• Clinical Research •

Medium-dose intravenous methylprednisolone pulse therapy for thyroid-associated orbitopathy

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Abstract

● **AIM:** To evaluate the efficacy and safety of a medium-dose intravenous methylprednisolone (IVMP) pulse regimen for moderate-to-severe active thyroid-associated orbitopathy (TAO), with change in clinical activity score (CAS) as the primary outcome.

● **METHODS:** This prospective interventional study was conducted at a tertiary eye care center in Bangladesh between February and November 2022. Patients with active moderate-to-severe TAO (CAS≥3) received IVMP totaling 4.0 g (500 mg daily for 3 consecutive days, followed by 500 mg every 3wk for 5 cycles). Clinical outcomes, including CAS, proptosis measured by Hertel exophthalmometry, best-corrected visual acuity (BCVA; logMAR), and intraocular pressure (IOP), were assessed at baseline and at 6mo.

● **RESULTS:** A total of 30 patients with active TAO were enrolled and completed the 6-month follow-up. The mean age of the participants was 38.63±12.11y, and 19 (63.3%) were male. The mean CAS decreased significantly from 3.66±1.03 to 0.87±0.63 (mean change −2.79±0.95; *P*<0.0001). The mean degree of proptosis decreased from 22.47±1.59 to 20.13±1.97 mm (−2.34±1.25 mm; *P*<0.0001). BCVA improved from 0.46±0.31 to 0.15±0.18 logMAR (−0.31±0.28; *P*=0.02). The mean IOP decreased from 16.80±3.56 to 14.93±1.73 mm Hg (−1.87±2.45 mm Hg; *P*<0.001). Eyelid swelling, conjunctival redness, chemosis, and retro-orbital pain resolved in more than 90% of patients. Adverse events, including transient increased IOP (26.66%), hyperglycemia (20.00%), and elevated SGPT (6.67%), were mild and reversible; no severe hepatic, cardiovascular, or psychiatric complications occurred.

● **CONCLUSION:** Medium-dose IVMP (4.0 g) significantly improve disease activity, proptosis, visual acuity, and IOP, with an acceptable safety profile. This regimen represents an effective and safer alternative to high-dose IVMP for active moderate-to-severe TAO, particularly in resource-limited settings. Larger, multicenter trials with longer follow-up periods are needed to confirm these findings.

● **KEYWORDS:** thyroid-associated orbitopathy; Graves' orbitopathy; intravenous methylprednisolone; low-dose pulse therapy; Bangladesh

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INTRODUCTION

Thyroid-associated orbitopathy (TAO), also known as Graves' ophthalmopathy, is a debilitating autoimmune disorder and the most common extrathyroidal manifestation of Graves' disease, affecting approximately 25%–50% of patients with hyperthyroidism[1]. Characterized by inflammation, expansion of orbital adipose and connective tissues, and extraocular muscle dysfunction, TAO presents along a broad clinical spectrum from mild symptoms such as dry eye and eyelid retraction to severe, vision-threatening complications, including dysthyroid optic neuropathy (DON) and corneal exposure[2-3]. The disease significantly impairs quality of life due to disfigurement, diplopia, photophobia, and functional limitations, imposing substantial psychological and socioeconomic burdens on affected individuals.

The pathophysiology of TAO centers on immune-mediated orbital inflammation and fibrosis. Autoreactive T cells, particularly CD4+ T helper 1 (Th1) cells, infiltrate the orbital compartment and interact with orbital fibroblasts that express thyroid-stimulating hormone receptor (TSHR). This interaction triggers fibroblast activation, leading to the production of glycosaminoglycans, especially hyaluronan, which increases osmotic pressure and causes edema and tissue expansion[4]. Concurrently, B cells produce stimulating autoantibodies

against TSHR (TRAb), further amplifying the inflammatory cascade. Over time, chronic inflammation drives adipogenesis and myofibroblast differentiation, culminating in irreversible fibrosis and structural remodeling of the orbit[4-5].

