• Clinical Research •

Combining orbital intensity modulated radiation therapy with periorbital triamcinolone acetonide injection for Graves' orbitopathy

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Abstract

● **AIM:** To evaluate the efficacy of combined orbital radiation and periorbital triamcinolone acetonide injection for patients with Graves' orbitopathy (GO) who experienced treatment failure with glucocorticoid pulse therapy (GPT).

● **METHODS:** A total of 57 eligible patients (35.09% males, mean age of 51.19±11.90y) were included in this case-series study. The medical information collected during each visit was evaluated and analyzed.

● **RESULTS:** Significant improvement was observed in patients six months after radiation therapy. Both the clinical activity score and the efficacy score showed substantial improvement (P<0.001). Furthermore, there was significant resolution of extraocular muscle inflammation on magnetic resonance imaging at three and six months after radiation therapy. The initial high signal intensity ratio (SIR) max was found to be associated with greater improvement in SIR sum (P<0.001, B=2.002, 95%CI: 1.377 to 2.628), while the presence of sight-threatening stage or moderate to severe diplopia negatively influenced the improvement of SIR sum (P=0.045, 0.008, 0.006; B=-1.966, -1.478, -0.997; 95%CI: -3.886 to -0.045, -2.552 to -0.403, -1.694 to -0.300; respectively).

● **CONCLUSION:** The combination therapy demonstrates significant effectiveness in treating patients with GO who experienced severe ocular inflammation and have previous GPT failure. Noticeable improvement is observed as early as one month after initiating radiation therapy, and patients with more severe inflammatory states showes greater benefit from the treatment.

● **KEYWORDS:** Graves' orbitopathy; thyroid ophthalmopathy; orbital radiation; periorbital injection; glucocorticoid pulse therapy

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INTRODUCTION

Graves' orbitopathy (GO) is an autoimmune disease, which is the most prevalent orbital condition and the extra-thyroid symptom of Graves' disease. The majority of GO patients have a history of hyperthyroidism, but it can also occur in cases of hypothyroidism or euthyroidism. Recent studies have revealed common antigens, such as the thyrotropin receptor (TSH-R) and the insulin-like growth factor 1 receptor, on both orbital fibroblasts and the thyroid gland. Activation of TSH-R on orbital fibroblasts triggers an immune cascade, resulting in the accumulation of glycosaminoglycans and enlargement of orbital fat tissue. Inflammation of the ocular adnexa and increased orbital pressure cause symptoms including pain, upper eyelid retraction, eyelid swelling, and restrictive dyskinesia, significantly impacting quality of life and potentially leading to vision impairment. Ultimately, fibrosis of the extraocular muscles leads to persistent mobility disorders[1-2].

Various treatment methods exist for GO patients at different stages and grades[3-4]. Intravenous administration of glucocorticoids is the first-line treatment for patients with moderate to severe and active stage GO. Glucocorticoids can also be administered orally or local injection. Recently, medications such as infliximab, teprotumumab, sirolimus, and rituximab have also shown promise[5]. Surgical intervention is primarily reserved for patients with sight-threatening conditions or restrictive dyskinesia[6]. Orbital radiotherapy (OR) has been used for years to control inflammation among active patients. More advanced radiation technologies, including intensity-modulated radiation therapy (IMRT), offer superior target coverage, better conformity index and

homogeneity index, as well as improved radiation sparing of normal structures[7].

However, orbital decompression surgery and the use of intravenous or oral glucocorticoids have limitations and disadvantages, particularly for patients with uncontrolled diabetes, older individuals, those in late pregnancy, and individuals with active tuberculosis. Furthermore, intravenous glucocorticoids may yield unsatisfactory results in certain patients[2]. Although studies have investigated the combined treatment of intravenous or oral glucocorticoids with OR[8], research on the efficacy of periorbital glucocorticoid injection combined with OR is lacking. This study demonstrated the therapeutic effect of combining periorbital triamcinolone acetonide (TA) injection with IMRT in GO patients who previously had unsatisfactory outcomes following glucocorticoid pulse therapy (GPT).

