through consensus or discussion with a third reviewer before the analyses were performed.

Meta-analysis

Data analysis was performed using RevMan (Review Manager) version 5.3 (Cochrane Collaboration). All statistical analyses were performed using the random-effects model. We adopted 95% as a confidence level and $P < 0.05$ as a threshold. The statistical heterogeneity was assessed using I^2 and the P value of the Chi-square test. The continuous outcomes (CAS, change in proptosis, change in lid fissure, NOSPECS score, and TRAbs) were represented as standardized mean difference (SMD) and pooled using the inverse variance weighting method. The dichotomous outcomes (adverse events and Gorman diplopia score) were expressed as odds ratio (OR) and pooled using the inverse variance weighting method. We performed subgroup analysis based on the type of monoclonal antibody used: RTX, teprotumumab, and TCZ.

Risk-of-bias assessment

Two reviewers independently and in duplicate performed the risk-of-bias assessment for the included RCTs using the revised Cochrane risk-of-bias assessment tool. The potential of publication bias for each outcome was assessed by visual inspection of the funnel plot and assessment of symmetry. Evidence of publication bias is considered possible when it is asymmetrical.

Results

The flowchart of this systematic review, including the justification for exclusion of studies, is shown in Figure 1. In the literature search, we identified 1075 records, of which 59 duplicates were excluded. After screening the titles and abstracts, there were 23 potentially eligible studies assessed

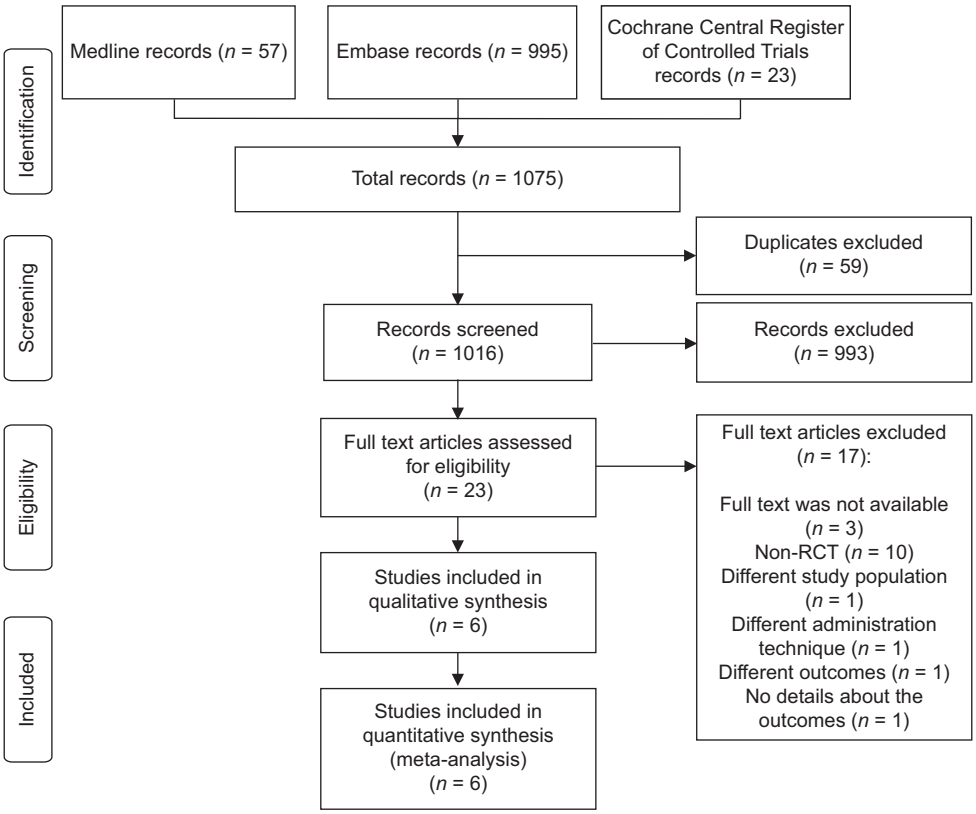

Figure 1: Study flow diagram. RCT: Randomized controlled trial

for inclusion. Only six RCTs, eventually, were eligible, and all of them were included in the meta-analysis. Three articles assessed RTX monoclonal antibody. Two studies evaluated the effect of teprotumumab monoclonal antibody. Only one study assessed TCZ monoclonal antibody.

Trial characteristics

A total of 571 individuals were included in this systematic review. Of whom, 101 (17.6%) were randomized to RTX, 84 (14.7%) were randomly assigned to teprotumumab, and 15 (2.6%) were randomized to the TCZ group. The mean age ranged from 45 to 61 years for the control group and 47 to 57 years for the monoclonal antibody group. Table 1 shows the detailed characteristics of the included studies.

Risk-of-bias assessment

Three of the six RCTs had an overall low risk of bias. Two RCTs had some concerns. One RCT had an overall high risk of bias due to deviation from the intended intervention. Figures 2 and 3 demonstrate the risk-of-bias assessment of the included RCTs.

Clinical activity score

All included RCTs reported on CAS ($n = 571$).[1,3,4,10,12,13] The monoclonal antibody groups showed a significant difference in CAS compared to glucocorticoid/placebo (SMD = −1.44, 95% confidence interval (CI): −1.91–−0.97, $P < 0.00001$, $I^2 = 74\%$). Three RCTs reported significantly better CAS in the RTX group in comparison to the glucocorticoid/placebo group (SMD = −1.51 points, 95% CI: −2.19–−0.82, $P < 0.0001$, $I^2 = 67\%$). Similarly, Douglas, 2020, and Smith, 2017, also found a significant difference in CAS between the teprotumumab and placebo groups (SMD = −1.46, 95% CI: −2.67–−0.25, $P = 0.02$, $I^2 = 92\%$). Moreover, Perez-Moreiras, 2018, also showed a significant difference in CAS between TCZ and placebo (SMD = −1.18, 95% CI: −1.94–−0.42, $P = 0.002$, I^2 = not applicable) [Figure 4a]. The funnel plot was symmetrical on visual inspection, and no evidence of publication bias was noted [Figure 4b].