Current management strategies emphasize controlling disease activity during the inflammatory phase. According to the European Group on Graves' Orbitopathy (EUGOGO) guidelines, intravenous glucocorticoids (GCs), particularly intravenous methylprednisolone (IVMP), are recommended as first-line therapy for moderate-to-severe active TAO and sight-threatening DON[6]. High-dose regimens (cumulative doses up to 8.0 g) have demonstrated efficacy in reducing proptosis, improving motility, and preserving vision[7]. However, these benefits are associated with significant safety concerns. Dose-dependent adverse effects include hepatotoxicity, cardiovascular complications, psychiatric disturbances, and metabolic derangements[8]. Acute liver injury has been reported in up to 4% of patients receiving high-dose IVMP, necessitating routine monitoring of liver enzymes, which may be impractical in resource-limited settings[8].

This risk-benefit imbalance underscores the need for optimized dosing strategies. Emerging evidence suggests that medium-doses (*e.g.*, 4.0 g) may offer comparable efficacy with improved safety profiles. A recent single-center study demonstrated favorable outcomes using a nonstandard IVMP regimen involving three consecutive days of 1 g pulses followed by tapering intramuscular doses, supporting the feasibility of dose reduction without compromising the therapeutic effect[7]. Nevertheless, robust data on medium-dose protocols remain limited, particularly outside high-income countries.

Notably, there is a critical gap in real-world evidence from low- and middle-income countries (LMICs), where healthcare infrastructure, patient demographics, disease presentation, and access to monitoring differ substantially from those in Western populations. Patients in South Asia often present with more advanced disease due to delayed diagnosis and treatment initiation, which is influenced by socioeconomic barriers and fragmented healthcare systems. Moreover, comorbidities such as preexisting metabolic conditions may heighten susceptibility to IVMP-related toxicity, making safety optimization even more imperative.

This study in Bangladesh provides a unique opportunity to generate contextually relevant evidence on the use of a 4.0 g IVMP protocol in a previously underrepresented population. These findings will inform local clinical practice while contributing globally to the refinement of steroid-sparing approaches in TAO management. By evaluating both efficacy and safety within a resource-constrained setting, this research addresses an important knowledge gap and supports the development of equitable, guideline-adapted treatment algorithms applicable across diverse healthcare environments. Therefore, this study aimed to assess the efficacy and safety of medium-dose IVMP pulse therapy in patients with active, moderate-to-severe TAO in Bangladesh.

PARTICIPANTS AND METHODS

Ethical Approval The protocol received approval from the Ethical Review Committee of Ispahani Islamia Eye Institute & Hospital, Dhaka (Reference No: IIEI&H-ED/2982/2022). Written informed consent was obtained from all participants; confidentiality was maintained throughout.

Study Design and Setting We conducted a prospective interventional study in the Department of Oculoplasty & Ocular Oncology, Ispahani Islamia Eye Institute & Hospital, Dhaka, over 10mo (from 1 February, 2022, to 30 November, 2022).

Participants Moderate-to-severe active TAO was defined according to the EUGOGO criteria. Patients were considered to have active disease if they had a clinical activity score (CAS) ≥3[9-10]. The clinical features used to determine disease activity include spontaneous retrobulbar pain, eye movement pain, eyelid erythema, conjunctival redness, eyelid edema, conjunctival edema (chemosis), and inflammation of the caruncle or plica[11].

Disease severity was classified as moderate-to-severe when patients demonstrated one or more of the following features: moderate or marked soft tissue involvement, exophthalmos measuring ≥3 mm above the normal range for sex and ethnicity, diplopia attributable to extraocular muscle involvement, and the absence of sight-threatening manifestations such as DON or corneal breakdown[12]. Patients with inactive disease (CAS <3) or with sight-threatening complications were excluded. Individuals with uncontrolled diabetes mellitus, defined as a fasting plasma glucose level of ≥126 mg/dL (7.0 mmol/L) or a random plasma glucose level of ≥200 mg/dL (11.1 mmol/L)[13], and those with uncontrolled hypertension, defined as persistently elevated blood pressure with systolic values ≥140 mm Hg or diastolic values ≥90 mm Hg[14], were also excluded from the study. Participants were enrolled *via* consecutive sampling, whereby all eligible patients who presented during the study period were included.

