ORIGINAL

Overall safety and efficacy of high-dose and low-dose intravenous glucocorticoid therapy in patients with moderate-to-severe active Graves' ophthalmopathy

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Abstract. The objective of this study was to compare the safety and efficacy of high-dose and low-dose intravenous (iv) glucocorticoid (GC) therapy in patients with Graves' ophthalmopathy (GO) and to investigate which factors may help determine appropriate iv GC doses. The medical records of 43 patients who received different doses of iv GCs for GO were retrospectively reviewed. Twenty patients received high-dose iv GCs (HD group, cumulative dose 9.0–12.0 g) and 18 received low-dose iv GCs (LD group, cumulative dose 4.5 g). Five patients with previous treatment for GO were excluded. Changes in ophthalmic parameters after treatment and frequencies of adverse effects due to GCs of the 2 groups were compared. We also reviewed the incidence of GO progression and hepatic dysfunction after patients were discharged. We evaluated correlations among pretreatment (before treatment) ophthalmic parameters and investigated useful predictive factors for determining iv GC doses. There were no significant differences in ophthalmic parameters reflecting treatment efficacy or overall safety between the groups. Among baseline ophthalmic parameters, corrected signal intensity ratio (cSIR) correlated well with magnetic resonance imaging findings and were more strongly associated with changes in ophthalmic parameters after treatment in the HD group than in the LD group, indicating that pretreatment cSIR might be useful for determining iv GC doses. In conclusion, there were no significant differences in overall safety and efficacy between high-dose and low-dose iv GC therapy in patients with active GO. Further randomized clinical trials with longer observation periods are required to establish the optimal treatment regimen of GO.

Key words: Graves' ophthalmopathy, Thyroid-associated ophthalmopathy, Intravenous glucocorticoid therapy, MRI, STIR

GRAVES' OPHTHALMOPATHY (GO) is characterized by periorbital edema, proptosis, extraocular muscle dysfunction, and optic nerve compression. It is the most characteristic and common extrathyroidal manifestation of Graves' disease (GD) [1].

Since GO is generally considered an autoimmune disorder, glucocorticoid (GC) therapy has been used for GO for the last few decades. Different routes of administration and dosages have been used, and various studies have attempted to identify the optimal regimen

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Abbreviations: GO, Graves' ophthalmopathy; GD, Graves' disease; GC, glucocorticoid; iv, intravenous; mPSL, methylprednisolone; EUGOGO, European Group on Graves' Orbitopathy; MRI, magnetic resonance imaging; CAS, Clinical Activity Score; SIR, signal intensity ratio; PSL, prednisolone; CAS, clinical activity score; STIR, short tau inversion recovery; T1W, T1-weighted; ROIs, regions-of-interest; cSIR, corrected SIR; ANCOVA, analysis of covariance.

[2]. Until recently, regimens with high-dose intravenous (iv) methylprednisolone (mPSL) have been commonly used. However, severe and acute liver damage, including 4 fatalities, have been associated with high-dose iv GC therapy (cumulative GC dose of 8.3 g to 15.0 g) [3, 4]. Le Moli *et al.* proposed that cumulative doses up to 8.0 g are safe [5] and the European Group on Graves' Orbitopathy (EUGOGO) recommends a cumulative mPSL dose of <8.0 g during a course of iv GC therapy [6]. However, evidence on the safety and efficacy of different cumulative doses of iv GC therapy remains insufficient to establish the optimal treatment regimen for GO.

In the evaluation of GO patients, a panel of ophthalmic measurements has been recommended [7]. Magnetic resonance imaging (MRI) is a good objective tool for the diagnosis and follow-up of GO [8]. The cross-sectional area or volume of the enlarged extraocular muscles [9], T2 relaxation time [10], and signal intensity ratio (SIR) of the extraocular muscles [11] have been suggested as useful MRI parameters. However, the data on the correlation between MRI findings and treatment response is very limited [12].

In this study, we retrospectively evaluated the clinical manifestations, laboratory data, and MRI findings of patients with GO treated at our institution. We compared the safety and efficacy of conventional high-dose and low-dose iv GC therapy, and assessed the incidence of GO progression and GC-induced hepatic dysfunction during the follow-up period after iv GC therapy. We also evaluated the relationship between pretreatment (before treatment) clinical and imaging ophthalmic parameters. Furthermore, we investigated useful predictive factors for determining the dose of iv GCs by comparing the associations between pretreatment ophthalmic parameters with post-treatment changes between the 2 different iv GC doses.

Methods

Patients

Forty-three consecutive patients with a clinically confirmed diagnosis of GD and GO admitted for iv GC therapy at Kyoto University Hospital between January 1, 2006 and January 31, 2014 were retrospectively reviewed in this study. Indications for iv GC therapy to treat active GO at our institution included NOSPECS class ≥ 3 [13]; progressive eye symptoms such as pain, increasing proptosis, decreasing eye movement, and

decreasing visual acuity; and one or more enlarged extraocular muscles with high intensity signals on T2-weighted MRI. Patients with active infection, inflammatory disease, or uncontrolled diabetes mellitus with proliferative retinopathy were excluded from iv GC therapy. Among patients with indications for iv GC therapy, those who were previously treated with GCs, other immunosuppressive agents, orbital radiation, or surgery for GO before this hospital admission for iv GC therapy were excluded from the analysis. Five patients were excluded based on these exclusion criteria, leaving 38 patients for evaluation in the study. Twenty patients admitted between January 1, 2006 and April 30, 2011 received high-dose iv GC therapy (HD group) and 18 patients admitted between April 1, 2010 and January 31, 2014 received low-dose iv GC therapy (LD group). The period between April 1, 2010 and April 31, 2011 was a transitional period from high-dose to low-dose iv GC therapy. All endocrinologists sequentially shifted their treatment regimen for GO to the low-dose regimen during this period. Thus, selection of the regimen for an individual patient was not arbitrary. Patients were followed at our institution or various clinics after discharge. The protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (E1934).