PARTICIPANTS AND METHODS

Ethical Approval The study was conducted in accordance with the guidelines of the Declaration of Helsinki, and approved by the review board of West China Hospital, Sichuan University, Chengdu, China (approval number 201973). Informed consent was obtained from individual participants included in the study.

Subject Selection Based on Bartley's criteria[9], a total of 57 patients were recruited for the study between October 2013 and January 2023. Patients were selected based on clinical symptoms, ocular signs, medical history, and imaging examination results. The inclusion criteria included: 1) patients diagnosed with GO at West China Hospital; 2) patients with severe extraocular muscle inflammation indicated by contrast-enhanced magnetic resonance imaging (CE-MRI) or computed tomography (CT); 3) patients with NOSPECS (a grading system of Graves' orbitopathy) grade equal to or above four; 4) patients who previously received GPT; 5) patients treated with OR and periorbital TA injection at West China Hospital; 6) patients with complete medical records and examination files; 7) patients who were followed up for at least six months after IMRT.

Exclusion criteria were as follows: 1) patients with prior OR treatment; 2) patients with a history of infectious diseases, autoimmune diseases, or other systemic connective tissue diseases; 3) patients with the presence of illnesses causing exophthalmos, extraocular muscle enlargement, high intraocular pressure (IOP), or soft tissue inflammation such as inflammatory pseudotumor and IgG4-related eye disease; 4) patients with severe contraindications to glucocorticoids, including serious diabetes, uncontrollable hypertensive disease, Cushing's syndrome, glaucoma, peptic ulcer, pregnant or lactating females, osteoporosis, and severe infectious or metabolic diseases.

Combination Therapy All patients accepted the combination therapy, which involved three periorbital TA injections (once a month) and IMRT (around the second periorbital injection). Follow-up examinations were conducted at one, three, and six months after IMRT.

The steps for periorbital TA injection were as follows: patients were positioned horizontally during the injection process. After disinfecting the periocular skin with povidone-iodine solution, a 26-gauge disposable needle was used by the same physician to inject a total of 40 mg of TA (Kunming Jida Pharmaceutical Co., LTD, China) into each orbit. The distribution of the 40 mg dose of TA varied based on the affected extraocular muscles. If only the upper eyelid with superior or medial rectus muscles was involved, 40 mg of TA was injected in the superior inner quadrant of the orbit. Similarly, when the inferior rectus muscle was the only one involved, 40 mg of TA was injected in the inferolateral orbit. In cases where the upper eyelid and multiple muscles, including the inferior rectus muscle, were involved, 20 mg of TA was injected in the superior inner and inferolateral quadrants of the orbit, respectively. Emergency situations such as high orbital pressure or arrhythmia served as stop signals for injection. Once the injection was complete, patients were instructed to press onto the injection site for 20min.

In this study, reversely planned 7-field IMRT was employed as the OR treatment strategy. To begin, patients were immobilized using a customized thermoplastic cast. A CT scan with a slice thickness of 3 mm was performed for imaging acquisition and target contouring. The clinical target volume included the main bulk, origins, and insertions of extraocular muscles, as well as retro-orbital fat of the target eye. A planning target volume was created with a 2 mm concentric margin around the clinical target volume. The globe, lens, and optic nerve were outlined as organs-at-risk. Patients received a total dose of 20 Gy in 10 fractions over a two-week period[10].

Medical Information All patients were evaluated, treated, and followed up by the same ophthalmologist. Medical information including age, gender, duration of GO and thyroid disease, past medical history, thyroid function, smoking history, and treatment history was collected. Symptoms and clinical signs were recorded in detail. Regular ophthalmology tests were conducted, which included best corrected visual acuity (BCVA) measurement, slit lamp microscope examination, IOP measurement *via* non-contact tonometry, exophthalmos assessment using a Hertel exophthalmometer, diplopia testing using the Hess screen, visual evoked potential testing, perimetry, eye movement testing, as well as upper eyelid retraction measurement. BCVA values were transformed into the logarithm of the minimal angle of resolution (logMAR) for statistical analysis. The semiquantitative scales counting

fingers (CF), hand motion (HM), light perception (LP), and no light perception (NLP) were replaced by 1.8 logMAR, 2.3 logMAR, 2.8 logMAR, and 3.0 logMAR, respectively.