Sample Size Calculation The sample size was calculated *via* Cochran's formula for estimating a population proportion. Assuming a prevalence of Graves' disease of 2%[15], on the basis of previously published literature, a 95% confidence level (Z=1.96), and a margin of error of 5%, the required sample size was calculated as 30 participants. Accordingly, a total of 30 patients were enrolled in the study to ensure adequate statistical precision and reliability of the findings.

Baseline Assessment Clinical diagnosis with a full ophthalmic examination, including exophthalmometry, ocular motility, eyelid retraction, and tonometry. Proptosis was quantified *via* Hertel exophthalmometry (proptosis was independently measured by two experienced ophthalmologists *via* the same Hertel exophthalmometer at the initial hospital visit). Measurements were obtained with the patient seated in primary gaze under standardized lighting conditions, with the examiner's eye level aligned with the patient's eyes. Three consecutive readings were taken by each observer for both eyes without repositioning the instrument, and the mean value was recorded. Measurements were expressed in millimeters to the nearest 0.5 mm using a one-mirror Hertel exophthalmometer (Oculus, Germany)[16]. Normal Hertel exophthalmometric values in an Asian (Chinese Han) adult population ranged up to approximately 19.0 mm, with values below this range considered within normal limits. Using these population-specific criteria helps minimize subjective bias in defining proptosis[17]. Best-corrected visual acuity (BCVA) was measured *via* a Snellen chart and recorded as Snellen fractions (*e.g.*, 6/6 indicating normal vision)[18]. All patients underwent baseline orbital computed tomography (CT) to assess extraocular muscles and exclude space-occupying lesions.

Intervention All patients received a medium-dose of IVMP (4.0 g over 6 cycles): 500 mg daily for three consecutive days (cycle 1) and then 500 mg every three weeks for five additional cycles. From cycle 4, azathioprine (50–100 mg/d) or mycophenolate mofetil (500–1000 mg/d) was added for 6mo. Azathioprine was administered to 18 patients, whereas mycophenolate mofetil was used in 12 patients on the basis of their drug affordability. The choice of immunosuppressive agent was influenced primarily by economic considerations rather than by disease severity.

Follow-up and Outcomes Patients were reviewed at weeks 3, 6, 9, 12, 15, and 18 and at 6mo. The primary outcome of this study was the change in CAS from baseline to 6mo following treatment with IVMP. The secondary outcome measures included changes in proptosis, measured *via* Hertel exophthalmometry; BCVA, recorded in Snellen notation and converted to logarithms of the minimum angle of resolution (logMAR) for statistical analysis; and intraocular pressure (IOP), measured *via* applanation tonometry. Additional secondary outcomes included improvements in clinical signs such as eyelid edema, conjunctival congestion, chemosis, and retrobulbar pain, as well as the occurrence of treatment-related adverse events. Missing data were not observed for the primary or secondary outcome variables, as all enrolled participants completed follow-up assessments. Therefore, no data imputation was needed.

Imaging Assessment Orbital CT was performed in all patients at baseline to support the diagnosis of TAO and to exclude alternative orbital pathology. Imaging commonly reveals enlargement of extraocular muscles, most frequently involving the inferior and medial recti, with relative sparing of the tendons. Variable degrees of orbital fat expansion were also observed.

Table 1 Baseline characteristics of the study participants (*n*=30)

Variables	Frequency (*n*=30)	Percentage (%)
Age (mean±SD, y)	38.63±12.11	
Gender		
Male	19	63.3
Female	11	36.7
Smoking history (smoker)		
Yes	14	46.7
No	16	53.3
Thyroid status		
Hyperthyroid	20	66.6
Hypothyroid	8	26.7
Euthyroid	2	6.7
Comorbidities		
None	20	66.7
Diabetes mellitus (DM)	6	20.0
Hypertension (HTN)	3	10.0
Both (DM+HTN)	1	3.3

SD: Standard deviation.