Treatment regimens

High-dose iv GC therapy consisted of iv mPSL 1.0 g daily for 3 consecutive days in weeks 1–3, followed by dose tapering with oral prednisolone (PSL). The initial dose of oral PSL for patients with body weight <50, 50–70, and >70 kg was 30, 35, and 40 mg/day, respectively, and these doses were tapered by 5 mg/week to 20 mg/day. The cumulative dose of iv mPSL was 9.0 g. Low-dose iv GC therapy consisted of iv mPSL 0.5 g daily for 3 consecutive days during weeks 1–3, followed by the same schedule of oral PSL as the HD group. The cumulative dose of iv mPSL was 4.5 g. During oral PSL therapy, all of the patients in both groups received orbital radiation therapy at a cumulative dose of 20 Gy in 10 fractions over a 2-week period. Patients were discharged when the dose of oral PSL was close to 20 mg/day. After discharge, patients continued to receive oral PSL therapy, which was tapered and discontinued based on the clinical judgment of each attending physician.

Clinical and ophthalmic measurements

Data from prior to treatment and at discharge were

extracted from the patients' medical records. Clinical ophthalmic parameters were measured by experienced endocrinologists and ophthalmologists. These included the 7-point Clinical Activity Score (CAS) [6, 14], diplopia score [15], proptosis measured using a Hertel exophthalmometer, and NOSPECS class [13] with modification of the definition of proptosis in class 3 based on the proposed guidelines for GO from the Japan Thyroid Association (JTA) as follows: grade o, <15 mm; grade a, <18 mm; grade b <21 mm, and grade c $\geq$ 21 mm (<http://www.japanthyroid.jp/doctor/img/basedou.pdf>).

Orbital MRI measurements

Orbital MRI was performed before treatment and at discharge using 10 different scanners. Short tau inversion recovery (STIR) MRI images of control subjects without lesions in the extraocular muscles or white matter were also evaluated. All control subjects gave informed consent. MRI of the orbit was independently analyzed with the freely available image processing software ImageJ (Wayne Rasband, National Institutes of Health, Bethesda, MD, USA) by an endocrinologist and a radiologist in a blinded manner. Measurements of the maximum cross-sectional area of each extraocular muscle and the retro-orbital space and the corrected SIR (cSIR) were included as imaging ophthalmic parameters. The maximum cross-sectional area of each extraocular muscle (levator palpebrae superioris and superior, lateral, medial, and inferior rectus) was estimated by manually outlining the muscle in a coronal T1-weighted (T1W) image taken perpendicular to the optic nerve. The superior rectus and levator palpebrae superioris were evaluated together because of their close proximity. The maximum cross-sectional area of the retro-orbital space was measured in a transverse T1W image. Extraocular muscle signal intensity was measured by manually outlining each muscle in a coronal STIR image. The mean signal intensity of the muscles was then calculated. The STIR slice with the most extraocular muscle inflammation before treatment was chosen, and the slice evaluated after treatment included the same areas. Three circular regions-of-interest (ROIs) of 0.10 cm² were placed in the ipsilateral white matter, excluding areas of ischemic change, and the mean signal intensity of these ROIs was calculated. SIR was expressed as the ratio of the mean signal intensity of the extraocular muscles to that of the ipsilateral white matter on the same slice.

To allow for a semiquantitative comparison of SIRs obtained from multiple institutions, we analyzed the SIRs of control subjects obtained using 6 scanners that were also used to evaluate study patients. MRI data acquired using the other 4 scanners were excluded from this evaluation because these scanners had a considerably shorter echo time or because STIR images for controls were unavailable. The corrected SIR (cSIR) for patients was determined as follows: SIRs of control subjects were calculated by the procedure described above, the mean SIR for all of the extraocular muscles of all the controls from each scanner was defined as the standard SIR for that scanner. cSIR was calculated as the ratio of the SIR for a given patient to the scanner-specific standard SIR.

Adverse effects

The incidence of the following common adverse effects associated with GC therapy during hospitalization were examined: hepatic dysfunction, hypertension, dyslipidemia, impaired glucose metabolism, gastric symptoms or bleeding, cardiovascular and cerebrovascular events, steroid psychosis, infection, and sleep disorder. The incidence of GC-induced hepatic dysfunction during oral PSL therapy after discharge was also examined. The definition of each adverse effect is shown in Supplementary Table 1.

Physical examination and vital signs

Patient height and weight were evaluated on admission. Vital signs, including blood pressure, pulse, and body temperature, were measured at least once daily, usually in the morning.

Laboratory testing

Blood samples were collected in the morning twice a week to monitor for hepatic dysfunction and impaired glucose metabolism and approximately once or twice a month for dyslipidemia during hospitalization. In addition, patients who had impaired glucose metabolism performed self-monitoring of blood glucose as needed. After discharge, outpatients underwent blood chemistry tests about once or twice every 2 months at our institution to monitor for hepatic dysfunction. TSH, free T3, and free T4 were assessed using the ECLusys kit (Roche Diagnostics GmbH, Mannheim, Germany). Thyroid stimulating antibodies (TSAb) were assessed using the TSAb kit (Yamasa, Tokyo, Japan). The manufacturer's reference ranges are shown in Table 1.

