A Retrospective Study on the effects of Rituximab on Graves' Orbitopathy at a Tertiary Care Center in Muscat

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Received: 1 July 2025

Accepted: 18 March 2026

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DOI 10.5001/omj.2026.72

Abstract

Objectives: The management of Graves' orbitopathy (GO) is complex and oftentimes ineffective. Studies done over the past decade on the efficacy of Rituximab (RTX) in treating Graves' orbitopathy have yielded controversial findings. This study aims to evaluate the effectiveness of Rituximab in treating patients with moderate to severe active Graves' orbitopathy and to assess its associated adverse effects. The study was conducted in a tertiary care center in Muscat, Oman. This study is the first of its kind in Oman and the Middle East.

Methods: This was a retrospective study of 19 patients diagnosed with moderate to severe active Graves' Orbitopathy (GO) who received intravenous rituximab (RTX) (1000 mg) twice at a 2-week interval. The primary endpoint was disease inactivation, measured as a decrease of the Clinical Activity Score (CAS) of at least two points or disease inactivation (CAS< 3). Secondary endpoints were improvement in the severity of GO, proptosis, and diplopia. The safety profile of rituximab was also assessed. The NOSPECS score (no physical signs or symptoms, only signs, soft tissue involvement, proptosis, extraocular muscle signs, corneal involvement, and sight loss) was utilized to assess severity of GO while the Gorman Score was used to assess diplopia. Improvement was defined as a decrease in any of the following: NOSPECS score ≥ 2, proptosis ≥ 2 mm, and diplopia score from 3 or 2 to 1 or 0 respectively.

Results: The average baseline CAS was 5.53 ± 0.96 prior to rituximab administration and it dropped to 1.89 ± 0.65 24 weeks following treatment (p=0.0002). 16/19 patients had disease deactivation within 24 weeks. Severity scores improved in 14/19 patients, with no relapses after 24 weeks. The average baseline NOSPECS score was 5.05 ± 0.34, and it dropped to 3 ± 0.57 after 24 weeks (p= 0.0021). However, there was no significant change in diplopia. Among the adverse events observed, the majority were mild infusion reactions. None of the patients experienced severe adverse effects.

Conclusions: Rituximab is a relatively safe treatment alternative for GO. In individuals with moderate to severe active GO, it can modify the natural course of the disease by shortening the active phase and thus limiting the damage by inflammatory processes in the orbit.

Keywords: Graves' Disease; Thyroid eye disease; Graves ophthalmopathy; Rituximab.

Introduction

Graves' disease (GD) is an autoimmune condition distinguished by its characteristic combination of thyrotoxicosis, goiter, and Graves' Orbitopathy. GD is caused by circulating antibodies that imitate the thyroid-stimulating hormone (TSH) by attaching to and activating its receptor (TSHR). This results in increased thyroid hormone production and release, causing hyperthyroidism and thyroid follicular cell enlargement causing goiter. Graves orbitopathy (GO), the most prevalent extrathyroidal symptom, affects around 50% of patients with GD.[1]

GO presents with a spectrum of manifestations which include lid retraction, seen in 57-98% of GO patients, proptosis in 63-74%, extraocular muscle involvement in 40-60%, and optic neuropathy in 5-7%.[2] The majority of patients with Graves' Disease only have mild-to-moderate eye involvement (around 50%). However, 3–4% experience severe ophthalmopathy, which, in its worst presentations, can cause compression of the optic nerves resulting in optic neuropathy, with a decrease and eventual loss of visual acuity.[3]

Although the pathogenesis of GO is not well understood, it is hypothesized that the main processes involved are cytokine production and inflammation, hyaluronan synthesis, adipogenesis, and myofibroblast differentiation. Extraocular muscles and connective tissues are infiltrated by immune cells from the thyroid, such as T cells, and to a lesser extent by plasmocytes, macrophages, and mast cells. Cytokines produced by leukocytes, such as IFN-γ, IL-1α (IL-5), and leukoregulin (a lymphokine produced by activated lymphocytes), lead to the synthesis of glycosaminoglycans (GAG). The accumulation of GAG leads to extraocular muscle edema. Orbital fibroblasts are activated by the inflammatory mediators (cytokines) or through direct cellular interaction. Excessive fibroblast activity contributes to the orbital tissue's expansion, remodeling, and fibrosis.[4]