Statistical Analysis Statistical analysis was performed on patient data. For patients with bilateral involvement, the mean value of both eyes was calculated and used for analysis to avoid intereye correlation and overestimation of statistical significance. Continuous variables are expressed as the means±standard deviations (SDs), whereas categorical variables are presented as frequencies and percentages. The normality of continuous variables was assessed visually *via* the Shapiro-Wilk test and was found to be approximately normal. Changes in clinical parameters, including the CAS, proptosis, IOP, and BCVA, between baseline and the 6-month follow-up were analyzed *via* paired *t*-tests. BCVA values were converted to logMAR for statistical analysis. Paired categorical outcomes were compared *via* McNemar's test, with Phi (φ) reported as an effect size measure. A P value<0.05 was considered statistical significance. Statistical analyses were performed *via* SPSS version 25.

RESULTS

A total of 30 patients with active TAO were enrolled and completed the 6-month follow-up. The mean age of the participants was 38.63±12.11y, with a male predominance. Most patients are hyperthyroid at presentation, and approximately two-thirds have no major systemic comorbidities. The baseline demographic and clinical characteristics are summarized in Table 1.

Table 2 Changes in clinical parameters before and after therapy (*n*=30) mean±SD

Parameters	Before therapy	After 6mo	Change (Δ)	*P*
BCVA, logMAR	0.46±0.31	0.15±0.18	-0.31±0.28	0.020
Hertel's exophthalmometer, mm	22.47±1.59	20.13±1.97	-2.34±1.25	<0.0001
CAS, score	3.66±1.03	0.87±0.63	-2.79±0.95	<0.0001
IOP, mm Hg	16.80±3.56	14.93±1.73	-1.87±2.45	<0.001

Effect size is represented as the mean change (Δ) with the corresponding SD. BCVA: Best-corrected visual acuity; logMAR: Logarithms of the minimum angle of resolution; CAS: Clinical activity score; IOP: Intraocular pressure; SD: Standard deviation.

Table 3 Improvements in clinical signs before and after therapy (*n*=30)

Symptoms	Before therapy (%)	After 6mo (%)	Change (%)	Phi (φ)	*P*
Swelling of the eyelid	23.3	0	-23.3	0.48	<0.001
Redness of the eyelid	33.3	6.7	-26.6	0.53	<0.001
Conjunctival congestion	13.3	0	-13.3	0.35	0.013
Chemosis	13.3	3.3	-10.0	0.30	0.041
Pain/pressure (retro-orbital)	16.7	3.3	-13.4	0.35	0.013
Proptosis	100	10.0	-90.0	0.91	<0.001

Following treatment, a significant improvement in all the assessed clinical parameters was observed. Disease activity showed marked resolution, as evidenced by a substantial reduction in the CAS. Proptosis also improved significantly, indicating an effective reduction in orbital inflammation and tissue congestion. Visual function demonstrated meaningful recovery, with a notable improvement in BCVA. In addition, the IOP decreased significantly while remaining within the normal physiological range (Table 2).

Figure 1 shows a gradual and sustained reduction in proptosis measured by Hertel exophthalmometry across successive follow-up visits, indicating the progressive resolution of orbital congestion during treatment. Figure 2 shows a consistent decrease in CAS over time, reflecting effective suppression of orbital inflammation. Notably, a meaningful reduction in CAS was already evident during the early follow-up period (weeks 3–9) prior to the initiation of adjunctive immunosuppressive therapy from the fourth treatment cycle, suggesting a primary early response to IVMP. The functional visual outcome is depicted in Figure 3, which illustrates the distribution of BCVA before and after therapy.

