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Intravenous Glucocorticoid Treatment for Korean Graves' Ophthalmopathy Patients

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Author Contributions

Conceptualization: Ahn HY, Lee JK. Formal analysis: Ahn HY. Investigation: Ahn HY. Data curation: Ahn HY. Methodology: Ahn HY, Lee JK. Software: Ahn HY. Validation: Lee JK. Writing - original draft: Ahn HY. Writing - review & editing: Lee JK.

ABSTRACT

Background: High-dose intravenous steroids are the first-line treatment for patients with moderate-to-severe and active Graves' ophthalmopathy (GO). We aimed to investigate the response rate of methylprednisolone (MPD) treatment among Korean patients with active moderate-to-severe GO and to identify predictive factors of treatment response.

Methods: This is a retrospective observational study. We included 54 active moderate-to-severe GO patients treated with 4.5 g intravenous MPD over 12 weeks between November 2011 and November 2018. Response was defined as an improvement in at least two of five indicators (clinical activity score [CAS], soft-tissue involvement, exophthalmos, diplopia, and visual acuity) at immediate and 3 months after treatment completion. We examined predictive factors for response using logistic regression analysis.

Results: Twenty-four (44.4%) and 22 (40.7%) patients showed response at immediate and 3 months after intravenous (IV) steroid treatment. Of the five ophthalmic parameters, all patients in the responsive group (100.0%) showed a decrease in CAS and 90.9% showed less soft tissue involvement after IV steroid treatment. Among variables, the sum of extraocular muscle width was positively (odds ratio [OR], 1.163; 95% confidence interval [CI], 0.973–1.389; $P = 0.096$) associated with treatment response. While, the OR of age was 0.918 (95% CI, 0.856–0.985; $P = 0.017$) and thyrotropin binding inhibitory immunoglobulin (TBII) was 0.921 (95% CI, 0.864–0.982; $P = 0.012$).

Conclusion: In Korean active moderate-to-severe GO patients, intravenous steroid treatment is not as effective as previously reported. Parameters associated with CAS and soft-tissue involvement were found to be influenced by IV MPD treatment. Extraocular muscle enlargement, younger age and lower TBII are predictive factors for a good steroid treatment response.

Keywords: Graves' Ophthalmopathy; Glucocorticoids; Clinical Activity Score; Response Rate

INTRODUCTION

Graves' ophthalmopathy (GO) is the most frequent extrathyroidal manifestation among patients with Graves' disease. Almost 50% of patients with Graves' disease report eye symptoms such as a dry and gritty sensation, excessive tearing, photophobia, double vision, and pain.¹ Three to five percent of patients with GO experience severe disease with

intense pain, inflammation, and sight-threatening corneal ulceration or compressive optic neuropathy.² Therefore, it is important to classify patients with GO by the level of activity and severity when planning treatment for patients with GO. The European Group on Graves' Orbitopathy (EUGOGO) recommends that the activity and severity of GO be assessed according to standardized criteria to select the most appropriate treatment for individual patients with GO.³ Activity is evaluated using the clinical activity score (CAS).⁴ Patients with a CAS of ≥ 3 of 7 items are classified as having active GO. The severity of GO can be classified as mild, moderate-to-severe, or sight threatening.³

As recommended by EUGOGO,³ high-dose intravenous (IV) steroids are the first-line treatment for patients with moderate-to-severe and active GO. In several randomized clinical studies, the response rate in the IV steroids group was about 70%–80%.⁵ However, each study used a different dose of IV steroids, and some studies^{6–8} even used more cumulative doses (6–10 g) of methylprednisolone (MPD) than recommended (4.5 g). Although there are differences in ethnic-specific features and symptoms of GO, little is known about the response rate of patients in the Korean population to IV steroid treatment. Furthermore, there are few established prognostic factors that can predict IV steroid treatment response.

Based on these uncertainties, we aimed to investigate the response rate of 4.5 g IV MPD treatment among Korean patients with active moderate-to-severe GO and to identify factors that can predict response to 4.5 g IV MPD treatment.

METHODS

Subjects

We included patients who were diagnosed with active moderate-to-severe GO and treated with 4.5 g IV MPD at Chung-Ang University Hospital between November 2011 and November 2018. Active GO was defined as GO with a CAS of ≥ 3 of 7 items.⁹ The severity of GO was also classified according to the guidelines of EUGOGO.⁹ IV MPD was administered by one endocrinologist for 12 weeks. For the first 6 weeks, 0.5 g of MPD was injected weekly on the same day, and 0.25 g was injected in the same manner for the remaining 6 weeks. Liver function and blood glucose levels were monitored regularly during IV MPD treatment. Patients who were followed up at our hospital for at least 3 months after the end of IV steroid treatment were included in this study to identify cases that worsened immediately after IV steroid treatment.