CE-MRI served as a useful objective indicator for extraocular muscle inflammation. Except for patients with contraindications for magnetic resonance imaging (MRI) such as metallic implants and cardiac pacemakers, all other patients underwent CE-MRI examinations before and after the combined treatment. Patients who exhibited an unsatisfactory therapeutic effect on MRI three months after IMRT underwent another MRI exam six months after IMRT. A 3T MR machine (Magnetom Trio, Siemens, Germany) equipped with a 12-channel head receiver coil array was used to perform the CE-MRI. The MRI scanning parameters were set with a slice thickness of 3 mm, no gap, a field of view of 200 mm, and a matrix size of 384×384. The MRI data was analyzed using the PACS imaging system by the same physician. The signal intensity ratio (SIR) in T1-weighted imaging (T1WI) with fat suppression sequence indicated the level of muscle inflammation, while T2-weighted imaging (T2WI) provided information about myoedema. In this study, T1WI was chosen to objectively assess extraocular muscle inflammation. The retrobulbar level at 4–6 mm on coronal T1WI with fat suppression sequence was selected for measuring the cross-sectional area (CSA) and SIR of the superior rectus (SR), inferior rectus (IR), medial rectus (MR), and lateral rectus (LR). SIR represented the calculation of signal intensity from the extraocular muscles to the homolateral temporalis. Total cross-sectional area (CSAsum) and total SIR (SIRsum) represented the summations of all extraocular muscles in each eye, while CSAmax and SIRmax denoted the maximum values among the extraocular muscles in each eye. In this study, SR encompassed both the SR and levator palpebral muscles due to difficulties in distinguishing them on images. MRI exophthalmic extent (MRIEE) was defined as the vertical distance from the corneal vertex to the line between the bilateral anterior zygomatic arch. Orbital fat thickness was defined as the maximum distance from the eyeball to the medial orbital wall.

Clinical Evaluation and Outcome Measurement All patients underwent evaluation using the clinical activity score (CAS), NOSPECS, and the European Group on GO (EUGOGO) classification of severity[6,11-12]. These validated scoring systems have been widely employed to assess the activity and severity of GO. Additionally, in accordance with the 2021 EUGOGO guideline[6], we established a comprehensive efficacy score (ES) to evaluate the condition and outcomes of GO patients. The ES prior to combination therapy was denoted as S_0, whereas the ES at each subsequent visit was recorded as Sa. The effectiveness ratio for each visit was calculated as $(S_0–Sa)/S_0×100\%$ and categorized into three groups (mild, moderate, and substantial) by 10% and 33%.

Statistical Analysis The data were analyzed using R software (version 4.2.3). Qualitative data were expressed as percentages, while quantitative data were presented as mean±standard deviation or medians and quartiles. To adjust the correlation between both eyes of the same subject, qualitative data were compared using a generalized mixed linear model, and quantitative data were compared using a mixed-effects model for normally distributed data, along with a clustered Wilcoxon rank-sum test for non-normally distributed data[13]. Factors influencing therapeutic effect and MRI changes were analyzed using a multiple linear stepwise regression model. A *P*-value <0.05 was considered statistically significant.

RESULTS

Clinical Information of Patients and Comparison Among Each Visit Among the 57 patients included in this study, 20 (35.09%) were males. The mean age was 51.19±11.90y (range 23–74y). All patients had bilateral GO, with varying degrees of severity and activity. Prior to the combined therapy, CE-MRI revealed severe extraocular muscle inflammation in all patients, characterized by distinct thickening and enhancement. Although the initial CAS was less than two for 38.60% of the eyes, these findings demonstrated the presence of inflammation. The most frequently reported symptom was eyelid swelling (88.60%), followed by shedding tears (52.63%), pain (40.35%), blurred vision (30.70%), photophobia (21.05%), foreign body sensation (17.54%), and dry eyes (12.28%). Three patients had hyperthyroidism, 49 were euthyroid, and five patients had hypothyroidism. Glucocorticoid intravenous injections were administered to all patients, starting with a dose of 0.5 g of methylprednisolone, and they received this treatment multiple times (mostly 6–12 times) before initiating our combined therapy. However, the results were unsatisfactory.