Inflammatory signs and symptoms significantly improved by the end of follow-up. Eyelid swelling, redness, conjunctival congestion, chemosis, and retro-orbital pain were markedly reduced after treatment. The majority of eyes also improved in terms of proptosis. The changes in signs are detailed in Table 3. The adverse events observed during therapy were generally mild and reversible. Transient elevation of IOP and hyperglycemia were the most frequently encountered complications, whereas nearly half of the patients experienced no treatment-related adverse events. The overall safety profile is summarized in Table 4.

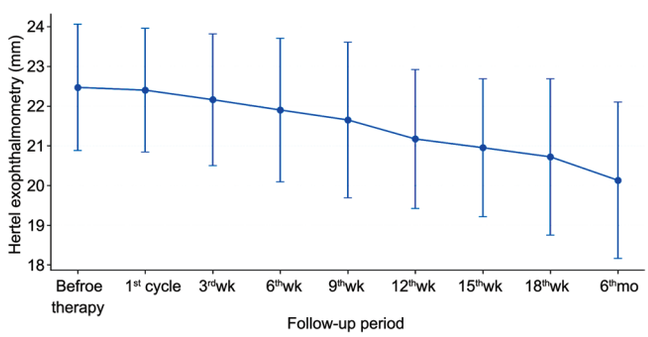

Figure 1 Proptosis trend measured by Hertel exophthalmometry during follow-up.

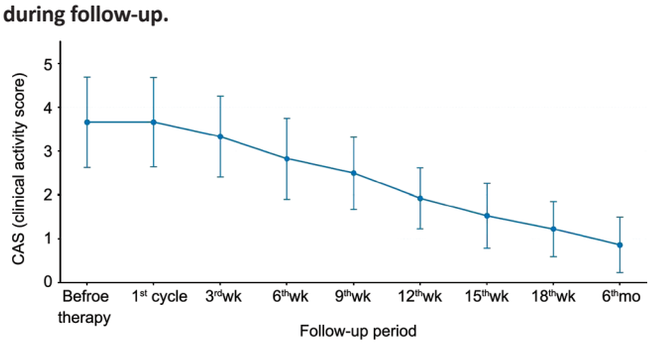

Figure 2 Trend of the clinical activity score (CAS) during follow-up.

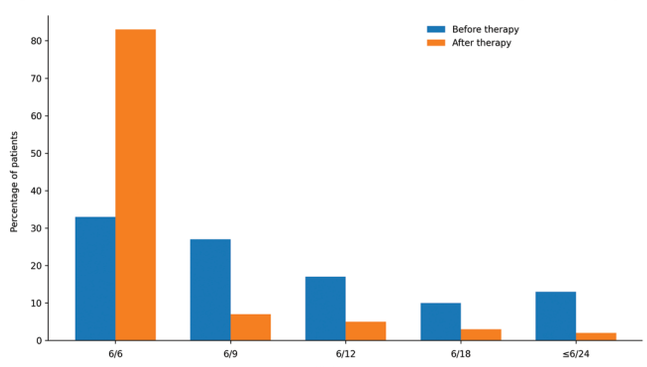

Figure 3 Distribution of best-corrected visual acuity (BCVA) before and after therapy.

DISCUSSION

The present study demonstrated statistically and clinically significant improvements in disease activity and orbital parameters following medium-dose IVMP therapy in patients with active moderate-to-severe TAO.

Table 4 Complications observed during therapy (*n*=30)

Adverse event	Frequency (*n*)	Percentage (%)
Raised IOP (transient)	8	26.66
Hyperglycemia	6	20.00
SGPT raised	2	6.67
No complication	14	46.67

SGPT: Serum glutamic pyruvate transaminase; IOP: Intraocular pressure.