Table 1 Baseline characteristics of the study patients by iv GC dose

	HD group	LD group	<i>P</i> value
Number of patients	20	18	
Age (years) ^a	56.5 ± 10.8	60.2 ± 15.9	0.400
[range]	(37–74)	(21–80)	
Female (n, [%])	13 (65.0%)	13 (72.2%)	0.734
Body weight (kg) ^a	56.1 ± 12.3	55.8 ± 14.3	0.854
[range]	(37.5–81.6)	(39.0–98.1)	
BMI ^a	22.3 ± 3.5	22.5 ± 3.7	0.853
[range]	(16.2–28.4)	(18.0–32.0)	
Duration of treatment for GD (months) ^b	7.5 (1.0–46.8)	2.5 (0.8–14.3)	0.318
[range]	(0.0–348.0)	(0.0–540.0)	
Current medication for thyroid disease (n, [%])			1.000
Only ATD	11 (55.0%)	10 (55.6%)	
ATD + LT4	2 (10.0%)	3 (16.7%)	
LT4 (after ATD)	1 (5.0%)	0 (0.0%)	
LT4 (after thyroidectomy)	2 (10.0%)	1 (5.6%)	
LT4 (after radioiodine therapy)	0 (0.0%)	1 (5.6%)	
No treatment	4 (20.0%)	3 (16.7%)	
GD in remission	1 (5.0%)	0 (0.0%)	
Euthyroid Graves' [†]	1 (5.0%)	1 (5.6%)	
Duration from onset of GO (months) ^b	4.5 (3.0–6.0)	4.0 (2.0–6.3)	0.496
[range]	(2.0–11.0)	(2.0–10.0)	
Highest NOSPECS class (grade) (N [n/n/n], % of N [%])			0.606
Class 6 (a/b/c)	1 (0/1/0) (5.0%)	2 (1/1/0) (11.1%)	
Class 5 (a/b/c)	0 (0/0/0) (0.0%)	0 (0/0/0) (0.0%)	
Class 4 (a/b/c)	17 (6/11/0) (85.0%)	16 (6/9/1) (88.9%)	
Class 3 (a/b/c)	2 (0/0/2) (10.0%)	0 (0/0/0) (0.0%)	
Class 2, 1, or 0	0 (0.0%)	0 (0.0%)	
Smoker (n, [%])	11 (55.0%)	8 (44.4%)	0.746
Free T4 (ng/dL, normal range 0.88–1.62) ^b	1.34 (1.17–1.54)	1.29 (1.11–1.88)	0.930
[range]	(0.983–4.09)	(0.78–3.68)	
Free T3 (pg/mL, normal range 2.33–4.00) ^b	2.96 (2.64–4.23)	3.20 (2.64–5.24)	0.930
[range]	(2.35–13.65)	(1.39–9.36)	
TSH (μIU/mL, normal range 0.500–5.000) ^b	0.379 (0.005–1.083)	0.010 (0.005–0.757)	0.397
[range]	(0.016–10.450)	(0.005–5.830)	
TSAb (%; normal range <180) ^b	472 (251–1,413)	353 (239–1,160)	0.520
[range]	(135–3,450)	(149–2,860)	
HCV antibody positive (n, [%]) [‡]	1 (5.0%)	1 (5.6%)	1.000
HBs antigen positive (n, [%]) [‡]	0 (0.0%)	0 (0.0%)	1.000
Comorbidity (n, [%])			
Hypertension	8 (40.0%)	5 (27.8%)	0.506
Dyslipidemia	7 (35.0%)	5 (27.8%)	0.734
Impaired glucose metabolism [*]	10 (50.0%)	13 (72.2%)	0.489
Diabetes mellitus	2 (10.0%)	4 (22.2%)	0.658
Sleep disorder	2 (10.0%)	2 (11.1%)	1.000
Duration from first day of treatment to discharge (days) ^a	43.2 ± 10.9	45.7 ± 6.9	0.416
[range]	(24.0–68.0)	(36.0–57.0)	
Cumulative dose of oral prednisolone (mg) ^a	633.5 ± 217.6	683.1 ± 137.5	0.413
[range]	(140.0–1,105.0)	(485.0–930)	

Data are expressed as ^a means ± SD or ^b medians (interquartile range). *P* values were calculated using the ^a *t*-test or the ^b Wilcoxon rank-sum test. [†] Euthyroid Graves' was defined as ophthalmopathy and positive TSH receptor antibodies or TSAb with normal free T4 and TSH. [‡] HCV antibody and HBs antigen were not tested in 3 patients in the HD group and 1 patient in the LD group. ^{*} Number of patients confirmed to have impaired glucose metabolism by the 75 g oral glucose tolerance test or number of patients with a confirmed diagnosis of diabetes mellitus are presented. iv, intravenous; GC, glucocorticoid; HD group, patients who received high-dose intravenous glucocorticoid therapy; LD group, patients who received low-dose intravenous glucocorticoid therapy; BMI, body mass index; GD, Graves' disease; ATD, antithyroid drugs; LT4, levothyroxine; GO, Graves' ophthalmopathy; TSAb, thyroid stimulating antibodies; HCV, hepatitis C virus; HBs, hepatitis B surface.