Change in proptosis

Five RCTs reported on change in proptosis.[1,3,4,10,12] The monoclonal antibody group showed a significantly better outcome in terms of proptosis compared to glucocorticoid/placebo (SMD = −4.96, 95% CI: −8.02–−1.89, $P = 0.002$, $I^2 = 99\%$). Three RCTs showed no significant difference in change in proptosis between RTX and glucocorticoid/placebo (SMD = −0.29, 95% CI: −0.97–0.39, $P = 0.40$, $I^2 = 73\%$). On the contrary, Douglas, 2020, and Smith, 2017, reported a significantly better change in proptosis when administrating teprotumumab over placebo (SMD = −12.52, 95% CI: −13.92–−11.12, $P < 0.00001$, $I^2 = 0\%$) [Figure 5a]. The funnel plot was symmetrical on visual inspection, and no evidence of publication bias was noted [Figure 5b].

Gorman diplopia score

Three RCTs reported on Gorman diplopia score.[1,4,10] Monoclonal antibodies showed significantly better

Table 1: Characteristics of the included studies

Study, Year	Intervention	Number of participants		Age (in years)		Measured outcomes
		Control	Monoclonal antibody	Control	Monoclonal antibody	
Li 2017	Rituximab Vs (A) Iodine-131, (B) Iodine-131 and Methylprednisolone	A=72, B=70	75	(A) 49.1±9.3, (B) 50.3±10.0	48.1±10.0	Hyperthyroidism treatment outcomes, orbital volumetric analysis through CT imaging, proptosis, eyelid width, soft tissue swelling, conjunctival hyperemia, intraocular pressure, visual acuity, CAS, serum Th1 and Th2 cytokine levels, and adverse events.
Salvi 2015	Rituximab Vs Methylprednisolone	16	15	50.4±11.4	51.9±13.1	CAS, proptosis, lid fissure, diplopia and eye muscle motility, and quality of life score, number of therapeutic responses, disease reactivation, and surgical procedures required during follow-up.
Stan 2015	Rituximab Vs Placebo	10	11	61.8±11.0	57.6±12.7	CAS, success and failure rates, proportions showing clinically significant improvement in proptosis, lid fissure width, diplopia score, lagophthalmos and disease severity, orbital fat/muscle volume and quality-of-life.
Douglas 2020	Teprotumumab Vs Placebo	42	41	48.9±13.0	51.6±12.6	Proptosis response, CAS, diplopia response, and Graves'ophthalmopathy-specific quality-of-life (GO-QOL).
Smith 2017	Teprotumumab Vs Placebo	44	43	54.2±13.0	51.6±10.6	CAS, proptosis, GO-QOL questionnaire, and adverse events.
Perez-Moreiras 2018	Tocilizumab Vs Placebo	17	15	45.07 (IQR=38.9-50.5)	47.5 (IQR=41.1-57.4)	CAS, patient global assessment (PtGA) of pain, quality of life evaluated by the generic SF-36 and GO-QoL, adverse events, death, and clinically significant changes in vital signs and laboratory tests.

QOL: Quality of life, PtGA: Patient global assessment, CAS: Clinical activity score, GO-QoL: Graves' ophthalmopathy-specific QOL, IQR: Interquartile range, CT: Computed tomography

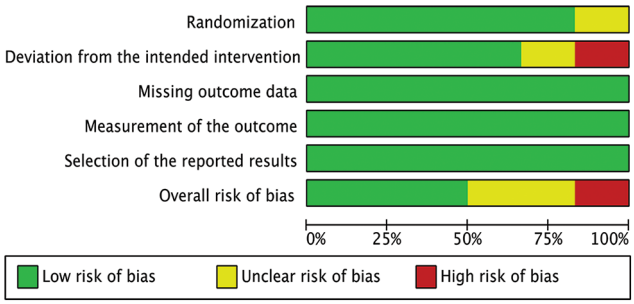

Figure 2: Risk-of-bias graph

scores in the Gorman diplopia score in comparison to the glucocorticoid/placebo group (OR = 3.42, 95% CI: 1.62–7.22, $P = 0.001$, $I^2 = 8\%$). Two RCTs showed a significant improvement in Gorman diplopia score in teprotumumab over placebo therapy (OR = 4.31, 95% CI: 1.98–9.39, $P = 0.0002$, $I^2 = 0\%$). Salvi, 2015, compared RTX to glucocorticoids in terms of Gorman diplopia score and showed no significant difference between the two interventions (OR = 1.08, 95% CI: 0.18–6.44, $P = 0.93$, I^2 = not applicable) [Figure 6a]. The funnel plot was symmetrical on visual inspection, and no evidence of publication bias was noted [Figure 6b].

Change in lid fissure

Two RCTs reported on change in lid fissure.[4,12] Both compared RTX to glucocorticoids (Li 2017) or placebo (Stan 2015) and showed no significant difference in change in lid fissure (SMD = −0.24, 95% CI: −0.54–0.06, $P = 0.12$, $I^2 = 0\%$) [Figure 7a]. The funnel plot was symmetrical on visual inspection, and no evidence of publication bias was noted [Figure 7b].