We excluded patients who received any immunosuppressive therapy or radiotherapy before IV MPD treatment, as well as patients younger than 20 years; pregnant patients; hepatitis carriers; and patients with a past medical history of other eye diseases such as glaucoma, diabetic retinopathy, maculopathy, and strabismus.

During the study period, 54 patients were treated with 4.5 g IV MPD. We examined the subjects' height, body weight, gender, age at MPD treatment, smoking status, duration of GO before MPD treatment, and history of use of anti-thyroid drugs or levothyroxine. Thyroid function test results (thyroid stimulating hormone [TSH] and free thyroxine [T4] levels), thyrotropin binding inhibitory immunoglobulin (TBII) and total cholesterol level were assessed before IV MPD treatment.

Ophthalmic assessment and response evaluation

Ophthalmic examinations were performed before and immediately after IV MPD treatment and at 3 months after IV MPD treatment. All ophthalmic examinations were performed by one ophthalmologist. The proptosis status, margin reflex distance 1 (MRD1, the vertical distance between the center of the pupil and the center of the upper eyelid margin), palpebral fissure height, intraocular pressure, diplopia status, visual acuity, and NOSPECS classification (N = No Symptoms or signs, O = Only symptoms, S = Soft tissue involvement, P = Proptosis, E = Extraocular muscle involvement, C = Corneal involvement, S = Sight loss due to optic nerve compression) and CAS scores were assessed and recorded at each visit. Proptosis was assessed via Hertel exophthalmometry (Oculus, Arlington, VA, USA). Palpebral fissure height was recorded as the sum of MRD1 and MRD2 (the distance between the center of the pupil and the center of lower eyelid margin). MRD1 and palpebral fissure height were measured using the custom-made PC-based software EAS (Eyelid Analysis Software; Biomedical Research Institute, Seoul, Korea) after photographs were taken in the primary position.¹⁰ Diplopia was assessed using the Gorman score.¹¹ Visual acuity was assessed using the Snellen chart. The modified CAS was assessed by assigning a point to each of the following seven items (spontaneous retrobulbar pain, pain on attempted upward or downward gaze, redness of eyelids, redness of the conjunctiva, inflammation of caruncle and/or plica, swelling of eyelids, and conjunctival edema).⁴ The modified NOSPECS score was used to assess the severity of GO.¹² Contiguous 1-mm sections of extraocular muscles for orbital computed tomography scans were obtained from the patients. The thickness of each extraocular muscle (superior, inferior, lateral, and medial rectus) was measured using ImageJ (<https://imagej.nih.gov/ij>). The horizontal diameters of the medial and lateral rectus and the vertical diameters of the superior and inferior rectus muscles were measured on a series of images; the largest diameter of the middle section of each muscle was selected. The sum of the thickness of the four (superior, inferior, lateral, and medial rectus) extraocular muscles was also calculated.

Response was defined as the presence of at least two of the following five ophthalmic parameters: 1) reduction in proptosis by at least 2 mm, 2) reduction in any of the class 2 NOSPECS signs by at least one grade, 3) improvement in CAS by at least 2 points or CAS < 3/7, 4) improvement in visual acuity on Snellen line and 5) decrease in the Gorman score (from constant to inconstant, inconstant to intermittent, or intermittent to absent).

We divided the study subjects into two groups: "responsive" and "nonresponsive" groups, according to the overall response at immediate and 3 months after IV MPD treatment. Patients who received additional radiation therapy shortly after the end of IV MPD treatment were classified as nonresponsive when assessing response at 3 months after IV MPD because radiation therapy was performed mainly when there was no change after IV MPD treatment or when symptoms worsened immediately after IV MPD treatment. Twelve patients received radiation therapy after IV MPD treatment.

Statistical analysis

Continuous variables are presented as means \pm standard deviations and analyzed using Student's *t*-test or the Mann-Whitney U test based on the result of the normality test. Categorical variables were analyzed using Pearson's χ^2 test. Binary logistic regression analysis was performed to analyze the effect of each clinical variable on the binary response of IV treatment. For analyzing combined effect of more than two variables on the IV steroid response, multivariate logistic regression analysis was performed using backward stepwise procedures as variable selection method to minimize Akaike information criterion (AIC). All

statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Analysis items with $P < 0.05$ were considered statistically significant.