At each visit, the clinical information was recorded and compared. The analysis showed a significant decrease in IOP, CAS, and ES from the first visit to the last visit (P=0.037, <0.001, <0.001, respectively). At the final visit, only three patients still experienced dysthyroid optic neuropathy (DON, P=0.019; Table 1, Figure 1). Upper lid retraction (P<0.001), pain (P<0.001), tear shedding (P<0.001), and other symptoms (P=0.002) also improved after the combined treatment. However, there was no statistically significant improvement in NOSPECS grade, EUGOGO classification, exophthalmic extent, strabismus, cornea involvement, BCVA, or von Graefe sign.

Effectiveness Ratio Analysis Our findings demonstrated a significant improvement (38%) in patients during their last visit (Figure 2).

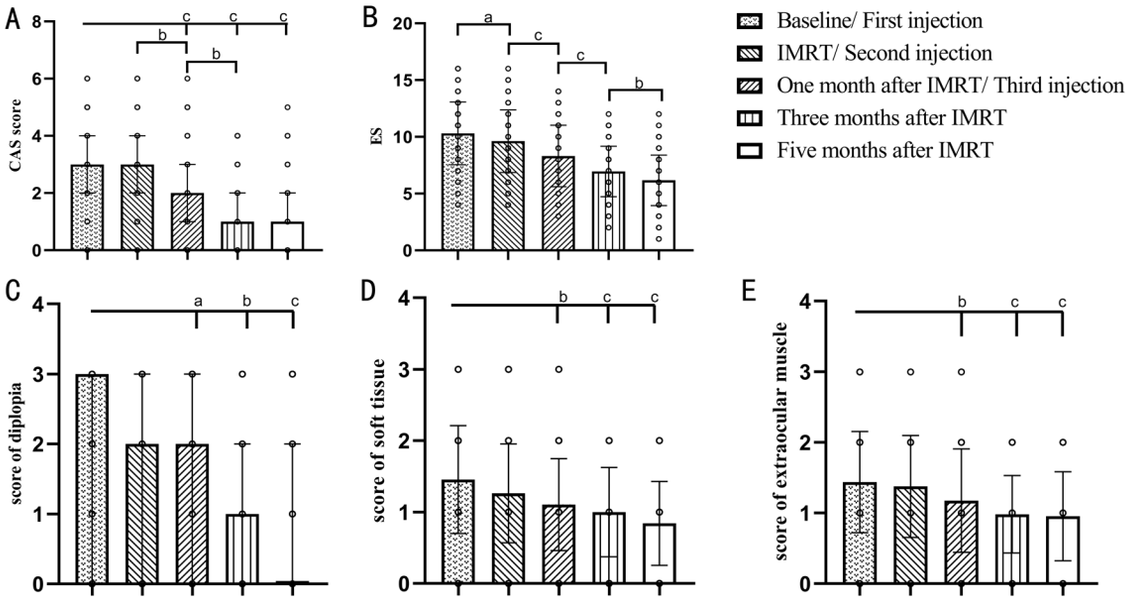

Figure 1 After the IMRT of combined therapy, most patients began to improve A: CAS score began to decrease at the third visit (1mo after IMRT) and stopped change after the fourth visit (3mo after IMRT); B: ES significantly declined each time compared to the prior visit (P<0.05); C, D: There were certain items improved from 1mo after IMRT and continued improving since then until the last visit, which contained diplopia, soft tissue situation, extraocular muscle situation. IMRT: Intensity modulated radiation therapy; CAS: Clinical activity score; ES: Efficacy score. [a]P<0.05; [b]P<0.01; [c]P<0.001.