Primary and secondary objectives

The primary objective was to compare the safety and efficacy of high-dose and low-dose iv GC therapy for GO. The efficacy of the 2 regimens was compared by evaluating the differences in changes and response rates of the ophthalmic parameters. A response in an ophthalmic parameter was defined as a decrease in CAS, diplopia score, and sum of the cross-sectional areas of the extraocular muscles or the retro-orbital space after treatment. A response in proptosis was defined as a ≥ 2 mm decrease in either eye after treatment without a ≥ 2 mm increase in the other eye. Worsening of an ophthalmic parameter was defined as an increase in CAS, diplopia score, and sum of the cross-sectional areas of the extraocular muscles and the retro-orbital space after treatment. A worsening of proptosis was defined as a ≥ 2 mm increase in either eye after treatment. No response in an ophthalmic parameter was defined as the absence of a response or worsening. Overall safety was evaluated based on the incidence of adverse effects, which was expressed as a number or proportion of patients with at least one adverse effect. All 38 patients were included in the analysis of safety and efficacy. We also performed an analysis of efficacy in the subset of patients who completed the treatment regimen (per protocol set) as a sensitivity analysis. To evaluate long-term safety and efficacy, we assessed the incidence of GO progression within 1 year of discharge and the incidence of GC-induced hepatic dysfunction after discharge while the patient remained on oral PSL therapy. The follow-up data for hepatic dysfunction were collected from medical records up to January 31, 2016. GO progression was defined as the need for hospitalization to receive additional iv GC therapy for GO.

The secondary objectives were to evaluate correlations among serum TSAb levels, CAS, proptosis, and pretreatment ophthalmic MRI parameters; compare the associations between pretreatment serum TSAb levels, CAS, and cSIR; and investigate differences in ophthalmic parameters after treatment at the 2 different iv GC doses.

Statistical analysis

The baseline characteristics of the patients in each group are expressed as means $\pm$ SD, medians (interquartile range or range), or percentages. These data were compared using Fisher's exact test for categorical variables and the *t*-test or the Wilcoxon rank-sum test

for continuous variables. To compare efficacy between the 2 groups, Fisher's exact test was used for categorical variables, and analysis of covariance (ANCOVA) adjusted for pretreatment values or the *t*-test was used for continuous variables such as changes in CAS, proptosis, sum of the cross-sectional area of the extraocular muscles and the retro-orbital space, and cSIR. Differences and 95% confidence intervals in proportions were calculated to compare the incidence of adverse effects between the 2 groups. To evaluate correlations among clinical and imaging ophthalmic measurements, Spearman's rank correlation coefficients (ρ) were used. In addition, to investigate the association between pretreatment ophthalmic parameters with ophthalmic changes after treatment in each group, regression analysis was conducted by treatment regimen, with change as the response variable and pretreatment values as explanatory variables. We also generated regression models that included group and interaction terms to compare the associations between the 2 groups. Missing values were not imputed. Statistical analyses were performed with JMP[®] Pro 11 (SAS Institute, Cary, NC, USA).

Results

Background

A study flow diagram is shown in Fig. 1. Three patients in the HD group and 1 patient in the LD group did not complete the treatment regimen. One of the patients in the HD group had recurrence of redness and swelling of the eyelids during oral PSL therapy and received additional iv GCs (final cumulative iv mPSL dose, 12.0 g) and an cyclosporine after iv GC therapy. Safety and efficacy data for this patient prior to the start of the immunosuppressive agent was used, instead of data at discharge. The remaining 3 patients were evaluated at discharge. There were no patients who discontinued the treatment regimen because of adverse events caused by GCs. The profiles of patients in each group are shown in Table 1. No significant differences in baseline characteristics and comorbidities were detected between the 2 groups. After discharge, 4 patients (1 patient in the HD group and 3 patients in the LD group) were followed at different clinics, leaving 34 patients (19 patients in the HD group and 15 patients in the LD group) who received follow-up at our institution, as shown in Fig. 1.

Fig. 1 Study flow diagram

GO, Graves' ophthalmopathy; iv GC, intravenous glucocorticoid; PSL, prednisolone.

Efficacy

Ophthalmic parameters before and after treatment are shown in Table 2. Except for the diplopia score ($P = 0.038$), there were no significant differences in pretreatment (before treatment) CAS ($P = 0.411$), NOSPECS ($P = 0.606$), proptosis ($P = 0.168$), sum of the cross-sectional area of the extraocular muscles and the retro-orbital space ($P = 0.685$ and $P = 0.816$, respectively), and cSIR ($P = 0.463$) between the groups.

There were no significant differences in changes and responses in ophthalmic parameters after treatment between the 2 groups. Very similar results were obtained in the per protocol set (data not shown).

GO progression was observed in 1 patient in each group within 1 year of discharge. The patient in the HD group received 9.0 g of iv GCs, as well as oral PSL and cyclosporine therapy. The patient in the LD group received 1.5 g of iv GCs and oral PSL therapy. After additional treatments, the clinical manifestations of these patients improved and GO stabilized.

Safety

Adverse effects were observed in 18 of 20 patients in the HD group (90.0%) and 16 of 18 patients in the LD group (88.9%). There were no significant differences in the overall incidence of adverse effects between the 2 groups (Table 3).