Ethics statement

The protocol of this retrospective observational study was approved by the Institutional Review Board (IRB) of Chung-Ang University Hospital (IRB No. 1905-004-16263). Informed consent was not required for this study considering its retrospective design.

RESULTS

Baseline characteristics of the responsive and nonresponsive groups

Of the study patients, 24 (44.4%) patients were assigned to the responsive group immediately after IV MPD treatment. Three months after IV MPD treatment, 22 (40.7%) were identified as responders. Five out of 24 responders immediately after IV MPD treatment changed to non-responders at 3 months after IV MPD treatment. On the other hand, 3 out of 30 non-responders immediately after IV MPD treatment were identified as responders at 3 months after IV MPD treatment (Fig. 1).

Table 1 showed the baseline characteristics of each group at post-treatment time point. The initial TBII values were found to be statistically low in the response group at both treatment points. In addition, immediately after IV MPD treatment, the responders had more than moderate soft tissue symptoms (100% vs. 76.7%, $P = 0.022$), and 3 months after IV MPD treatment, the responders were younger (42.1 ± 12.8 years old vs. 49.9 ± 11.6 years old, $P = 0.023$).

Response rates of each parameter in the responsive group

Of the five ophthalmic parameters, all patients in the responsive group (100.0%) showed a decrease in CAS and 90.9% showed less soft tissue involvement after IV steroid treatment. However, only 27.3% of patients in the responsive group showed an improvement in proptosis or diplopia. Only 18.1% of patients in the responsive group showed an improvement in visual acuity (Fig. 2A). Among all study subjects, 44.4% and 40.7% showed an improvement in CAS and soft-tissue involvement, respectively (Fig. 2B).

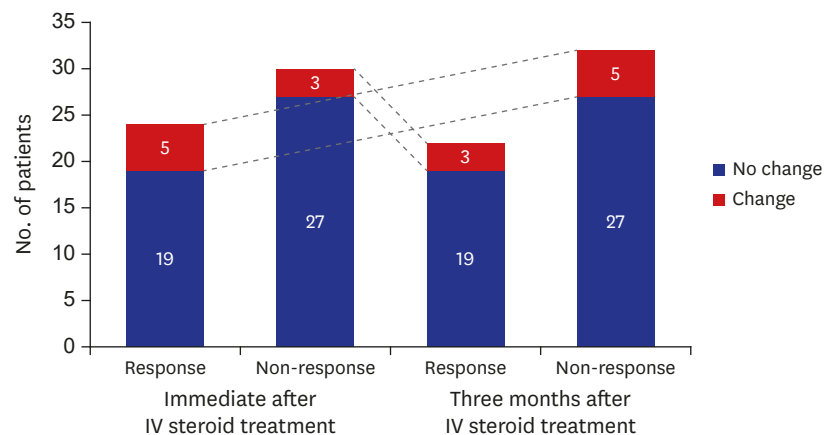


Fig. 1. Number of patients according to treatment response at immediate and 3 months after 12 weeks intravenous steroid treatment. Five patients who responded immediately after IV steroid treatment changed to non-responders after 3 months, while three patients who did not respond immediately belonged to the responders after 3 months.

Table 1. Baseline clinical and ophthalmologic characteristics of subjects according to response at immediate and 3 months after steroid treatment