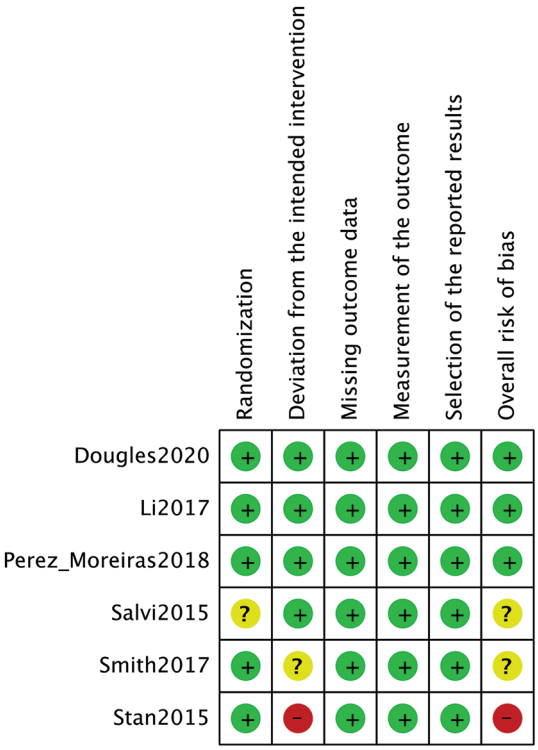

Figure 3: Risk-of-bias summary

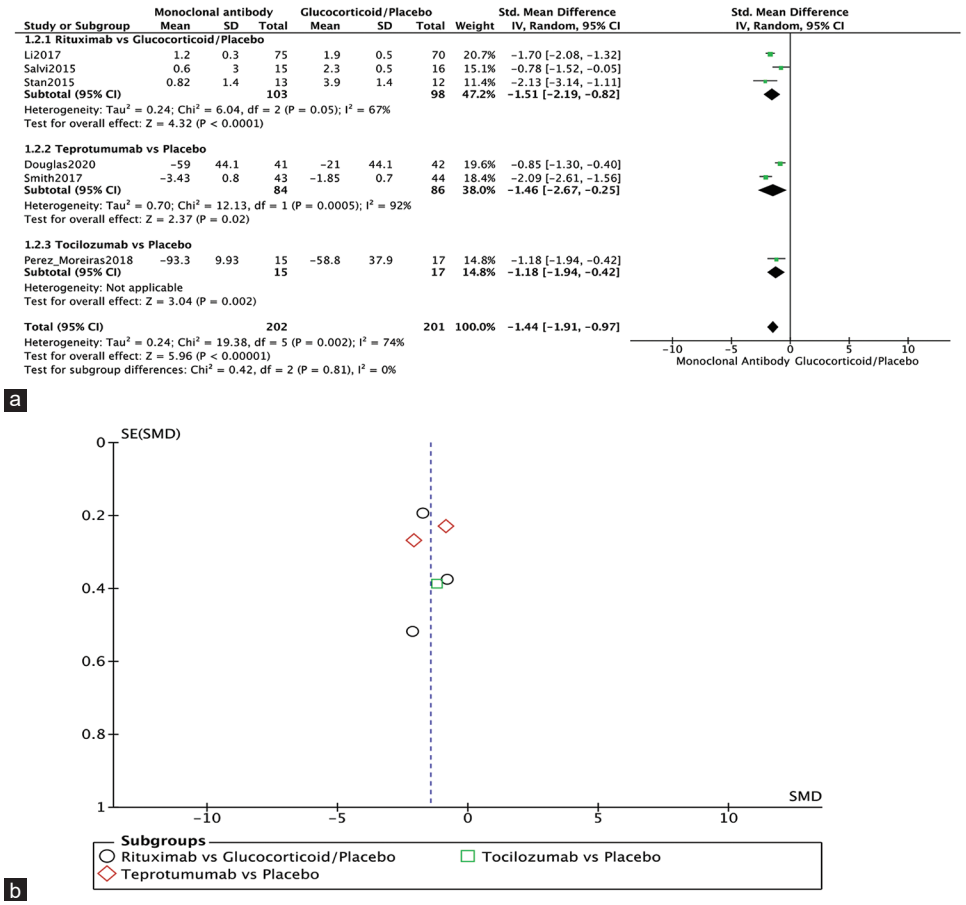

Figure 4: Clinical activity score. (a) Forest plot. (b) Funnel plot. CI: Confidence interval, IV: Inverse variance, RTX: Rituximab

Adverse events

All RCTs reported on adverse events.[1,3,4,10,12,13] The monoclonal antibody group showed significantly higher rates of adverse events compared to the glucocorticoid or placebo group (OR = 2.91, 95% CI: 1.12–7.56, $P = 0.03$, $I^2 = 62\%$). For RTX, only Li 2017 reported less adverse events with RTX compared to steroids. In Salvi, 2015, and Stan, 2015, RTX was associated with more adverse events compared to the control groups (OR = 2.54, 95% CI: 0.40–16.15, $P = 0.32$, $I^2 = 78\%$). Teprotumumab was associated with significantly higher rates of adverse events compared to placebo (OR = 3.06, 95% CI: 1.16–8.09, $P = 0.02$, $I^2 = 0\%$). Similarly, in Perez-Moreiras, 2018, TCZ was associated with significantly high rates of adverse events (OR = 4.88, 95% CI: 1.06–22.38, $P = 0.04$, I^2 = not applicable) [Figure 8a]. The funnel plot was symmetrical on visual inspection, and no evidence of publication bias was noted [Figure 8b].

NOSPECS score

Two RCTs reported on NOSPECS score.[4,12] Both compared RTX to glucocorticoids (Salvi, 2015) or placebo (Stan, 2015) and showed no significant difference in NOSPECS score (OR = 0.65, 95% CI: 0.18–2.42, $P = 0.53$, $I^2 = 0\%$) [Figure 9a]. The funnel plot was symmetrical on visual inspection, and no evidence of publication bias was noted [Figure 9b].

Quality of life

Four RCTs reported on QoT.[1,10,12,13] The monoclonal antibody group showed significantly improved QoT (SMD = 2.64, 95% CI: 0.50–4.79, $P = 0.02$, $I^2 = 97\%$). Two RCTs showed a significant difference in QoL between teprotumumab and placebo (SMD = 4.52, 95% CI: 3.95–5.10, $P < 0.00001$, $I^2 = 0\%$). Perez-Moreiras, 2018, also showed a significant difference in QoL between TCZ and placebo (SMD = 1.19, 95% CI: 0.43–1.96, $P = 0.002$, I^2 = not applicable). Stan, 2015, showed no significant difference between RTX and placebo (SMD = 0.33, 95% CI: −0.46–1.13, $P = 0.41$, I^2 = not applicable) [Figure 10a]. The funnel plot was symmetrical on visual inspection, and no evidence of publication bias was noted [Figure 10b].

TRAb levels

Two RCTs reported on TSH receptor antibodies (TRAbs).[4,12] In Salvi, 2015, RTX was found to be superior to IV methylprednisolone (IVMP) in reducing serum TRAb levels. In Stan 2015, however, no significant difference was found between RTX and placebo in this outcome. Overall, no significant difference was found in terms of reducing TRAb (SMD= −0.30, 95% CI: −1.19–0.59, $P = 0.51$, $I^2 = 64\%$) [Figure 11a]. The funnel plot was symmetrical on visual inspection, and no evidence of publication bias was noted [Figure 11b].