In the active phase of orbital changes, because of inflammatory cell infiltration and edema, the volume of tissues surrounding the eyes augments, leading to an increase in the intraocular pressure. Consequently, the eyeball moves beyond the bony edges of the orbit. The compression of the optic nerve can lead to optic neuropathy, along with impaired venous and lymphatic outflow. The active phase can last up to 24 months and is then followed by an inactive phase which involves fibrosis of the eye muscles.[5]

Treatment of GO is complex and is targeted towards smoking cessation, maintenance of euthyroidism, and the management of ocular repercussions.[6] Steroid therapy remains the first-line therapy for moderate/severe and severe vision-threatening GO.[7] However, withdrawal of steroids can result in a recurrence of symptoms. In most cases, normal orbital anatomy is not restored, requiring skilled rehabilitative surgery to reduce disfigurement and double vision and to preserve vision.[4] Recently, multiple newer agents such as rituximab, have been studied in the

treatment of GO.[8] In 2006, the first case describing the effective use of rituximab in a patient with moderate-to-severe GO was reported,[9] marking the beginning of its exploration as a targeted immunotherapy for this condition.

Rituximab (RTX) is a humanized chimeric anti-CD20 monoclonal antibody. The rationale for using it in Graves' orbitopathy (GO) is its potential effect on B-cell mediated immunity. RTX depletes B lymphocytes in peripheral blood, thyroid, and the orbits. Histological examination of orbital tissue from individuals treated with RTX has revealed an absence of both B and T cells. This could support the theory of RTX reducing B cell activity, thereby affecting their role as antigen-presenting cells and their subsequent interaction with helper T cells, both of which are necessary for the onset of the autoimmune process.[10]

RTX has been proposed as an alternative to corticosteroids in cases of lack of satisfying response, disease recurrence, or contraindications and has been effectively used several times to treat corticosteroid-resistant GO associated with optic neuropathy.[6,8,11] Recent reviews in 2022 suggest that if administered early, it can modify the natural course of GO, shortening the active phase and thus contributing to limiting the damage caused by the inflammatory processes in the orbit.[11] Rituximab may compare favorably to conventional glucocorticoid therapy and cause less collateral damage than retrobulbar orbital radiation and orbital decompression surgery.[12]

Methods

This retrospective study was conducted in a tertiary healthcare center in the Governorate of Muscat, Sultanate of Oman. Data was collected from the electronic medical records system Hospital Information System- TrakCare®.

The study included all adult patients aged 18 and above, diagnosed with moderate to severe active Graves' Orbitopathy defined by a CAS score of 3 and above, who received 1000 mg of rituximab twice at two-week intervals between January 1, 2010, and June 30, 2023. The sample size consisted of a total of 19 patients. Moderate-to-severe disease was defined according to the EUGOGO 2021 guidelines as eye disease with sufficient impact on daily life to justify immunosuppressive or surgical treatment, typically presenting with two or more of the following: lid retraction $\geq$ 2 mm, moderate or severe soft-tissue involvement, exophthalmos $\geq$ 3 mm above normal for race and gender, or inconstant/constant diplopia.[13]

The baseline assessment consisted of a review of the patient's medical history, a physical examination conducted by an endocrinologist, and an ocular examination by an ophthalmologist. Additional tests included an orbital CT scan, and measurements of TSH and free T4. The reference ranges were taken as 0.27-4.20 mIU/L for TSH and 13.1-21.3 pmol/L for FT4. The duration of the disease was calculated from the onset of symptoms to the diagnosis; if the onset was unclear, the date of the first recorded visual abnormality in the medical records was considered. Patients were re-evaluated at 12 and 24 weeks following rituximab treatment by both the endocrinologist and ophthalmologist. Adverse events were recorded and categorized as moderate if they required treatment and resolved with therapy, and severe if they required treatment and interfered with normal functioning.