Characteristics	Immediate after steroid treatment			Three months after steroid treatment		
	Non-responsive group (n = 30)	Responsive group (n = 24)	P value	Non-responsive group (n = 32)	Responsive group (n = 22)	P value
Age, yr	48.5 ± 12.3	44.6 ± 12.8	0.263	49.9 ± 11.6	42.1 ± 12.8	0.023
Gender, men	7 (23.3)	11 (45.8)	0.081	10 (31.3)	8 (36.4)	0.695
Body mass index, kg/m ²	22.7 ± 2.4	22.8 ± 2.7	0.889	22.67 ± 2.24	22.92 ± 2.95	0.732
Duration of GO, mon	14.6 ± 18.6	13.5 ± 14.9	0.808	15.1 ± 19.4	12.7 ± 12.8	0.616
Thyroid hormone medication	3 (10.0)	1 (4.2)	0.416	4 (12.5)	0 (0.0)	0.085
Never smoker	20 (66.7)	13 (54.2)	0.349	21 (65.6)	12 (54.5)	0.412
Sum of EOM, mm	21.11 ± 4.81	21.03 ± 4.45	0.952	20.91 ± 4.57	21.32 ± 4.77	0.755
TSH, µIU/mL	2.17 ± 4.11	1.38 ± 2.48	0.426	1.94 ± 4.02	1.62 ± 2.54	0.748
Free T4, ng/dL	1.36 ± 0.83	1.32 ± 0.58	0.873	1.38 ± 0.81	1.28 ± 0.58	0.635
Initial TBII, IU/L	21.74 ± 15.65	11.81 ± 9.84	0.008	20.80 ± 15.44	12.20 ± 10.40	0.021
Total cholesterol, mg/dL	200.9 ± 39.0	192.5 ± 46.4	0.485	202.1 ± 41.6	190.2 ± 42.8	0.325
MRD1, mm	3.94 ± 1.51	3.79 ± 1.54	0.725	3.73 ± 1.65	4.08 ± 1.28	0.411
Palpebral fissure, mm	9.56 ± 1.90	9.14 ± 2.48	0.490	9.08 ± 2.20	9.79 ± 2.09	0.240
Proptosis, mm	19.03 ± 2.99	18.50 ± 3.13	0.527	18.33 ± 2.84	19.48 ± 3.26	0.175
Any diplopia	14 (46.7)	13 (54.2)	0.584	15 (46.9)	12 (54.5)	0.580
NOSPECS class II, minimal/moderate/marked, %	23.3/66.7/10.0	0.0/95.8/4.2	0.022	18.8/71.9/9.4	4.5/90.9/4.5	0.219
CAS, 3/ ≥ 4, %	53.3/46.7	37.5/62.5	0.246	53.1/46.9	36.4/63.6	0.225

Data are presented as mean ± standard deviation or number (%).

GO = Graves' ophthalmopathy, EOM = extraocular muscle, TSH = thyroid stimulating hormone, TBII = thyrotropin binding inhibitory immunoglobulin, MRD = margin reflex distance, CAS = clinical activity score.

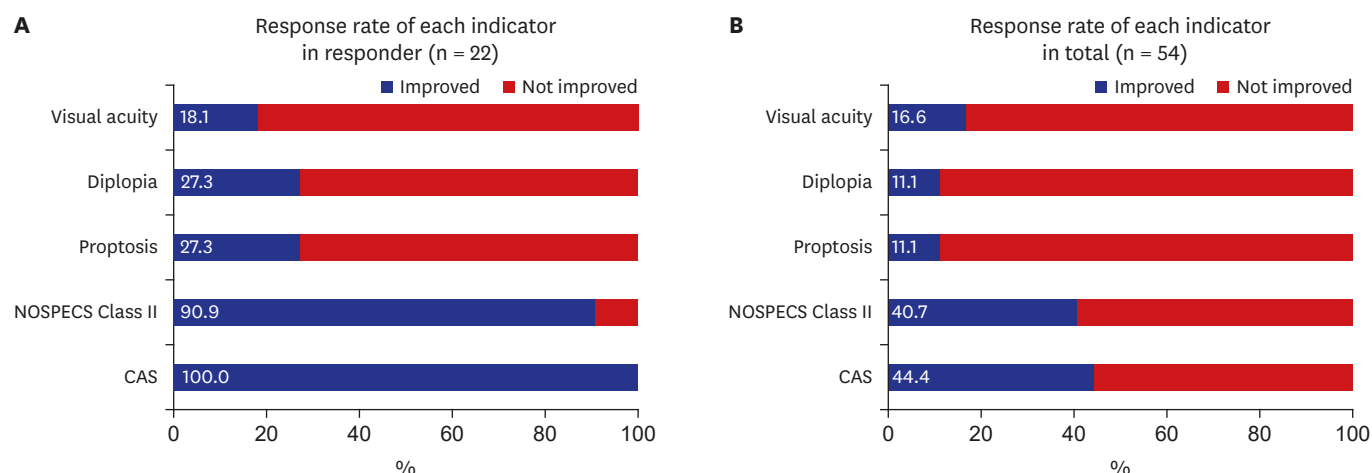


Fig. 2. Response rate of each indicator at 3 months after IV steroid treatment.

(A) Response rate in responders. In responder, the response rate was 100% in CAS, 90.9% in NOSPECS class II, 27.3% in proptosis and diplopia and 18.1% in visual acuity. (B) Response rate in total subjects. In total subjects, the response rate was 44.4% in CAS, 40.7% in NOSPECS class II, 11.1% in proptosis and diplopia and 16.6% in visual acuity.