Table 1 Comparisons of 114 eyes between the last visit (6mo after IMRT) and before the combined therapy

Parameters	Before treatment	Last visit	Effect size	P
IOP (mm Hg)	19.25 (16.83–22.43)	18.30 (17.33–19.23)	Z=2.087	0.037[a,d]
BCVA (logMAR)	0.10 (0–0.40)	0.10 (0–0.30)	Z=0.132	0.895[a]
Exophthalmic extent (mm)	17.35±2.92	17.09±2.95	t=1.662	0.972[b]
ES	10.31±2.76	6.17±2.22	t=17.992	<0.001[b,d]
CAS	3 (2–4)	1 (1–2)	t=7.285	<0.001[b,d]
NOSPECS, n (%)			Z=1.381	1[c]
Grade 2	0	4 (3.51)		
Grade 3	0	16 (14.04)		
Grade 4	98 (85.96)	88 (77.19)		
Grade 5	5 (4.39)	3 (2.63)		
Grade 6	11 (9.65)	3 (2.63)		
EUGOGO, n (%)			Z=2.320	0.204[c]
M	37 (32.46)	74 (64.91)		
MS	67 (58.77)	37 (32.46)		
S	10 (8.77)	3 (2.63)		
DON	11 (9.65)	3 (2.63)	Z=3.108	0.019[c,d]

[a]Clustered Wilcoxon rank sum test; [b]Mixed effect model; [c]Generalized mixed linear model; [d]P<0.05. IMRT: Intensity-modulated radiation therapy; IOP: Intraocular pressure; BCVA: Best corrected visual acuity; NOSPECS: A grading system of Graves' orbitopathy; CAS: Clinical activity score; ES: Efficacy score; EUGOGO: European Group on Graves' orbitopathy; M: Mild; MS: Moderate-to-severe; S: Sight-threatening (very severe); DON: Dysthyroid optic neuropathy.

The multiple linear stepwise regression model was performed to find influence factors for the final effectiveness ratio. The results revealed that disease course (P=0.047, B=-0.003, 95%CI=-0.006 to 0.000), strabismus (P=0.006, B=-0.120, 95%CI=-0.203 to -0.036), moderate (P=0.012, B=-0.227, 95%CI=-0.403 to -0.051) or severe (P<0.001, B=-0.322, 95%CI=-0.458 to -0.187) diplopia, exophthalmic extent (P=0.001, B=-0.029, 95%CI=-0.046 to -0.012), and mild (P<0.001, B=-0.360, 95%CI=-0.495 to -0.225) or moderate eye movement dysfunction (P<0.001, B=-0.442, 95%CI=-0.586 to -0.299), as well as initial SIRsum (P=0.024, B=-0.103, 95%CI=-0.192 to -0.014) had a negative impact on the

Table 2 Comparisons of MRI between the initial and the final examination

Parameters	Group A (60 eyes)				Group B (52 eyes)			
	Initial	3mo after IMRT	Effect size (*t*)	*P*	Initial	6mo after IMRT	Effect size (*t*)	*P*
CSA of IR (cm^2)	0.57±0.24	0.47±0.25	3.718	<0.001	0.68±0.45	0.55±0.31	3.464	<0.001
CSA of MR (cm^2)	0.44±0.26	0.39±0.24	2.182	0.032	0.46±0.28	0.41±0.22	2.069	0.042
CSA of SR (cm^2)	0.56±0.25	0.49±0.29	2.375	0.024	0.61±0.26	0.45±0.14	5.069	<0.001
CSA of LR (cm^2)	0.50±0.19	0.45±0.18	1.981	0.057	0.53±0.20	0.47±0.15	1.707	0.1
CSAsum (cm^2)	2.07±0.64	1.80±0.69	3.753	<0.001	2.27±0.74	1.88±0.55	5.179	<0.001
SIR of IR	1.62±0.38	1.39±0.28	3.585	0.001	1.70±0.56	1.48±0.42	2.218	0.036
SIR of MR	1.50±0.39	1.34±0.32	2.787	0.009	1.61±0.50	1.43±0.32	2.066	0.049
SIR of SR	1.45±0.37	1.32±0.33	2.329	0.027	1.60±0.45	1.38±0.31	3.473	0.002
SIR of LR	1.29±0.32	1.18±0.26	2.327	0.027	1.44±0.44	1.27±0.32	2.625	0.015
SIRsum	5.86±1.22	5.22±1.01	3.196	0.003	6.35±1.80	5.57±1.24	2.745	0.011
MRIEE (cm)	2.03±0.24	1.98±0.26	2.493	0.019	2.15±0.31	2.05±0.27	3.159	0.004
Orbital fat thickness (cm)	0.74±0.12	0.76±0.12	-1.126	0.27	0.77±0.16	0.79±0.13	-1.158	0.258