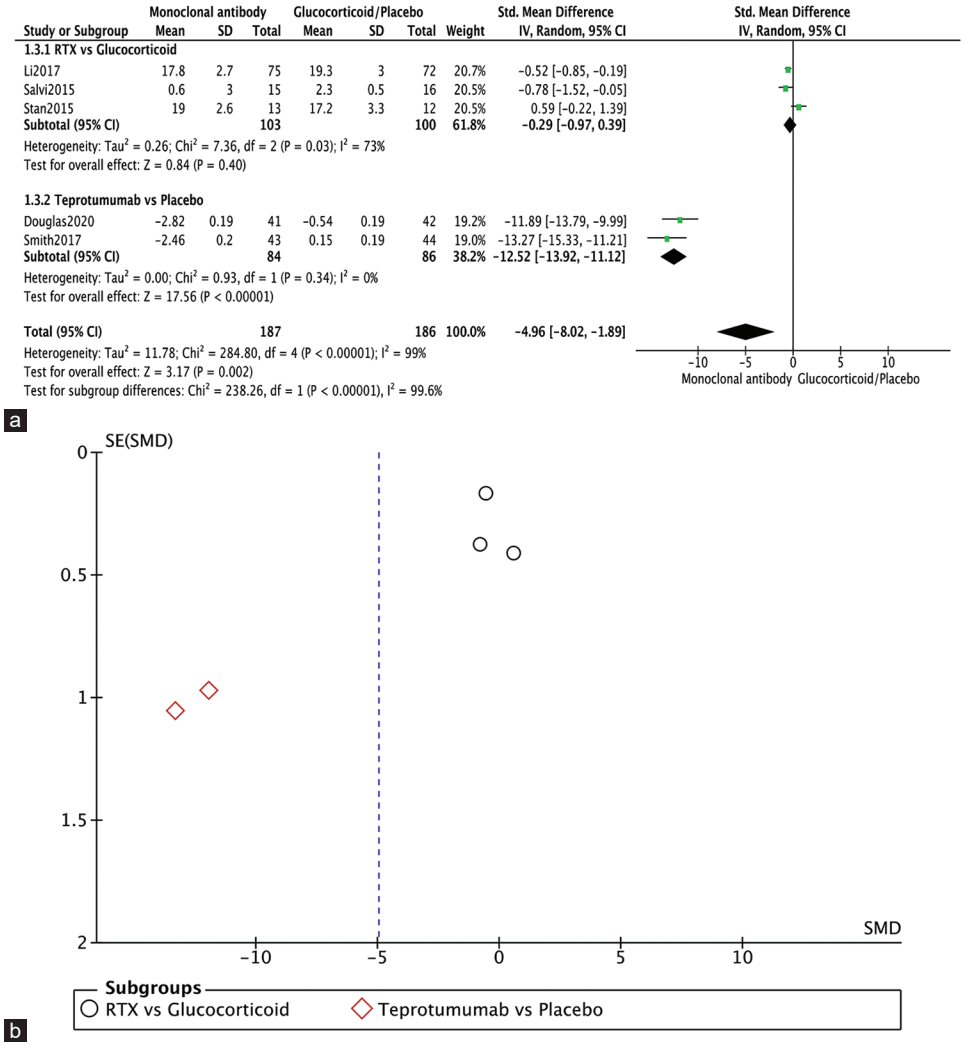

Figure 5: Change in proptosis. (a) Forest plot. (b) Funnel plot.

Discussion

Glucocorticoids have been the mainstay therapy of GO for decades. However, due to their potential hepatic and cardiovascular risks, safer and more effective treatments were sought. Among these, novel treatment options are monoclonal antibodies such as RTX, teprotumumab, and TCZ. RTX, which was first approved in 1997 for oncology patients, is an anti-CD20 monoclonal antibody. Many symptoms of GO are caused by B-cell-induced production of TSH receptor-directed immunoglobulins. RTX works by blocking the surface protein CD20 on B-lymphocytes, causing depletion of B-cells.[14,15] Teprotumumab has a different mechanism of action than RTX; it is a monoclonal antibody that blocks the insulin-like growth factor I receptor, a major contributor in GO.[1] TCZ is a monoclonal antibody targeted against IL-6 receptors which are important for the activation of B-cells and the development of antibody-producing plasma cells.[16]

This systematic review and meta-analysis of 6 RCTs representing 571 individuals with GO compared the safety and efficacy of the aforementioned monoclonal antibodies to the standard steroid therapy or placebo in treating GO. The pooled effect estimate showed a statistically significant difference between monoclonal antibodies and glucocorticoids/placebo in terms of CAS, adverse events, change in proptosis, QoL, and Gorman score for diplopia. However, no significant difference was found with respect to lid fissure, NOSPECS, and TRAb levels.

The CAS can be used to estimate disease activity based on the presence of pain, redness, and swelling. A reduction in CAS signifies higher therapeutic effects.[17] Our study demonstrated that RTX significantly improved the CAS. Similar findings were reported in a 2018 systematic review where there was a reduction from a mean baseline CAS of 5.5 to approximately 1.0.[18] Similarly, a reduction from 4.7 to 1.8 was reported in another study by Salvi *et al*. despite being a pilot study comparing only 20 patients.[19] Teprotumumab also showed a significant difference in reducing CAS compared to placebo. This was in accordance with a cohort study published in 2021, where a statistically significant reduction by 2.2 ± 1.4