The incidence of each adverse effect is shown in Table 3. Ten patients had hepatic dysfunction, including 3 with hepatotoxicity due to GCs (one in the HD group and 2 in the LD group) and 7 due to medications that were started just before or during treatment, including lansoprazole and thiamazole. One patient in the LD group without hepatitis B and C serologic testing had hepatic dysfunction due to lansoprazole. All the other patients with hepatic dysfunction due to GCs were negative for at least hepatitis B surface antigen. The patient in the HD group with GC-associated hepatotoxicity had positive hepatitis C serology and fatty liver. Alanine aminotransferase (ALT) in this patient were slightly elevated before treatment (32 U/L; upper limit of normal,

Table 2 Clinical and imaging ophthalmic parameters before and after treatment by group

Parameter	HD group (n=20)		LD group (n=18)		Difference in response [†] between groups <i>P</i> value ^a	Difference in change (after – before treatment) between groups	
	Before treatment	After treatment	Before treatment	After treatment		Adjusted mean ^c (95% CI)	<i>P</i> value
CAS [20/18] * (range)	2.1 ± 1.8 (0–7)	0.7 ± 1.1 (0–4)	2.6 ± 1.5 (0–5)	0.9 ± 1.0 (0–3)		0.05 (–0.25, 0.36)	0.727 ^b
0 (n, [%])	4 (20.0%)	12 (60.0%)	1 (5.6%)	8 (44.4%)			
1 (n, [%])	4 (20.0%)	5 (25.0%)	4 (22.2%)	6 (33.3%)			
2 (n, [%])	5 (25.0%)	2 (10.0%)	5 (27.8%)	2 (11.1%)			
3 (n, [%])	4 (20.0%)	0 (0.0%)	3 (16.7%)	2 (11.1%)			
4 (n, [%])	1 (5.0%)	1 (5.0%)	2 (11.1%)	0 (0.0%)			
5 (n, [%])	1 (5.0%)	0 (0.0%)	3 (16.7%)	0 (0.0%)			
6 (n, [%])	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
7 (n, [%])	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Decrease (n, [%])		13 (65.0%)		13 (72.2%)	0.734		
No change (n, [%])		7 (35.0%)		5 (27.8%)			
Increase (n, [%])		0 (0.0%)		0 (0.0%)			
Diplopia score [19/18] *							
1) Absent	0 (0.0%)	1 (5.3%)	1 (5.6%)	1 (5.6%)			
2) Intermittent	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
3) Inconsistent	9 (47.4%)	12 (63.2%)	14 (77.8%)	17 (94.4%)			
4) Constant	10 (52.6%)	6 (31.6%)	3 (16.7%)	0 (0.0%)			
Decrease (n, [%])		6 (31.6%)		3 (16.7%)	0.447		
No change (n, [%])		12 (63.2%)		15 (83.3%)			
Increase (n, [%])		1 (5.3%)		0 (0.0%)			
Proptosis (mm) [18/17] * (range)	20.5 ± 3.4 (14.5–27.5)	18.8 ± 3.0 (14.5–24)	18.6 ± 3.6 (12.5–22.8)	18.1 ± 2.9 (12.5–22.5)		0.37 (–0.15, 0.89)	0.153 ^b
Decrease ≥ 2 mm (n, [%])		11 (61.1%)		5 (29.4%)	0.092		
No change <2 mm (n, [%])		6 (33.3%)		10 (58.8%)			
Increase ≥ 2 mm (n, [%])		1 (5.6%)		2 (11.8%)			
MRI findings							
Sum of the cross-sectional area of the extraocular muscles (mm ²) [18/18] * (range)	439.8 ± 132.3 (289.2–751.3)	362.3 ± 92.6 (250.9–609.1)	462.4 ± 146.0 (303.3–783.1)	387.1 ± 114.0 (262.5–622.4)		4.42 (–6.97, 15.81)	0.436 ^b
Decrease (n, [%])		18 (100.0%)		17 (94.4%)	1.000		
Increase (n, [%])		0 (0.0%)		1 (5.6%)			
Sum of the cross-sectional area of the retro-orbital space (mm ²) [20/17] * (range)	1,518.0 ± 229.2 (1,174.2–1,974.0)	1,424.4 ± 191.6 (1,042.7–1,771.1)	1,500.0 ± 235.0 (1,208.7–1,940.6)	1,447.6 ± 234.2 (1,036.0–1,862.0)		18.93 (–13.84, 51.69)	0.249 ^b
Decrease (n, [%])		15 (75.0%)		12 (70.6%)	1.000		
Increase (n, [%])		0 (0.0%)		5 (29.4%)			
cSIR [15/13] * (range)	1.63 ± 0.47 (0.87–2.31)	1.19 ± 0.40 (0.80–2.36)	1.51 ± 0.35 (1.01–2.19)	1.15 ± 0.35 (0.78–2.09)		0.02 (–0.08, 0.12)	0.679 ^b
Decrease (n, [%])		14 (93.3%)		13 (100.0%)	1.000		
Increase (n, [%])		1 (6.7%)		0 (0.0%)			

Data are expressed as means ± SD or medians (interquartile range). * Number of patients with available data in the HD group / LD group.

[†] Response was defined as an improvement in the value or grade of an ophthalmic parameter after treatment. *P* values: ^a Fisher's exact test for comparing responses between groups; ^b ANCOVA for comparing changes between groups. ^c Adjusted mean is the estimate of the change with treatment based on analysis of covariance (ANCOVA) or the *t*-test between groups (ΔLD group – ΔHD group). HD group, patients who received high-dose intravenous glucocorticoid therapy; LD group, patients who received low-dose intravenous glucocorticoid therapy; CI, confidence interval; CAS, Clinical Activity Score; MRI, magnetic resonance imaging; cSIR, corrected signal intensity ratio.