Data was compared using the mixed effect model. MRI: Magnetic resonance imaging; CSA: Cross-sectional area; IR: Inferior rectus; MR: Medial rectus; SR: Superior rectus; LR: Lateral rectus; SIR: Signal intensity ratio; MRIEE: MRI exophthalmic extent; IMRT: Intensity modulated radiation therapy.

final effectiveness ratio. Conversely, older (P=0.007, B=0.005, 95%CI=0.001 to 0.008) patients with mild diplopia (P=0.044, B=0.226, 95%CI=0.007 to 0.445), a high initial ES (P<0.001, B=0.079, 95%CI=0.057 to 0.101), or a high initial CSAmax (P=0.028, B=0.146, 95%CI=0.017 to 0.276) demonstrated better treatment effectiveness.

MRI Data Analysis Out of the total 57 patients, four received CT scans due to contraindications for MRI. Furthermore, 15 patients had CE-MRI results from external hospitals, and among them, 12 exhibited a noticeable decline in signal and/or CSA of the ocular rectus. In our hospital, only 38 patients underwent comprehensive CE-MRI examinations, and their data was subsequently analyzed.

For nonmedical reasons, only eight patients underwent an MRI scan at the sixth month after IMRT. In contrast, among the remaining 30 patients who underwent a second CE-MRI at the third month after IMRT (group A), 12 patients (40%) displayed significant improvement and did not require a third MRI examination (Figure 3). Conversely, 18 patients (60%) had unsatisfactory results and underwent another CE-MRI six months after IMRT, along with the additional eight patients (group B). Both the third and sixth month post-IMRT comparisons of MRI data demonstrated significant decreases in CSAsum, SIRsum, and MRIEE (Table 2). Conversely, there was no observed improvement in orbital fat thickness at either time point.

We obtained data from patients who underwent CE-MRI at both the third and sixth months after IMRT (Figure 4). At the third month after IMRT, we observed no statistical improvement in CSAsum, SIRsum, MRIEE, and orbital fat thickness. However, after three months, only CSAsum exhibited a significant decrease compared to the initial data (P=0.023, t=3.034).

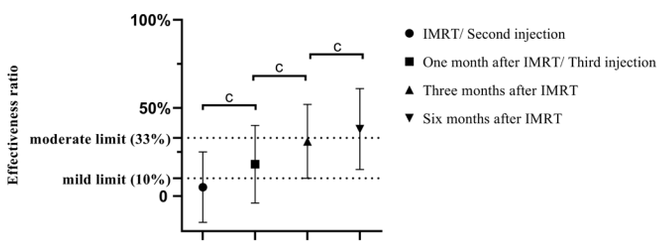

Figure 2 The effectiveness ratio of each visit IMRT: Intensity modulated radiation therapy. ^cP<0.001.

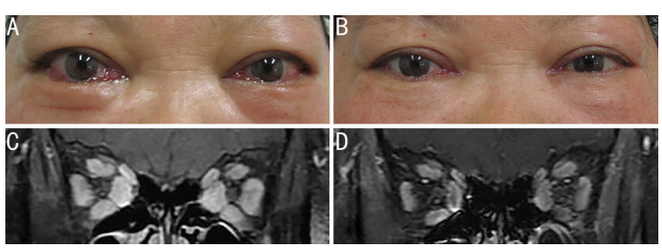

Figure 3 The ocular appearance and coronal contrast-enhanced T1WI with fat suppression sequence comparison of a 53-year-old female patient at the initial situation and 3mo after IMRT A, C: The patient had severe inflammation of ocular soft tissue and extraocular muscles at the initial visit, with swelling and redness on the eyelid and bulbar conjunctiva of both eyes. The MRI imaging revealed muscle thickening and signal enhancement (compared to temporalis signal) of four rectus for both eyes; B, D: Three months after IMRT, there was a significant resolution of inflammation both on her ocular appearance and MRI imaging. T1WI: T1 weighted image; IMRT: Intensity modulated radiation therapy; MRI: Magnetic resonance imaging.