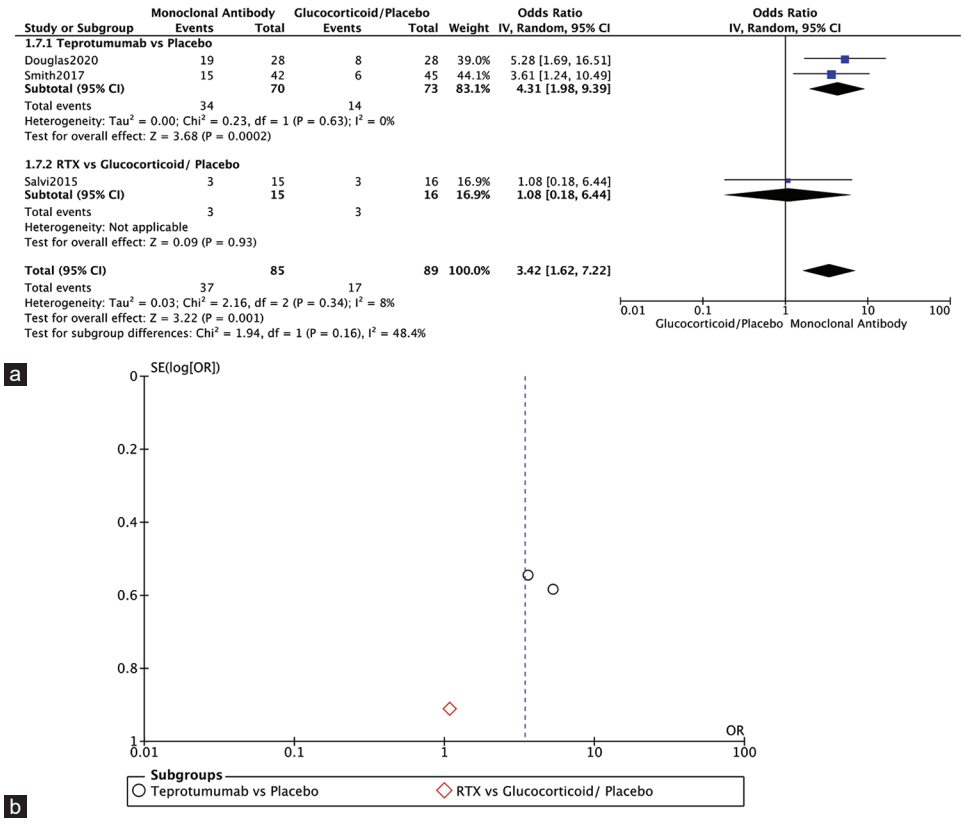

Figure 6: Gorman diplopia score. (a) Forest plot. (b) Funnel plot

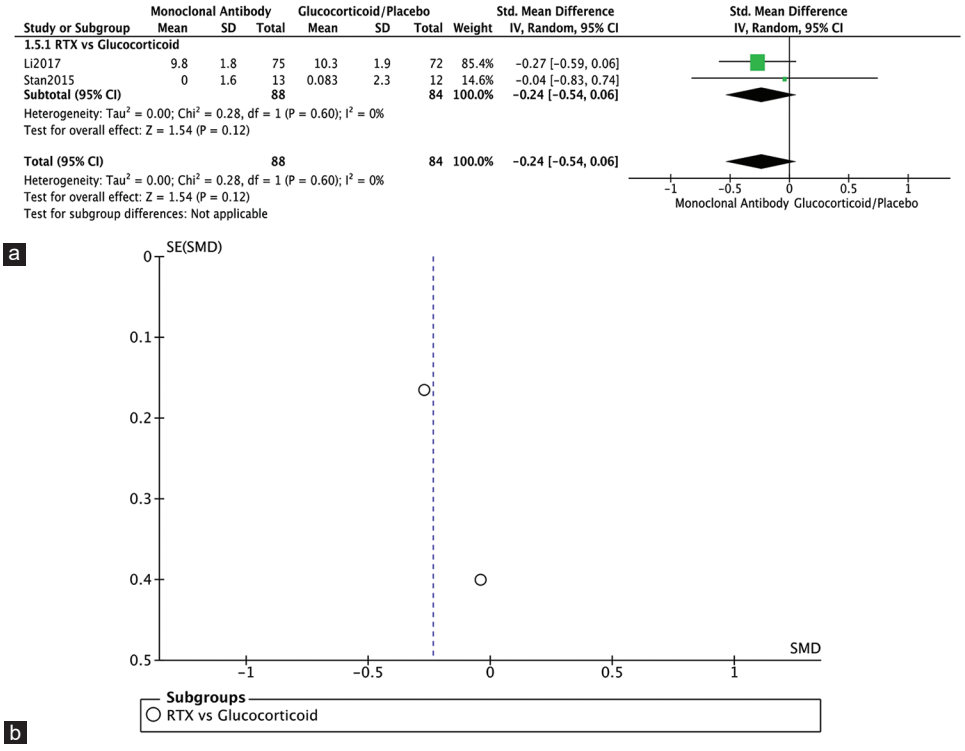

Figure 7: Change in lid fissure. (a) Forest plot. (b) Funnel plot

in CAS was found.[20] For TCZ, Perez-Moreiras *et al*. showed similar results as the two other monoclonal antibodies.[13] Unfortunately, no other RCTs were done to compare the effect of TCZ on CAS in patients with GO. However, in an