Our cohort was relatively young, with a male preponderance and nearly half being smokers; most patients were hyperthyroid, and one-third had systemic comorbidities. Several reports highlight demographic patterns of TAO that differ from our sample[19-20]. The primary efficacy outcomes were significant reductions in CAS and proptosis. CAS decreased significantly, and mean Hertel exophthalmometry decreased at six months. The reduction in inflammation is consistent with the known immunosuppressive effect of GCs, which diminishes the infiltration of lymphocytes and fibrocytes and suppresses cytokine-induced hyaluronan accumulation[9-10]. Our findings align with evidence that IVMP regimens of 4.5–5.0 g over 12wk result in substantial CAS reduction[21]. Concomitant immunosuppressive therapy may have influenced the treatment outcomes in this study. Azathioprine or mycophenolate mofetil was introduced from the fourth treatment cycle and is known to exert delayed immunomodulatory effects[22]. As clinical improvement was already evident before adjunctive therapy, early response was likely attributable to IVMP, whereas sustained improvement during later follow-up probably reflects combined therapy, as reported in previous studies[23]. The standard EUGOGO-recommended regimen for moderate-to-severe active TAO consists of a cumulative IVMP dose of approximately 4.5 g administered over 12wk[22]. The 4.0 g regimen used in the present study yielded comparable improvements in disease activity and orbital inflammation while potentially reducing steroid-related toxicity, as the cumulative dose is a key determinant of adverse events[23]. Our sustained reduction at 6mo may reflect ongoing immunomodulation across 18wk. Conversely, some authors note that GCs rarely induce a clinically significant reduction in proptosis because they do not reverse adipogenesis, whereas targeted biologics such as teprotumumab block insulin-like growth factor 1 receptor (IGF-1R) and achieve greater mean reductions[24]. The modest but significant improvement in our cohort underscores that medium-dose IVMP remains effective for inflammation but may not address fibro-adipose expansion, and further research on combination therapy or early biologic use in smokers may be warranted.

Visual outcomes improved markedly in our study. The proportion of eyes with 6/6 BCVA increased significantly. High-dose IVMP studies have shown comparable functional improvements, with Liu *et al*[25] reporting significant gains in visual acuity both at 1mo and at the final follow-up. Another study reported that the mean BCVA improved from 0.85±0.63 to 0.63±0.63 logMAR at 1wk, and 76.5% of orbits gained ≥0.2 logMAR[26], albeit with high-dose pulses. Our results, therefore, demonstrate that a lower cumulative dose can achieve comparable functional recovery, perhaps because our patients had less severe initial impairment and were treated earlier. The improvement in BCVA is likely attributable to the exclusion of patients with established DON and the predominance of early, inflammation-related disease in the study population. In such cases, visual impairment is largely reversible following the suppression of orbital inflammation with IVMP[27]. A reduction in IOP further supports decreased orbital congestion, and high-dose IVMP also results in similar IOP reductions[25]. Transient IOP elevations occurred in slightly more than a quarter of our patients, which is consistent with glucocorticoid-induced ocular hypertension; however, the average IOP decreased over time, indicating the resolution of inflammation and effective control with topical therapy. In contrast, a recent radiotherapy study reported that posterior scleral distance, a proxy for proptosis and IOP, temporarily worsened after intravenous steroids and improved only after adjuvant radiotherapy[28]. Our finding of improved IOP with medium-dose IVMP alone highlights that careful dosing may mitigate steroid-related fluid retention. The clinically meaningful improvement in BCVA and IOP underscores the capacity of medium-dose IVMP to preserve visual function, particularly when it commences before irreversible optic nerve damage.