CAS = clinical activity score, NOSPECS = N, No Symptoms or signs, O, Only symptoms, S, Soft tissue involvement, P, Proptosis, E, Extraocular muscle involvement, C, Corneal involvement, S, Sight loss due to optic nerve compression.

Predictive factors for response to IV MPD treatment

Multivariate logistic regression analysis was performed to identify the predictive factors for response to IV MPD treatment (Table 2). The odds ratio (OR) of the sum of extraocular muscle diameter was 1.163 (95% confidence interval [CI], 0.973–1.389; $P = 0.096$); thus, the thicker the diameter of the extraocular muscle, the better the expected therapeutic response. The OR of age was 0.918 (95% CI, 0.856–0.985; $P = 0.017$) and that of initial TBII was 0.921 (95% CI, 0.864–0.982; $P = 0.012$). These results suggested that increasing age and TBII values were poor prognostic factors for response to IV MPD treatment. We summarize the

Table 2. Predictive factors for the response of IV steroid treatment by logistic regression analysis performed using backward stepwise procedures

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age	0.947	0.902–0.955	0.030	0.918	0.856–0.985	0.017
Gender, men	0.795	0.253–2.502	0.696			
Body mass index, kg/m ²	1.041	0.834–1.301	0.721			
Duration of GO, mon	0.991	0.957–1.026	0.612			
Smoking	1.591	0.523–4.873	0.413			
Sum of EOM, mm	1.020	0.905–1.148	0.749	1.163	0.973–1.389	0.096
TSH, μ IU/mL	0.972	0.820–1.153	0.743			
Free T4, ng/dL	0.814	0.353–1.877	0.629			
Pretreatment TBII, IU/L	0.952	0.908–0.997	0.038	0.921	0.864–0.982	0.012
Changes of TBII for 12 wk	0.959	0.901–1.021	0.193			
Total cholesterol, mg/dL	0.993	0.979–1.007	0.320			
MRD1, mm	1.171	0.809–1.694	0.404			
Proptosis, mm	1.139	0.944–1.374	0.174			
Diplopia	1.360	0.458–4.042	0.580			
NOSPECS Class II, \geq b	4.846	0.540–43.464	0.159	7.204	0.544–95.386	0.134
CAS, \geq 4	1.983	0.652–6.031	0.227			

IV = intravenous, CI = confidence interval, OR = odds ratio, GO = Graves' ophthalmopathy, EOM = extraocular muscle, TSH = thyroid stimulating hormone, TBII = thyrotropin binding inhibitory immunoglobulin, MRD = margin reflex distance, CAS = clinical activity score.

Table 3. Predictive factors for response of IV steroid treatment in active Graves' ophthalmopathy patients

Year	Authors	Country	Patient, No.	Response rate of IV steroid Tx, %	Outcomes for IV steroid Tx	Variables	OR (95% CI)	P value
2015	Xing et al. ¹³	China	92	54.3	No response	Smoking	13.4 (1.2–128.14)	0.035
2018	Wang et al. ¹⁴	China	90	57.8	Response	Duration of eye symptoms	0.984 (0.972–0.997)	0.012
						Restoration of euthyroidism	3.282 (1.062–10.142)	0.039
2019	Hu et al. ¹⁵	China	302	54.0	Response	Duration of eye symptoms	0.878 (0.790–0.977)	0.017
						Pretreatment CAS	3.506 (1.973–6.228)	< 0.001
						Positive pretreatment TRAB, > 9.31 U/L	0.061 (0.018–0.214)	< 0.001
						High pretreatment triglyceride, \geq 150 mg/dL	0.090 (0.022–0.372)	0.001
						Elevated TSH levels during treatment, > 5 μ IU/mL	0.145 (0.037–0.561)	0.005
2020	Ahn and Lee (present study)	Korea	55	40.7	Response	Age	0.918 (0.856–0.985)	0.017
						Pretreatment TBII, IU/L	0.921 (0.864–0.982)	0.012

IV = intravenous, Tx = treatment, CAS = clinical activity score, TRAB = thyrotropin receptor antibodies, TSH = thyroid-stimulating hormone, OR = odds ratio, CI = confidence interval.

prognostic factors associated with IV steroid treatment presented in the present study and other previous studies in **Table 3**.¹³⁻¹⁵

Adverse event during IV steroid treatment

Patients complained of various side effects during IV steroid treatment, but most of them were mild and temporary. Specifically, palpitation (5.6%), weight gain of more than 3 kg (12.9%), digestive system disorders (5.6%), liver function abnormality (9.3%), hyperglycemia (14.8%), sleep disorders (20.4%), facial edema (16.7%), and hot flush (12.9%) were the common side effects.