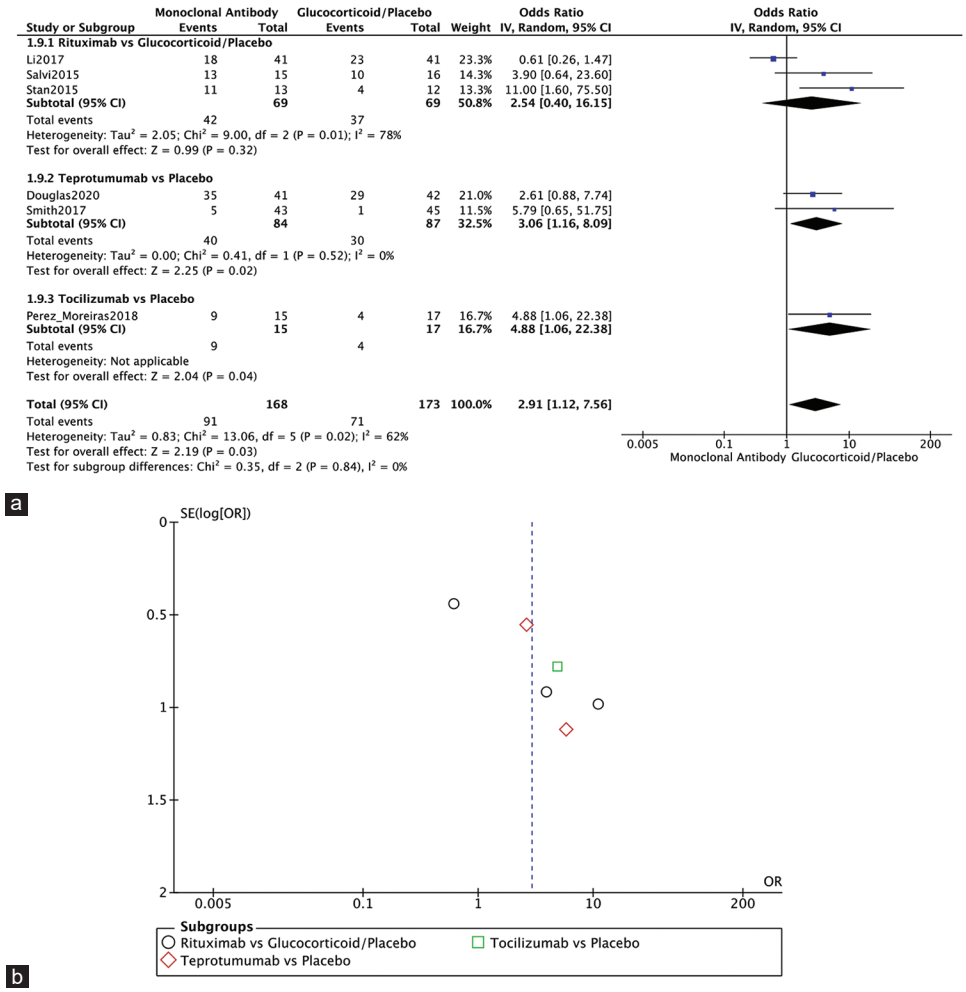

Figure 8: Adverse events. (a) Forest plot. (b) Funnel plot

observational study published by the same author, an absolute response of CAS (meaning CAS = 0 or 1) was seen in 55% of patients, and a relative response (reduction ≥2 points) was seen in 90.9% of patients.[21] In a case report published in 2017, two patients with moderate-to-severe GO who received a maximal dose of IV glucocorticoids and underwent orbital decompression but had persistent ocular symptoms showed improved CAS after receiving TCZ therapy.[22] These findings most likely explain why these treatments were approved for GO; in other words, they reduce the disease activity.

Regarding the change in proptosis, our findings showed an overall better RTX effect on proptosis though with no significant difference to the standard of care or placebo. However, the results of the three individual RCTs were conflicting. Unlike the other two, Stan *et al*. showed better results when placebo was used.[12] This study, however, has a high risk of bias with regard to the deviation from the intended intervention, so results should be interpreted carefully. A 2018 systematic review of 293 patients supports our previously mentioned findings regarding the effect of RTX on proptosis.[9] Another systematic review of 167 showed a significant difference in terms of change in proptosis in favor of RTX. This difference could be explained by the nature of the studies included, as the latter systematic review included mostly observational studies.[18] Teprotumumab shows promising results, especially with regard to the change in proptosis, filling the gap left by RTX. A recently published meta-analysis of 16 studies with a total of 663 patients assessed changes in proptosis and diplopia in 3 different arm groups: teprotumumab, IVMP, and placebo. It showed a significantly greater improvement from baseline proptosis compared to IVMP.[23] Moreover, a retrospective series of nine patients with chronic TED, a mean proptosis reduction of 4.2 ± 2.8 mm in the more severely affected eyes and 2.6 ± 2.3 mm in the less affected eye, were reported. The results of these individual cases were slightly higher though still consistent with ours, which could be due to relatively small sample size.[24] To our knowledge, no RCTs evaluated proptosis using TCZ. NOSPECS classes assess the severity of the disease, including the presence of proptosis (no signs or symptoms; only signs, no symptoms; signs only; proptosis; eye muscle involvement; corneal involvement; and sight visual acuity reduction). A reduction was reported in two of the included studies. Both RCTs, Salvi *et al*. and Stan *et al*., evaluated RTX and showed similar yet nonsignificant results compared to IVMP or placebo, respectively.[4,12]