The ophthalmic evaluation included proptosis measurement using an exophthalmometer, assessment of the Gorman diplopia score and NOSPECS score. An orbital CT scan was repeated at 24 weeks for 8 of the 19 patients.

Table 1: Clinical activity score.

Clinical

	For initial CAS score items 1-7
1	Spontaneous orbital pain
2	Gaze evoked orbital pain
3	Eyelid swelling that is considered to be due to active GO
4	Eyelid erythema
5	Conjunctival redness considered due to active GO
6	Chemosis
7	Inflammation of caruncle or plica
	Follow-up after 1-3 months score items including 8-10
8	Increase of >2 mm proptosis
9	Decrease in uniocular ocular excursion in any one direction of >8 degrees
10	Decrease of acuity equivalent to 1 Snellen line

One point is given for the presence of each of the parameters assessed. The sum of all points define clinical activity: Active ophthalmopathy if score is >3/7 at first examination or >4/10 in successive examination. GO – Graves' orbitopathy

The primary endpoint of this study was the inactivation of Graves' orbitopathy , defined as either a reduction in CAS by at least two points from baseline or an absolute CAS of 3/10 or less at 12 and 24 weeks following treatment with any rituximab (RTX) dose. CAS is based on specific signs and symptoms, including pain, redness, swelling, and impaired eye movements. The score ranges between 0 and 10, with higher values suggesting more disease activity. A score of ≥ 3/7 at the first examination or ≥ 4/10 in the successive examination is considered 'Active GO' [Table 1].[14] The secondary endpoints of the study included the following measures of change from baseline to 12 or 24 weeks: 1) a reduction in GO severity, defined as a decrease of 2 or more points in the NOSPECS severity classification system [Table 2]; 2) a reduction in proptosis of 2 mm or more, as measured by a Hertel exophthalmometer and CT scan; 3) a decrease of at least one class in the Gorman's score for diplopia (Bahn and Gorman, 1987); and 4) the occurrence of any major adverse events.

The Statistical Package for the Social Sciences Software (SPSS, version 25) was used to analyze data collected from patients who met the inclusion criteria. Data was presented as mean ± standard error (SE), range, and percentages. Normality was tested using the Shapiro–Wilk test. For non-normally distributed continuous variables, the Wilcoxon Signed Ranks Test was used. A p-value of 0.05 or less was considered significant.

Cli

Table 2: NOSPCES score.

	NOSPECS score			
	0	1	2	3
Lid retraction	No	Yes		
Soft tissue inflammation[a]	0	1–4	5–8	>8
Proptosis	<17 mm	17–18 mm	19–22 mm	>22 mm
Site difference	<1 mm	1–2 mm	3–4 mm	>4 mm
Extraocular muscle involvement	No		>20° upgaze, >35° abduction	≤20° upgaze, ≤35° abduction
Corneal defects	No	Yes		
Optic nerve compression	No			Yes

a Upper lid edema, 0–2; lower lid edema, 0–2; conjunctival injection, 1; and conjunctival chemosis, 1.

The Medical Research Ethics Committee (MREC) of the College of Medicine and Health Sciences (CoMHS) approved the study (MREC#2978) on October 6, 2022.

Results

Table 3 displays clinical and demographic information from 19 individuals (11 males and 8 females). The median age was 49 years (range: 38–65 years old), and all individuals were non-smokers. The median CAS before treatment with RTX was 6/10 (range: 5–6), and the median GO duration was six years (range: 2-18 years). All patients had had prior glucocorticoid therapy with varying regimens. The duration between the last glucocorticoid course and the first RTX injection ranged from two to ten months. All previous thyroidectomies and radioiodine treatments were completed at least 6 months prior to RTX therapy. RTX was administered to 19 individuals with persistent active GO. 12/19 patients had a low TSH level at baseline, and two patients had a transiently elevated TSH before receiving RTX. All the patients had elevated levels of FT4. During every patient visit, thyroid function tests were repeated, and medications were modified as necessary to maintain euthyroid status.

Table 3: Baseline characteristics of studied patients (n = 19).