The patient's clinical symptoms improved substantially. Eyelid swelling, conjunctival redness, chemosis, pain, and pressure decreased significantly, and proptosis was present in only 10% of the eyes at 6mo. High-dose IVMP studies have shown similar improvements in soft tissue signs, with Liu *et al*[25] reporting significant reductions in CAS subscores for eyelid edema and conjunctival injection. However, soft tissue remission is not universal. A 2025 systematic review[21] reported that weekly IVMP regimens lead to variable improvements in eyelid swelling and diplopia, with smokers responding less favorably. Our high proportion of smokers yet near-complete resolution of swelling suggests that early intervention and adherence to therapy may override smoking-related resistance. The study by Ye *et al*[29] supports the use of adjunctive mycophenolate mofetil with IVMP to enhance composite outcomes, reporting response rates of 91.3% with combination therapy compared with 67.9% with IVMP alone at 24wk. We achieved comparable symptom relief without mycophenolate, but our follow-up was limited

to 6mo; late relapses remain possible. Overall, our findings support medium-dose IVMP as an effective first-line therapy for symptomatic relief in patients with active TAO, although combination strategies may further enhance outcomes.

This study revealed that medium-dose IVMP was well tolerated. Adverse events were very rare, and nearly half of the patients experienced no complications. No severe hepatic, cardiovascular, or psychiatric events occurred. Safety comparisons highlight the importance of dosing. Eguchi *et al*[8] evaluated 175 patients treated with high-dose IVMP and reported severe liver dysfunction in 7 patients, along with mild alanine aminotransferase elevation in 35% and moderate elevation in 6%. The identified risk factors included male sex, cumulative doses exceeding 8 g, age over 50y, and preexisting viral hepatitis. Similarly, fatal liver failure and acute cardiovascular events have been associated with high cumulative doses, prompting the EUGOGO to recommend a maximum total dose of 8 g[30-31]. Our cumulative dose of 4 g is well below this threshold, which likely contributed to the absence of serious adverse effects. A recent systematic review reported that medium-dose regimens (3–4.5 g) had fewer side-effects than high-dose regimens did[21]. The 2022 update highlights the importance of vigilant monitoring for hyperglycemia, hypertension, glaucoma, hip osteonecrosis, and psychosis during glucocorticoid therapy[30]. In our study, regular monitoring enabled timely management of transient ocular hypertension and hyperglycemia. The absence of psychiatric or infectious complications may also reflect our younger population and exclusion of individuals with multiple comorbidities. These findings reinforce that medium-dose IVMP provides a balance between efficacy and safety, particularly in settings where biologic agents are unavailable or unaffordable.

Recent publications have focused predominantly on the clinical characterization, phenotypic profiling, and activity stratification of TAO, including the evaluation of clinical features, disease subtypes, and biomarkers associated with disease activity, rather than on prospective assessments of standardized intravenous glucocorticoid regimens[32-33]. In contrast, the present study provides real-world prospective evidence on the efficacy and safety of a cumulative 4.0-g IVMP protocol in patients with moderate-to-severe active TAO, supported by structured longitudinal follow-up. This approach addresses an important therapeutic gap, particularly in resource-limited settings where access to biologic therapies remains restricted.

This study has several limitations. The relatively small sample size and single-center design may limit the generalizability of the findings. The six-month follow-up may be insufficient to capture late relapses or long-term adverse effects of medium-dose IVMP. Notably, meaningful clinical improvement was observed during the early follow-up period prior to the initiation of adjunctive immunosuppressive agents, suggesting that the initial treatment response was primarily attributable to IVMP. The absence of a control or comparison group precludes definitive conclusions regarding comparative efficacy, although the observed clinical improvements are comparable to those reported in randomized trials. Adjunctive immunosuppressive therapy with azathioprine or mycophenolate mofetil, introduced from the fourth treatment cycle in a subset of patients, may have contributed to sustained responses, limiting attribution to IVMP alone. Smoking status could not be analyzed due to the small sample size. The study was not designed to compare different immunosuppressive regimens, and quantitative radiological grading was not performed. Larger, multicenter randomized studies with longer follow-up periods are warranted.

Medium-dose IVMP pulse therapy was found to be an effective and safe treatment option for patients with moderate-to-severe active TAO. Significant improvements in the CAS, proptosis and visual function were achieved, with minimal and reversible adverse effects. This regimen offers a favorable balance between efficacy and safety. However, larger multicenter studies with longer follow-up periods are warranted to confirm these findings and optimize therapeutic protocols.

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