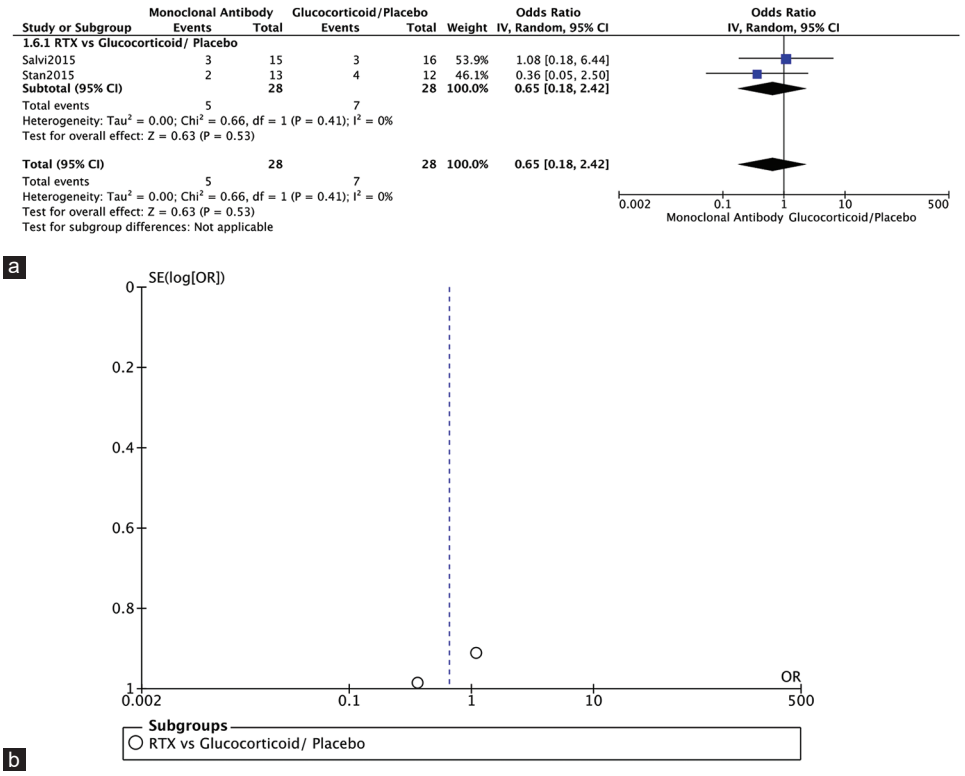

Figure 9: NOSPECS score. (a) Forest plot. (b) Funnel plot

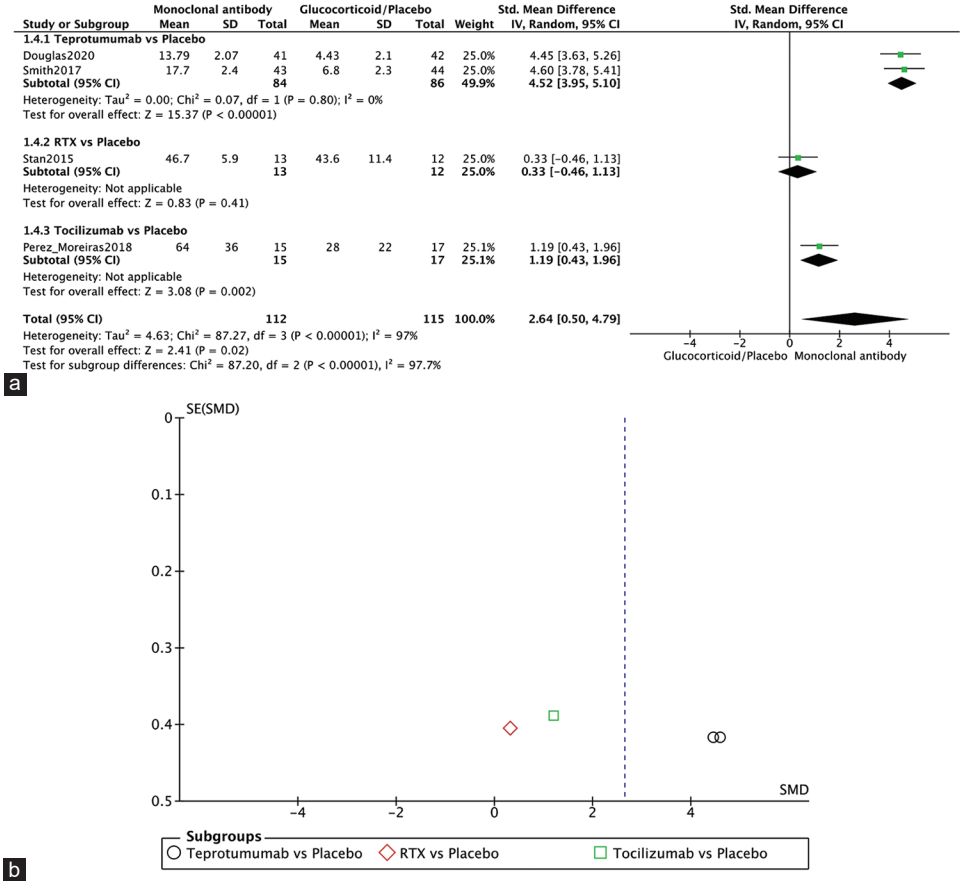

Figure 10: Quality of life. (a) Forest plot. (b) Funnel plot

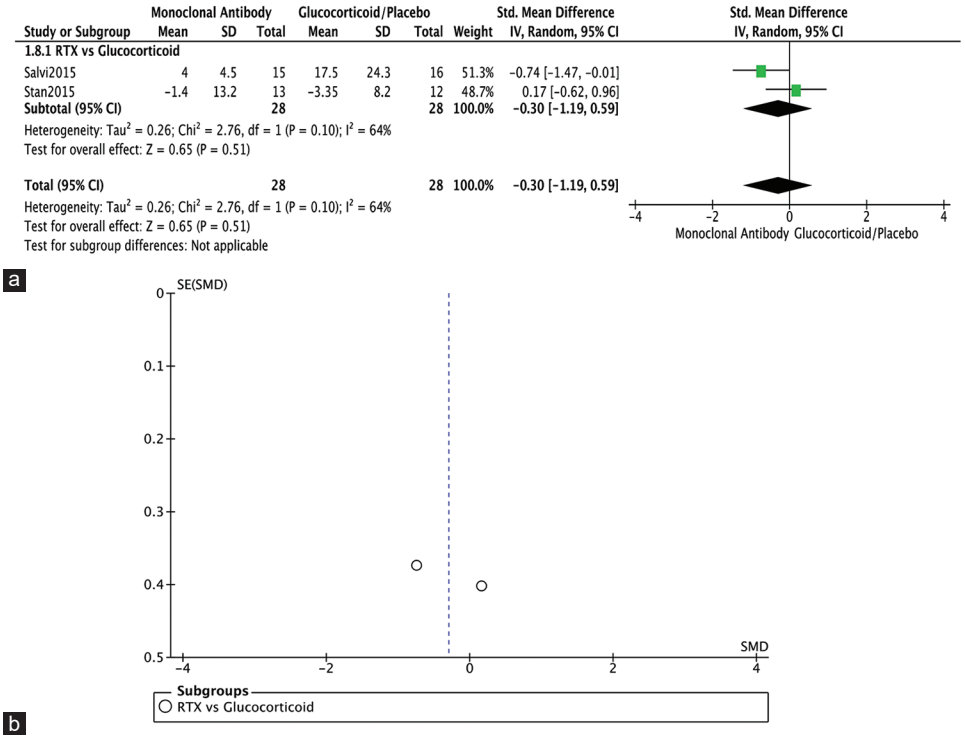

Figure 11: TRAb. (a) Forest plot. (b) Funnel plot. TRAb: TSH receptor antibody

The Gorman scale is a subjective scoring system used to assess diplopia or double vision; a maximum score of 3 indicates constant diplopia, a score of 2 indicates inconstant diplopia, and a score of 1 or 0 indicates intermittent or no double vision. Improvement in diplopia using RTX was only assessed in one of the included RCTs, however, with no significant difference to glucocorticoids.[4] Very few studies evaluated the Gorman diplopia scale, perhaps due to its subjective nature. However, in a retrospective case series of 14 patients, only one of them showed improvement.[25] As for teprotumumab, both included RCTs have shown superior results in comparison to placebo. This was consistent with a 2022 meta-analysis that showed that teprotumumab was associated with more clinically relevant changes in diplopia and was more likely to have 1 grade or more reduction in diplopia compared to IVMP.[23]