DISCUSSION

In this retrospective study, we evaluated the response rate for 4.5 g IV MPD treatment in Korean moderate-to-severe active GO patients and attempted to determine the predictive factors for IV MPD treatment response.

Surprisingly, we found that the response rate of IV MPD treatment was less than 50% (44.4% immediately after IV MPD treatment or 40.7% at 3 months after IV MPD treatment). Most patients in the responsive group were found to have improved CAS and soft-tissue involvement; however, improvement in proptosis, diplopia, and visual acuity were not effective with IV MPD treatment. Even if improvement in CAS or soft-tissue involvement is considered the only response criterion, the response rate of IV MPD treatment is less than 50% in our study subjects. Why is the response rate of IV MPD treatment lower in Korean GO patients than that in previous studies?

First, there is a possibility of differences in IV MPD treatment response due to differences in race. Response rates from studies conducted on Chinese GO patients of the same Asian ethnicity were 54.3%–57.8% for IV MPD treatment.^{13,14,16} In contrast, a randomized study of 35 German GO patients reported that 77% of patients responded to IV MPD treatment.¹⁷ In addition, in a randomized study of 52 Turkish GO patients, the response rate of IV MPD treatment was found to be 72% after 3 months of treatment.¹⁸ Although only six patients were included, a study in Netherlands showed a high response rate of 83% for IV MPD treatment.⁶

Second, because each study used different time points to evaluate responses to steroid treatment, the response rates are likely to be different. Our study evaluated the responsive group according to response status immediately and 3 months after the end of steroid treatment; however, the response rate was low regardless of the time of evaluation after IV MPD treatment. Currently, it is unclear when to assess response after IV steroid treatment. However, considering that some patients may show an immediate deterioration in their condition after IV steroid treatment and may consider other therapy, it may be accurate to evaluate the response rate at least 3 months after IV steroid treatment. In a previous study, 12%–13% of patients showed a deterioration in their condition after 12 weeks of IV MPD treatment.¹⁹ In our study, 5 (9.3%) patients showed an immediate response to IV MPD treatment; however, their condition subsequently worsened and they were classified as the nonresponsive group.

The thicker the extraocular muscle, the better the response rate to IV MPD treatment. In active GO patients, edema occurs because of an inflammatory response of the orbital fibroblast. Hydrophilic hyaluronan accumulates between the intact extraocular muscle fibers and causes an increase in the muscle volume.¹ Our result suggests that IV MPD treatment might be effective for edematous changes. Similarly, another study reported that the inferior rectus/fat ratio on MRI is predictive of the response to glucocorticoid therapy in GO patients.¹⁶

The higher the TBII, the lower the response to IV MPD treatment. Expression of the thyrotropin (TSH) receptor in orbital tissue is elevated in active phase GO patients, which suggest an important role of thyrotropin antibodies (TRAbs) in the pathogenesis of GO.^{20,21} In several previous studies, the TBII titer was strongly associated with clinical activity and severity of GO.^{22,23} In addition, Eckstein et al.²⁴ reported that the TBII levels remained elevated after steroid treatment in 93% of very active GO patients (non-responder) compared with 42% of inactive GO patients ($P = 0.02$). Given that steroids can reduce or change the number or function of immune cells and decrease the level of immunoglobulin and cytokines,²⁵ patients with high TBII levels have a more severe immune reaction, and these patients may require stronger immunosuppressive treatment than IV steroid or a higher dose of IV steroid treatment.

The limitation of our study is that, firstly, because this study was conducted in a tertiary hospital, there may be a selection bias in patient selection. It is possible that more severe GO

patients were included in our study. Secondly, our study was a retrospective observational study and included a relatively small number of GO patients, which may have influenced the results.

In conclusion, it appears that IV MPD treatment for active moderate-to-severe GO patients is not as effective as reported previously. Parameters associated with CAS and soft-tissue involvement were found to be influenced by IV MPD treatment. An enlarged extraocular muscle, younger age, and TBII were predictive factors for a good response to IV MPD treatment. Therefore, if GO patients were selected by considering these factors before IV MPD treatment, more appropriate treatment would be possible.

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