Characteristics of the patients	n(%)	Median (Q1-Q3)
Age (year)	-	49 (38-65)
Gender (male)	11 (58%)	
GO duration (year)	-	6 (2-18)
Antithyroid drugs AT+LT	9 (47.4%)	-
Goiter before	5 (26.3%)	-
Smoking	0 (0%)	-
DM	6 (31.6%)	-
HTN	4 (21.1%)	-
Antiglaucoma drops	6 (31.6%)	-
Radio iodine	3 (15.8%)	-
Thyroidectomy	4 (21.1%)	-
Eyelid surgery	2 (10.5%)	-
CAS – baseline	-	6 (5-6)
TSH (mIU /L)	-	0.1 (0.01-2.54)
FT4 (pmol /L)	-	22.8 (21.5-26.8)

All patients who received RTX had a lower CAS score at 12 and 24 weeks than at baseline. The median (IQR) CAS score decreased from 6 (5–6) at baseline to 3 (2–4) at 12 weeks, and to 2 (1–2) at 24 weeks. On assessing data to see if RTX therapy may speed disease inactivation (CAS < 3), it was found that at 12 weeks, 6/19 patients had the inactive disease ($p = 0.0001$), and by 24 weeks, it was 16/19 RTX-treated individuals ($p = 0.0002$) [Table 4].

Table 4: Detailed clinical active score (CAS) at baseline and 12 and 24 weeks post-Rituximab.

Clinical outcome	Baseline	12 weeks	24 weeks
Pain (gaze), n (%)	14 (73.7%)	9 (47.4%)	7 (36.8%)
Pain (rest), n (%)	9 (47.4%)	4 (21.1%)	1 (5.3%)
Conjunctival injection, n (%)	16 (84.2%)	11 (57.9%)	7 (36.8%)

Eyelid oedema, n (%)	15 (78.9%)	9 (47.4%)	4 (21.1%)
Eyelid erythema, n (%)	15 (78.9%)	8 (42.1%)	4 (21.1%)
Chemosis, n (%)	17 (89.5%)	13 (68.4%)	12 (63.2%)
Inflammation of caruncle, n (%)	11 (57.9%)	6 (31.6%)	6 (31.6%)
Increase of proptosis ≥ 2 mm (1–3 months), n (%)	0 (0%)	0 (0%)	0 (0%)
Decrease of eye movement > 8°, n (%)	0 (0%)	0 (0%)	0 (0%)
Decrease of visual acuity <1 line, n(%)	0 (0%)	0 (0%)	0 (0%)
CAS/10, median (Q1–Q3)	6 (5-6)	3 (2-4)	2 (1-2)

The three most common clinical signs assessed in GO patients were chemosis, eyelid edema, and eyelid erythema. The sign that showed the most improvement after 12 weeks was eyelid erythema. After 24 weeks, maximum improvement was noted in the severity of eyelid edema.

At 12 weeks, 10/19 of RTX-treated patients improved by 1 class in NOSPECS score, while five patients improved by ≥ 2 classes (p=0.0185). By 24 weeks, 5/19 of the patients improved by 1 class, and 14/19 of the patients improved by ≥ 2 classes (p=0.0021). Interestingly, four patients experienced worsening of GO according to the NOSPECS score at 12 weeks, likely reflecting an early inflammatory flare or orbital edema following B-cell depletion. However, by 24 weeks, all four improved, suggesting this was a temporary phase before disease stabilization [Table 5].

Table 5: Assessment of NOSPECS at baseline and 12 and 24 weeks post-rituximab (RTX).

	Baseline	**12 weeks post RTX**	**24 weeks post RTX**
NOSPECS(mean ± SD)	**5.05** ± 0.34	**3.58** ± 0.98	**3** ± 0.57
p value	-	0.0185	0.0021

The average change in proptosis from baseline to 24 weeks, as measured by ophthalmometer, was higher in the left eye ($p = 0.0001$). Improvements by ≥ 2 mm in both eyes were observed in 13/19 patients at 24 weeks [Table 6]. CT scans to evaluate proptosis were repeated in only eight patients; however, the reason for the limited follow-up imaging was not clearly documented. Among those who underwent repeat scans, an overall improvement in proptosis was observed.