Adverse events, including infusion reactions and hearing impairment, were overall lower in the groups receiving placebo than groups treated with different monoclonal antibodies. However, when IVMP was compared to RTX, conflicting results were reported depending on the adverse events measured. Li *et al*. found that symptoms, such as flushing and dyspepsia, were relatively low using RTX.[3] Salvi *et al*. found that minor adverse events (e.g. infusion reactions) occurred more with RTX, but major adverse events (e.g. increase in liver enzymes and HbA1c) occurred more with IVMP, with the exception of cytokine release syndrome (causing decreased vision).[4] The disparity in these results was also found in other systematic reviews and requires further investigation as risk/benefit ratio is yet to be established for RTX as a treatment of GO.[9] As for teprotumumab, the two included RCTs reported more adverse events in the treatment group. However, the majority of these events were considered minor (e.g. nausea, headache, dry skin, and hearing impairment); only one deemed major event (infusion reaction) occurred that was considered related to teprotumumab.[1,10] The first patient with chronic GO treated with teprotumumab reported no side effects apart from fatigue postinfusion that spontaneously resolved.[26] Otologic symptoms, such as tinnitus and ear plugging, were strongly associated with teprotumumab with most of them resolving after cessation of teprotumumab. However, for persistent or worsening sensorineural hearing loss, prior history of hearing loss may be a risk factor.[27] Perez-Moreiras *et al*. reported no significant adverse event in most patients treated with TCZ. However, one patient experienced a moderate increase in transaminases, and another had an acute pyelonephritis.[13] A 2021 case series reported hypercholesterolemia, neutropenia, elevated liver enzymes, and infusion reactions as possible side effects of TCZ. This study also highlights the potential benefits of administrating TCZ subcutaneously, as it may be less time and resource-consuming with comparable clinical efficacy to intravenous administration. However, further high-quality trials are needed.[28] In our study, glucocorticoids and placebo were joined in the same arm against the monoclonal antibodies for the sake of including a large sample size. However, this resulted in showing a safer margin with glucocorticoids compared to monoclonal antibodies, as it was combined with placebo, which is known to be safe, making steroids appear as safe as placebo which is inaccurate.

As for the change in lid fissure, it was only measured in two of the included studies, Li *et al*. and Stan *et al*., both

comparing RTX to IVMP or placebo, respectively.[3,12] Other meta-analyses have not reported on this outcome; however. Regarding the QoL,it was evaluated in four out of the six RCTs included, using questionnaires that assess the effects of GO as patients perceived them in two aspects: visual functioning and the change in their appearance. Relatively considerable discrepancies were found for the three monoclonal antibodies, which may be due to the different QoL measurement tools used in each one. For teprotumumab, the 16-item GO-QOL questionnaire was used; for TCZ, the GO-QOL and SF-36 questionnaires were used; and for RTX, the SF-12 questionnaire, a shorter version of SF-36, was used. Only teprotumumab was found to significantly improve the QoL, as well as TCZ, though to a lesser extent. Better esthetic and functional outcomes (e.g. reduced proptosis and diplopia) and less side effects from therapy may be the main contributors to an improved QoL.

To this day, teprotumumab is the latest Food and Drug Administration (FDA)-approved drug for the treatment of GO. Douglas, 2020, which was named the OPTIC study, is one of two RCTs that played a central role in obtaining the FDA approval.[29] Recently, the OPTIC-X study, an extension of the OPTIC study, was published. It aimed to answer further questions about the safety and efficacy of additional treatment with teprotumumab. Patients from the OPTIC study who had a longer disease duration, who were initial nonresponders, and those with disease exacerbations received additional infusions of teprotumumab. Improvement in proptosis, CAS, diplopia, and QoL was almost mirroring the results of the OPTIC study, and overall results were very similar. Furthermore, no additional safety concerns were raised. Hence, the study demonstrated the effectiveness and safety of teprotumumab with extended treatment.[30]

As for the strengths of this systematic review and meta-analysis, this study is the first to compare three available monoclonal antibodies with standard glucocorticoid treatment or placebo. Also, systematic search according to prespecified strategies was performed and only RCTs were included, which in turn contributes to a higher level of evidence. Moreover, our study included a relatively large sample size when compared to other previous meta-analyses on this topic. Finally, this meta-analysis was done with respect to several primary and secondary outcomes in order to have a larger clinical picture.

We also acknowledge that this systematic review has limitations. First, only a small number of RCTs met our inclusion criteria. Second, not all of them reported on the secondary outcomes we aimed to measure, which might affect our results. Third, the risk of bias was not equal in all the included studies, especially with regard to deviation from the intended intervention, with one study having a high risk of bias. Finally, both studies evaluating teprotumumab were conducted by the same research team, thus additional studies are warranted to further validate the results.

Conclusion

Overall, this meta-analysis demonstrated that monoclonal antibodies were associated with more favorable clinical outcomes than standard steroid therapy or placebo, especially with regard to CAS, change in proptosis, diplopia, and QoL, with teprotumumab being superior. No significant difference was found with respect to lid fissure, NOSPECS, and TRAb levels. Moreover, only minor safety concerns were identified though fewer than traditional steroids. However, more high-quality RCTs comparing the different monoclonal antibodies (teprotumumab, RTX, and TCZ) with glucocorticoids are still warranted in order to have a better understanding of their efficacy and safety as well as to confirm the superiority of teprotumumab and, possibly, set it as the new standard of care for GO.

However, we recommend further studies to compare the different monoclonal antibodies to glucocorticoids in order to have a better understanding of their efficacy and safety.

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Conflicts of interest

There are no conflicts of interest.

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