The initial and final MRI data of all 38 patients were analyzed to determine the potential influencing factors for MRI changes. The final multiple linear stepwise regression model revealed that patients with hyperthyroidism (compared

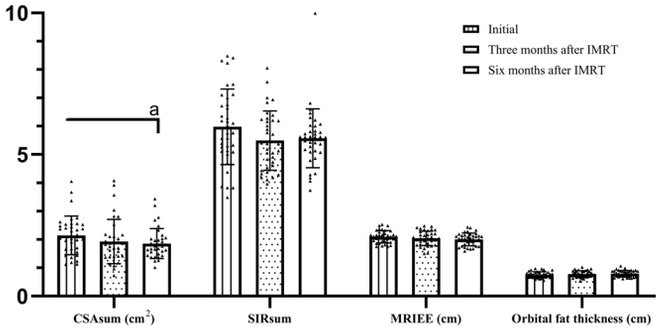

Figure 4 MRI data comparison of 18 patients who underwent MRI scan on both the third and sixth month after IMRT IMRT: Intensity modulated radiation therapy; CSA: Cross-sectional area; SIR: Signal intensity ratio; MRIEE: MRI exophthalmic extent. [a]*P*<0.05.

to hypothyroidism, *P*=0.045, *B*=0.362, 95%CI=0.008 to 0.717) and a higher initial CSAsum (*P*<0.001, *B*=0.475, 95%CI=0.357 to 0.593) or SIRmax (*P*=0.032, *B*=0.589, 95%CI=0.051 to 1.128) experienced greater improvements in CSAsum). Additionally, patients in the moderate-to-severe stage (according to the EUGOGO classification) exhibited a smaller decrease in CSAsum following treatment (*P*=0.045, *B*=-0.170, 95%CI=-0.336 to -0.004).

Patients classified in the sight-threatening stage (EUGOGO classification, *P*=0.045, *B*=-1.966, 95%CI=-3.886 to -0.045) or those experiencing moderate (*P*=0.008, *B*=-1.478, 95%CI= -2.552 to -0.403) to severe (*P*=0.006, *B*=-0.997, 95%CI= -1.694 to -0.300) diplopia showed a smaller reduction in SIRsum. Furthermore, higher initial SIRmax values led to greater improvements in SIRsum following combined therapy (*P*<0.001, *B*=2.002, 95%CI=1.377 to 2.628).

DISCUSSION

According to the clinical practice guidelines of EUGOGO, GO can be classified into three severity grades: mild, moderate-to-severe, and sight-threatening[6]. Additionally, GO can be categorized into active and inactive stages based on the CAS scoring system[12]. Severe inflammation of the extraocular muscles in GO patients can result in pain, restrictive dyskinesia, and other unpleasant symptoms. Early control of inflammation is crucial in managing the condition. In this study, we recruited GO patients who had previously failed glucocorticoid pulse treatment and were still in the active stage. Radiological images of all patients indicated severe inflammation of the extraocular muscles, while the CAS scores showed asynchronization. It is important to note that the CAS scoring system has limitations due to its subjectivity and duality[14]. However, our results demonstrated the significance and accuracy of CE-MRI in assessing the activity of GO[15]. Furthermore, most patients in our study experienced varying degrees of eye movement restrictions.

Intravenous glucocorticoids are well-established as the first-line treatment for moderate-to-severe and active GO patients[16-17]. Orbital decompression surgery and intravenous glucocorticoids are recommended for patients with DON[18-20]. However, individuals with severe corticosteroid contraindications are not suitable candidates for intravenous or oral glucocorticoid treatment[21]. Unlike IMRT, orbital decompression surgery primarily aims to expand orbital volume rather than reducing soft tissue inflammation, which may lead to traumatic inflammation. Additionally, general anesthesia is not advisable for patients with uncontrolled diabetes mellitus or hypertension, elderly individuals, those in the late trimester of pregnancy, or those with active tuberculosis.