Table 6: Assessment of right and left eye proptosis at baseline and 12 and 24 weeks post-rituximab (RTX).

	Number of patients (%)	**Baseline**	**12 weeks post RTX**	**24 weeks post RTX**
Proptosis, right eye (exophthalmometer) mm	**19 (100%)**	**24.58** ± 2.52	**23.11** ± 2.61	**21.26** ± 2.47
p value		-	0.0003	0.0223
Proptosis, left eye (exophthalmometer) mm	**19 (100%)**	**24.47** ± 1.98	**22.68** ± 2.24	**21.11**± 1.88
p value		-	0.0001	0.0162
Proptosis, right eye (CT)	**8 (42.1%)**	**24.42** ±4.45	-	**21.47**±5.56
p value		-	-	0.0362
Proptosis, left eye (CT)	**8 (42.1%)**	**23.95**± 4.63	-	**21.89**± 4.96
p value			-	0.0305

Diplopia was intermittent in two patients, inconstant in two, and constant in four; eleven patients had no diplopia. Two patients showed a slight improvement from baseline to 12 weeks. At 12 or 24 weeks, the percentage of patients who showed improvement remained unchanged [Table 7].

Table 7: Assessment of diplopia at baseline and at 24 weeks post RTX as per Gorman score.

Diplopia	**n (%)**
Present at baseline	8 (42.1%)
Improvement at 12 weeks	2 (10.5%)
Improved at 24 weeks	2 (10.5%)
Gorman Score	
At baseline (n =19)	
Absent	11 (57.9%)
Intermittent	2 (10.5%)

Inconstant	2 (10.5%)
Constant	4 (21.1%)
At 24 weeks	
Absent	13 (68.4%)
Intermittent	2 (10.5%)
Inconstant	2 (10.5%)
Constant	2 (10.5%)

A total of 13 AEs were recorded and are depicted in Graph 1. 12 patients experienced AEs (63.16%), of which no events were severe. Most adverse events (AE) happened during the first infusion and the majority were mild infusion responses (8/12). None of the patients experienced dysthyroid optic neuropathy (DON).