27 U/L), peaked at 5 weeks after the start of treatment (121 U/L), and gradually returned to baseline 6 months after the completion of oral GC therapy. Serum alkaline phosphatase (ALP) in this patient stayed in the normal range during the course of treatment. The 2 patients in the LD group with GC-associated hepatotoxicity had no serologic evidence of viral hepatitis. They had elevated hepatic enzymes at 1 and 4 weeks, respectively, after starting treatment. In one patient, peak ALT was 114 U/L (upper limit of normal, 42 U/L) and ALP was within normal range at week 1. In the other patient, peak ALT was 159 U/L (upper limit of normal, 27 U/L) and ALP was 562 U/L (upper limit of normal, 359 U/L) at week 4. They had spontaneous improvement over the next 2 months. However, whether elevation of hepatic enzymes in these 2 patients was related to other drugs, including verapamil, bisoprolol, heparin, or thiamazole, which were started just before treatment, was not clear. During post-discharge follow-up, GC-induced hepatic dysfunction was observed in 3 patients in each group

while on oral PSL therapy. The profiles of patients with hepatic dysfunction are shown in Table 4. In these patients, elevated hepatic enzymes gradually decreased into the normal range or to baseline values after oral PSL was tapered or discontinued.

The incidence of dyslipidemia was non-statistically significantly higher, and the incidence of impaired glucose metabolism was significantly lower in the HD group ($P = 0.100$ and $P = 0.045$, respectively). All patients with impaired glucose metabolism have a history of this condition before treatment. More specifically, 2 of 10 patients in the HD group and 7 of 13 patients in the LD group with impaired glucose metabolism before treatment required new medication or adjustment of medication dose for better management of their glucose profile. No patients with impaired glucose metabolism had proliferative diabetic retinopathy or exacerbation of retinopathy during treatment. There was no significant difference in the incidence of other adverse effects between the 2 groups (Table 3).

Table 3 Incidence of adverse effects associated with iv GC therapy by group

	Number of patients (proportion)		Difference in proportions between groups (LD group – HD group)		
	HD group (n=20)	LD group (n=18)	Estimate (%)	95% CI (% , %)	P value
Any adverse event	18 (90.0%)	16 (88.9%)	-1.1	(-22.6, 19.9)	0.900
Hepatic dysfunction	1 (5.0%)	2 (11.1%)	6.1	(-13.8, 25.6)	0.557
Hypertension	0 (0.0%)	1 (5.6%)	5.6	(-10.3, 21.2)	0.498
Dyslipidemia	7 (35.0%)	2 (11.1%)	-23.9	(-46.8, 4.1)	0.100
Impaired glucose metabolism	2 (10.0%)	7 (38.9%)	28.9	(0.5, 52.2)	0.045
Gastric symptoms	2 (10.0%)	1 (5.6%)	-4.4	(-23.1, 15.8)	0.714
Infection	1 (5.0%)	2 (11.1%)	6.1	(-13.8, 25.6)	0.557
Sleep disorder	15 (75.0%)	11 (61.1%)	-13.9	(-41.1, 15.7)	0.380

iv, intravenous; GC, glucocorticoid; HD group, patients who received high-dose iv GC therapy; LD group, patients who received low-dose iv GC therapy; CI, confidence interval.

Table 4 Profile of all patients with GC-induced hepatic dysfunction during oral PSL therapy

Patient	Group	Age (years)	Sex	BW (kg)	HCV serology	Cumulative dose of iv GCs (g)	Cumulative dose of oral PSL at the onset of hepatic dysfunction (mg)	Duration from the first day of treatment to the onset of hepatic dysfunction (days)	Peak ALT/ALP *** (U/L / U/L)
1	HD	66	M	64.4	N	18.0	4,245	383	240 ** / 152
2	HD	69	M	45.6	Not tested	9.0	820	58	67 ** / data not available
3	HD	42	F	64.1	N	9.0	830	49	255 * / 139
4	LD	80	F	46.5	N	4.5	2,365	282	11 ** / 457
5	LD	73	M	63.7	N	4.5	630	45	25 ** / 566
6	LD	46	M	61.5	N	4.5	1,845	141	24 ** / 527

GC, glucocorticoid; PSL, prednisolone; BW, body weight; HCV, hepatitis C virus; ALT, alanine aminotransferase; ALP, alkaline phosphatase; HD, group of patients who received high-dose intravenous glucocorticoid therapy; LD, group of patients who received low-dose intravenous glucocorticoid therapy; M, male; F, female; N, negative. The upper limit of the normal range for ALT was * 28 U/L or ** 43 U/L. *** The upper limit of the normal range for ALP was 359 U/L.

Correlations among pretreatment clinical and imaging ophthalmic parameters

Correlations among pretreatment clinical and imaging parameters are shown in Table 5. Serum TSAb levels were correlated with CAS, proptosis, and MRI parameters ($\rho > 0.400$). CAS was correlated with proptosis and the sum of the area of the retro-orbital space, while cSIR was correlated with the sum of the cross-sectional area of the extraocular muscles and the sum of the cross-sectional area of the retro-orbital space ($\rho > 0.400$).

Comparison of associations in ophthalmic parameters with response to treatment

The associations between pretreatment serum TSAb level, CAS, and cSIR and changes in CAS, proptosis,

and MRI parameters are expressed as slope estimates by treatment group (Table 6). Baseline serum TSAb level, CAS, and cSIR were negatively correlated with changes in ophthalmic parameters in both groups, except for CAS and the change in the sum of the area of the extraocular muscles in the HD group and cSIR and the change in CAS and the sum of the area of the retro-orbital space in the LD group. Some slope estimates were statistically significant, but there were no significant differences between the 2 groups in each slope estimate (P for interaction > 0.05). However, the slope estimates for baseline cSIR and changes, especially in MRI findings, appeared to be steeper in the HD group than in the LD group, indicating that pretreatment cSIR might be clinically useful for determining the iv GC dose.