Although local injection of glucocorticoids has its own contraindications and complications, such as high IOP and cataract formation, our study did not record any adverse effects[22-25]. IMRT is widely recommended for the active stage of GO[7,10,26]. By combining periorbital TA injection with IMRT and following up for six months after treatment, as recommended, we obtained promising results[6]. According to the GO scoring system we developed, which encompasses both activity and severity states, the ES significantly decreased after the first injection and continued to decline statistically with each subsequent assessment. Objective MRI data also demonstrated excellent control of inflammation, including reduced volume and enhanced degree of extraocular muscles. Improvement in CAS scores, soft tissue inflammation, pain, and other symptoms was mostly observed one month after IMRT and remained stable until the final follow-up. Regrettably, no MRI scan was performed one month after IMRT. Nevertheless, MRI results at the third month after IMRT showed a significant decrease in CSAsum, SIRsum, and MRIEE in some patients. This suggests that inflammation can be effectively controlled one month after IMRT with two periorbital TA injections, followed by a sustained pace of improvement until the last visit. The trend in the effectiveness ratio also supports this conclusion. Previous studies have investigated OR combined with systemic glucocorticoid therapy as well as OR therapy alone[8,27-29]. However, none of these studies had performed a one-month follow-up, despite reporting favorable long-term prognoses.

No significant changes were observed in the NOSPECS classification, EUGOGO severity classification, corneal condition, BCVA, or exophthalmic extent after the entire treatment. It should be noted that the goal of this combined treatment is to control inflammation of the orbital tissue, and severity does not necessarily reflect activity. Therefore, it is reasonable that the NOSPECS and EUGOGO severity classifications did not show statistical improvement. In our study, only a small proportion of patients had corneal involvement. Therefore, although the corneal condition of some patients did improve following treatment, the statistical

significance might be limited. Visual impairment in GO patients is primarily caused by DON and corneal damage[30]. After treatment, there was a significant decrease in the proportion of patients with DON, and very few patients experienced corneal impairment. The lack of significant improvement in BCVA among all patients may be attributed to other underlying conditions such as cataracts and corneal macula. While there were no significant changes in exophthalmic extent, MRIEE showed a substantial decrease after therapy. It is important to consider that the sample sizes for these two measurements were different, which may account for the discrepancy observed between MRIEE and changes in exophthalmic extent.

We sought to identify factors that influenced the effectiveness ratio. Disease course, strabismus, moderate or severe diplopia, exophthalmic extent, and mild or moderate eye movement dysfunction were found to have a negative impact on the effectiveness ratio. Furthermore, our results revealed that a higher initial SIRsum was associated with a lower effectiveness ratio, whereas patients with higher ES, initial CSAmax, and mild diplopia experienced better effectiveness. It seems self-contradictory since SIR is an inflammatory index. However, it is important to note that the effectiveness ratio was based on the ES, which took into account both activity and severity. Therefore, the effectiveness ratio might not be synchronized with improvements in inflammation alone. To address this, we conducted an analysis of MRI parameters.

SIR represents the inflammation state of the extraocular muscles. Analysis of SIRsum revealed that patients with severe initial inflammation could benefit more from our therapy. Furthermore, the analysis demonstrated a relationship between a significant decrease in CSAsum and higher initial CSAsum or SIRmax. Although CSA does not strictly reflect inflammatory conditions, patients with high CSA values may exhibit reduced activity, while inflamed muscles typically appear swollen with high CSA. Nevertheless, the decrease in CSAsum retains its reference significance for evaluating the curative effects of inflammation. Therefore, the conclusion drawn from the analysis of CSAsum aligns with the findings from the SIRsum analysis. Compared to patients with hypothyroidism, those with hyperthyroidism prior to treatment experienced more substantial improvements in CSAsum. In our study, patients with hyperthyroidism had higher initial CAS scores and SIRsum values than patients with hypothyroidism, indicating a greater degree of inflammation. However, it is important to note that only three individuals in our study had hyperthyroidism. Considering the low proportion, the statistical result may be attributed to the ocular inflammation state rather than thyroid function.

There were certain limitations in our study. The MRI images were manually measured, which introduced the possibility of inaccuracies compared to the actual measurements. Since this was a case-series study relying on patient-provided medical histories, certain details were missing, and accessing the medical information before GPT was not feasible. Additionally, the ES itself had limitations. It consisted of both activity and severity, making it challenging to assess the inflammation state using the ES alone.

In conclusion, our study demonstrated the significant therapeutic effect of combined periorbital TA injection with IMRT in GO patients who had previously failed GPT. Patients with more severe inflammation states experienced greater improvements.

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