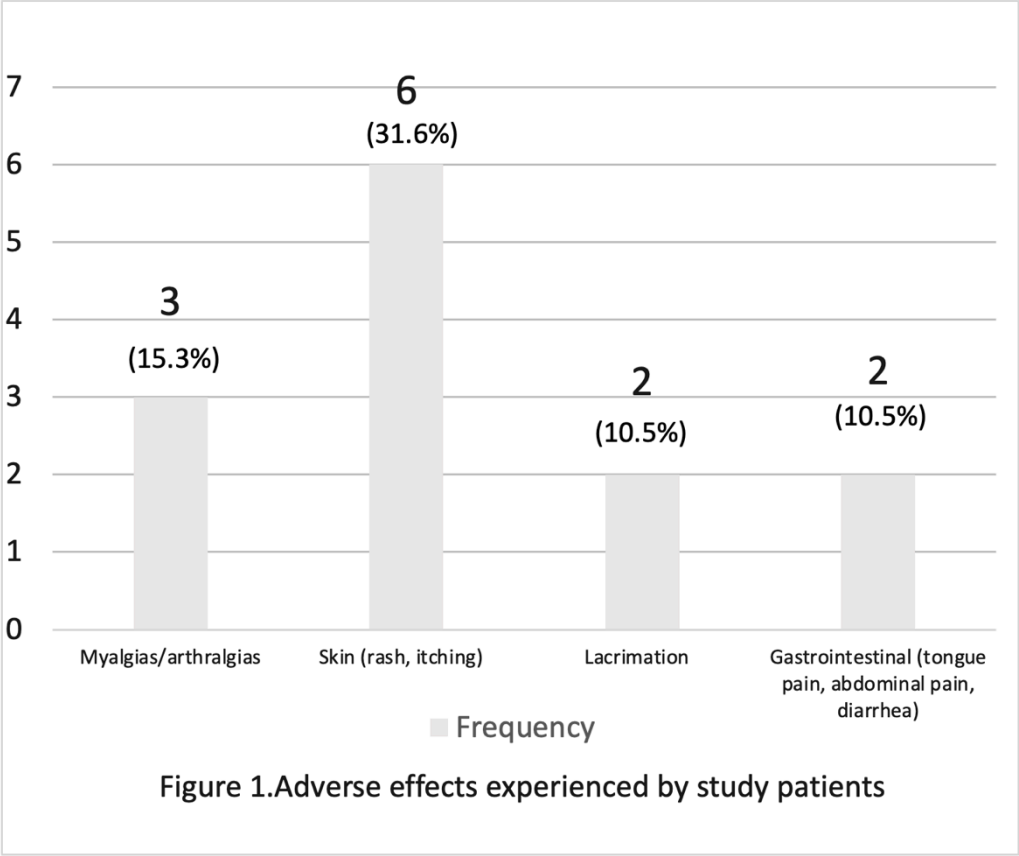

Figure 1: Adverse effects experienced by the study patients.

Discussion

For many years, RTX has been the focus of attention for treating GO. In 2006, the first case detailing the effective use of rituximab for the treatment of moderate-to-severe GO was described.[9] Since then, several studies have been published, including short, constrained retrospective analyses and well-designed, randomized, prospective trials; the majority demonstrating that the clinical action of GO was significantly suppressed once rituximab was administered. The course of treatment was both safe and long-lasting. Numerous investigations have been conducted since then, with encouraging results.[11,15] However, a randomized controlled trial by Stan et al. reported no additional benefit of rituximab over placebo in moderate to severe active GO (Stan *et al*., 2015). Yet another trial showed only slightly better efficacy of rituximab as compared to IV methylprednisolone pulses (Salvi *et al*., 2015).

The absence of standardized reporting practices in trials focused on Graves' orbitopathy (GO) remains a prominent issue. The Clinical Activity Score (CAS) remains the most prevalent scale for evaluating disease activity. Our study had a mean baseline CAS score of 5.53 ± 0.96 which declined to 1.89 ± 0.65 after 24 weeks following RTX treatment (p=0.0002). A comparable improvement was observed by Karasek *et al.*(2015) in a prospective study of ten patients with active moderate-to-severe GO (8 women, 2 men; mean disease duration 8.9 ± 5.7 months), who received a single 100 mg intravenous dose of RTX. The mean CAS decreased from 3.6 ± 0.9 to 0.8 ± 0.4 at week 24 (p = 0.001). A study by Salvi et al. indicated that 100% of individuals treated with RTX were inactive at week 24 (17). A meta-analysis of 12 published studies, which included the results of 152 patients revealed that the CAS score was considerably lower than the baseline value at 1,6 and 12 months following RTX therapy.[15] In contrast, some studies showed little or no significant effectiveness of RTX in the inactivation of GO. A randomized controlled trial by Stan et al. enrolled 25 patients (13 in the RTX group and 12 in the placebo group), and it revealed no significant difference in CAS scores.[18]

Variability in response to RTX in Graves' orbitopathy may be influenced by multiple factors. The natural course of GO is often self-limiting, and spontaneous improvement can occur over time, which may partly explain improvements observed in placebo groups.[18] In addition, genetic and ethnic differences can affect treatment response. Naik highlight that variations in immune system genes play a key role in GO pathogenesis and may influence RTX efficacy by altering immune responses and B-cell activity.[19] These factors could partly explain why some populations respond better to RTX than others. Overall, contradictory findings across studies may reflect differences in patient characteristics, GO activity levels, disease duration, and genetic or ethnic background.