Table 5 Spearman's rank correlation coefficients (ρ) for serum TSAb level, CAS, and cSIR with respect to clinical and imaging ophthalmic parameters before treatment

Parameter before treatment	Serum TSAb level	CAS	cSIR
	ρ	ρ	ρ
Serum TSAb level	—	0.442 **	0.488 **
CAS	0.442 **	—	0.244
Proptosis (mm)	0.473 **	0.504 *	0.282
MRI findings			
Sum of the cross-sectional area of the extraocular muscles (mm ²)	0.517 **	0.329	0.666 **
Sum of the cross-sectional area of the retro-orbital space (mm ²)	0.401 *	0.440 **	0.424 *

* $P < 0.05$, ** $P < 0.01$. TSAb, thyroid stimulating antibodies; CAS, Clinical Activity Score; cSIR, corrected signal intensity ratio; MRI, magnetic resonance imaging.

Table 6 Associations between pretreatment CAS, cSIR, and serum TSAb level and changes in ophthalmic parameters after treatment by group

Change in ophthalmic parameter after treatment	Serum TSAb level ($\times 100\%$)			CAS			cSIR		
	HD group	LD group	P value for interaction ^b	HD group	LD group	P value for interaction ^b	HD group	LD group	P value for interaction ^b
	Slope estimate ^a (95% CI)	Slope estimate ^a (95% CI)		Slope estimate ^a (95% CI)	Slope estimate ^a (95% CI)		Slope estimate ^a (95% CI)	Slope estimate ^a (95% CI)	
Δ CAS	-0.01 (-0.08, 0.06)	-0.06 (-0.15, 0.04)	0.471	-0.60 (-0.86, -0.34)	-0.55 (-0.84, -0.26)	0.884	-0.45 (-2.53, 1.64)	0.10 (-2.75, 2.94)	0.741
Δ Proptosis (mm)	-0.04 (-0.13, 0.04)	-0.05 (-0.14, 0.04)	0.913	-0.32 (-0.82, 0.17)	-0.49 (-0.92, -0.05)	0.624	-2.11 (-4.24, 0.02)	-0.72 (-3.19, 1.76)	0.380
MRI findings									
Δ Sum of the cross-sectional area of the extraocular muscles (mm ²)	-2.47 (-4.78, -0.17)	-3.84 (-6.82, -0.85)	0.457	0.55 (-15.23, 16.33)	-10.29 (-26.97, -6.38)	0.328	-89.62 (-146.68, -32.55)	-23.83 (-106.15, 58.49)	0.161
Δ Sum of the cross-sectional area of the retro-orbital space (mm ²)	-3.27 (-7.96, 1.41)	-4.60 (-11.88, 2.68)	0.746	-18.27 (-45.55, 9.01)	-8.30 (-48.06, 31.47)	0.660	-127.11 (-222.43, -31.79)	16.66 (-222.32, 255.64)	0.181

^a Slope estimates from the results of the regression analysis; ^b P value was calculated by analysis of covariance (ANCOVA); CAS, the Clinical Activity Score; cSIR, corrected signal intensity ratio; TSAb, thyroid stimulating antibodies; HD group, patients who received high-dose intravenous glucocorticoid therapy; LD group, patients who received low-dose intravenous glucocorticoid therapy; MRI, magnetic resonance imaging; CI, confidence interval.

Discussion

In this study, we retrospectively evaluated the safety and efficacy of high-dose and low-dose iv GC therapy in patients with GO. This is the first study in which the efficacy of the 2 regimens was compared using MRI. No significant differences in safety and efficacy between the 2 regimens were detected in this study. No serious adverse events, including severe hepatic dysfunction, occurred during the observation period.

This is also the first study to compare the safety and efficacy of conventional high-dose (cumulative iv GC dose >8.0 g) and low-dose (cumulative iv GC dose ≤ 8.0 g) iv GC therapy with the same treatment protocol. To the best of our knowledge, there were 2 randomized clinical trials investigating the optimal dose and schedule of iv GC therapy [16, 17]. When Bartalena *et al.* compared the safety and efficacy of 3 low-dose iv GC regimens (cumulative doses of 2.25 g, 4.98 g, and 7.47 g), they concluded that the higher-dose regimen provided a short-term advantage in efficacy, but had slightly greater toxicity [16]. In this study, although the HD group had slightly better changes in ophthalmic parameters and response rates, no statistically significant differences were detected in ophthalmic parameters or the safety profile between patients on the 2 regimens. In the follow-up study, 1 in each group had GO progression within 1 year after discharge. As for hepatotoxicity, 3 patients in each group had GC-induced hepatic dysfunction during oral PSL therapy after discharge. However, in the follow-up study for safety and efficacy, the effects of different cumulative doses of oral PSL and possible variations in clinical courses of GD need to be considered when long-term safety and efficacy are evaluated in detail.

The overall incidence of adverse effects did not differ significantly between the groups on high-dose and low-dose iv GC therapy, and no serious cardiovascular and cerebrovascular events or severe hepatic dysfunction occurred during the observation period. The total incidence of adverse effects, approximately 90%, was higher than the 17–56% reported in previous studies [18, 19]. This difference may be due to different criteria for adverse effects among the studies. Hepatic dysfunction is a major concern in GC therapy for GO patients. Severe hepatic dysfunction occurs in 0.8% of GO patients, especially during treatment with high-dose iv GCs [4]. Hepatic dysfunction occurred more frequently during treatment with iv GC and during oral