In this study, the severity of GO was measured using the NOSPECS score. NOSPECS score shows improvement by ≥ 2 points in 14/19 patients at 24 weeks (p=0.002). Similar improvement has been reflected in certain open studies and numerous case reports.[20-22] However, other retrospective interventional case studies did not show a meaningful effect of rituximab on changes in GO severity.[18] The reason for this variation could be that GO severity improvement is long-lasting, and other factors (genetics, ancestry, gender, thyroid function, local anatomical conditions, smoking, radioactive iodine therapy, etc.) might affect this process.[23]

Proptosis is caused by the expansion of orbital contents, such as orbital fat and extraocular muscles, which, in turn, force the eye forward. It has been found that the probability of compressive optic neuropathy is increased even with mild proptosis.[24] In this study, 13/19 RTX-treated patients showed improvement in proptosis by 2 mm or more at 24 weeks as compared to only 2/13 RTX-treated patients in a previous study.[18] However, yet another study done by Salvi shows slightly similar results to our research, where 100% (9/9) of the patients show significant improvement in proptosis.[25] A meta-analysis that indicated that proptosis improvement was seen at least one month after taking RTX further validates our findings.[15]

In our study, diplopia improved in only 2/19 RTX-treated patients at 12 weeks and Gorman's score was unchanged at 24 weeks. A randomized controlled trial by Stan et al. showed no change in diplopia at 24 weeks and worsening at 52 weeks (18), findings which were echoed in yet another study by Salvi et al.[25] The diplopia experienced by patients with Graves' orbitopathy can result from various mechanisms, including muscle fibrosis, inflammation, or nerve damage. Rituximab may not address all these underlying causes effectively, especially if fibrosis or structural changes have already occurred. The EUGOGO 2021 guidelines recommend temporary corneal protection in the active phase, reserving decompression surgery for severe cases. In the inactive phase, persistent diplopia may require strabismus surgery, indicating that medical therapy alone is often insufficient for long-standing or fibrotic diplopia.[13]

The safety profile of a drug is perhaps the most decisive factor to consider prior to its widespread use. In our study, mild to moderate adverse effects were observed in 5 patients, including myalgia and arthralgia in 3 patients (15.8%) and lacrimation in 2 patients (10.5%). Infusion-related reactions occurred in 8 patients (42.1%), consisting of gastrointestinal symptoms (nausea and vomiting) in 2 patients (10.5%) and rash and itching of the skin in 6 patients (31.6%). These infusion reactions are likely induced by the production of proinflammatory cytokines from monocytes, macrophages, natural killer cells, and lymphocytes. All events were mild and self-limiting. None of the patients experienced any severe adverse effects. A pooled analysis of 3,194 rheumatoid arthritis patients treated with RTX over 9.5 years compared with 818 patients on placebo and methotrexate showed similar severe infection rates (3.94 vs. 3.79 per 100 patient-years), indicating no significant increased risk of infection with RTX. The possibility of Dysthyroid Optic Neuropathy (DON) following RTX therapy is the most serious safety concern in patients with GO. It is claimed that the quick release of cytokines from killed B-cells invading the ocular region may contribute to tissue swelling, resulting in DON.[25]

Limitations

The main drawbacks of the study were the low sample size and the open, uncontrolled nature of the trial. Age variance, GO duration, and prior therapy all contributed to the treated group's variability. Similar limitations were seen in other previously published studies, probably due to low disease incidence. Multicentre trials involving a larger sample size are necessary to overcome these shortcomings. Another drawback is due to missing patient information in the system; some patients were diagnosed in Oman and treated elsewhere, and these patients had to be excluded from the study. Another limitation was the inability to repeat CT scans to measure proptosis in all 19

study patients, which prevented an accurate calculation of the decrease in CT-measured proptosis. Finally, the relatively short 24-week follow-up may underestimate relapse rates.

Conclusion

Rituximab appears safe and potentially effective in reducing clinical activity in patients with active moderate-to-severe Graves' orbitopathy, but larger randomized controlled trials are needed.

Acknowledgments

The authors would like to thank Prof. Yahya Al-Farsi for his assistance in statistical analysis, Dr. Khalid Al-Harthi for interpreting CT scans, the Hospital Information System staff for assisting during data collection, and the Deanship of Research of Sultan Qaboos University for funding this study.

Disclosure

The study was funded by the Research Administration Department, Deanship of Research, Sultan Qaboos University using the SQU Undergraduate Research Fund.

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