PSL therapy in this study (Table 3), but this higher frequency may be due to the criteria we used, which was proposed for the initial screening of drug-induced liver injury (Supplementary Table 1) [20–22]. The mechanism of GC-related hepatic dysfunction is unclear, but the presence of positive viral hepatitis markers has been suggested as a risk factor for liver damage [5]. We did not find a GC dose-dependency for hepatotoxicity or a relationship between positive serology for viral hepatitis and GC-induced hepatotoxicity. Since even a low dose of iv GCs can cause severe hepatic dysfunction [23], careful monitoring is required for patients on iv GC therapy at any dose. The incidence of dyslipidemia was non-statistically significantly higher with the high-dose regimen, suggesting a dose-dependent effect of GCs on lipid metabolism. The incidence of impaired glucose metabolism was significantly higher in the low-dose regimen. This result was probably due to selection bias, since more patients in the LD group (72.2%) had a pretreatment history of impaired glucose metabolism than in the HD group (50.0%) (Table 1). Patients diagnosed with impaired glucose metabolism are likely to receive more intensive glucose management than those without this condition. In this study, we have to consider the possibility that patients in the LD group, which included more recent cases, received more intensive and careful management of their glucose profiles as well as other possible adverse effects during iv GC therapy. Therefore, the safety results for iv GC therapy need to be interpreted with caution.

In this study, we examined correlations among pretreatment clinical and imaging ophthalmic parameters and investigated factors that may be useful for determining the iv GC dose. Pretreatment serum TSAb levels correlated well with ophthalmic parameters, as previously reported [24]. They were negatively correlated with post-treatment changes in ophthalmic parameters, as well as CAS and cSIR. However, serum TSAb levels were not useful in determining the dose of iv GCs. CAS is reported to represent disease activity in GO and correlates with SIR on MRI, which represents the inflammatory activity of orbital tissues [25]. In this study, CAS correlated well with proptosis, but not so well with MRI findings including cSIR. This may be because pretreatment CAS in our study was relatively low, making it difficult to detect any correlations, or that CAS may not necessarily reflect the inflammatory condition of the retro-orbital tissues, especially the extraocular muscles. On the other hand, pretreatment cSIR showed stronger

correlations with the sum of the cross-sectional area of the extraocular muscles than other ophthalmic parameters, reflecting the inflammatory activity of the muscles. In addition, pretreatment cSIR in the HD group appeared to have stronger clinical associations with changes in MRI findings than in the LD group, although slope estimates were not statistically different between the 2 groups. These results suggest that a high-dose iv GC regimen may be recommended for GO treatment when patients have a high cSIR on MRI. However, the clinical significance of correlations between pretreatment cSIR and posttreatment changes in other ophthalmic parameters by iv GC dose and the appropriate cSIR cut-off value for determining the optimal dose of iv GCs still need to be investigated in further studies.

This study has several limitations. At our institution, we attach great importance to treating patients with progressing eye symptoms, such as worsening of eye movement, and administer iv GCs to patients with a lower CAS. Thus, pretreatment CAS was relatively low in this study, in contrast to other recent studies. This makes it difficult to detect a difference in the efficacy of different iv GC doses using CAS. For MRI evaluation, it is desirable to use the same scanner with a uniform pulse sequence for comparing ophthalmic parameters among patients to minimize inter-scanner variability. However, we were unable to estimate inter-scanner variability and inter-individual variability among scanners. Consequently, we were unable to suggest reasonable cut-off values for each ophthalmic MRI parameter to judge the response to treatment. We calculated cSIRs to partly overcome this problem of inter-scanner variability in SIRs. Since this is not a standard method for comparing SIRs from different MRI scanners, this approach requires further verification. We did not define the outcome of GO by evaluating a combination of changes in ophthalmic parameters because we were not able to collect complete information about ophthalmic parameters that were

evaluated in prior large prospective studies [16, 17]. For example, we were not able to obtain grades in each class of the NOSPECS classification from the patients' medical records. Thus, we presented only the number of patients in each class and grade before treatment in Table 1. Consequently, we evaluated only pretreatment and posttreatment changes in each ophthalmic parameter to avoid the efficacy results becoming arbitrary. Regarding adverse effects, minor effects of GCs might have gone undetected because of the criteria that we used in this study and the small number of patients, which may be insufficient for detecting rare adverse effects.

In conclusion, there were no significant differences in overall safety and efficacy between high-dose and low-dose iv GC therapy for patients with moderate-to-severe active GO at our institution. Randomized clinical trials with longer observation periods and evaluation with MRI are required to establish the optimal regimen of iv GC therapy for patients with GO.

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Disclosures

The authors have nothing to disclose.

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Supplementary Table 1 Definition of adverse events associated with iv GC therapy

Hepatic dysfunction: ALT more than twice the upper limit of the normal range or ALP above the upper limit of the normal range associated with GC therapy was defined as drug-induced hepatic dysfunction according to the criteria in the 2004 Digestive Disease Week-Japan (DDW-J) scale. When ALT or ALP was above the upper limit of the normal range before treatment, drug-induced hepatic dysfunction was defined as an increase in ALT or ALP during the course of treatment. Cases of hepatic dysfunction due to medications other than GCs were excluded. GC-induced hepatic dysfunction during oral PSL therapy was defined as laboratory changes described above after discharge that required tapering or discontinuation of PSL.

Hypertension, hyperlipidemia, impaired glucose metabolism, gastric symptoms, infection, and sleep disorder (new onset or exacerbation): Requiring new medication or any adjustment in medication to achieve better management was defined as new onset or exacerbation, respectively.

Other: Any occurrence of gastric bleeding, cardiovascular or cerebrovascular events, steroid psychosis, or other adverse events considered to be due to GCs was recorded.

iv, intravenous; GC, glucocorticoid; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PSL, prednisolone.

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