Efficacy and Safety of Three Different Cumulative Doses of Intravenous Methylprednisolone for Moderate to Severe and Active Graves' Orbitopathy

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Background: Optimal doses of iv glucocorticoids for Graves' orbitopathy (GO) are undefined.

Methods: We carried out a multicenter, randomized, double-blind trial to determine efficacy and safety of three doses of iv methylprednisolone in 159 patients with moderate to severe and active GO. Patients were randomized to receive a cumulative dose of 2.25, 4.98, or 7.47 g in 12 weekly infusions. Efficacy was evaluated objectively at 12 wk by blinded ophthalmologists and subjectively by blinded patients (using a GO specific quality of life questionnaire). Adverse events were recorded at each visit.

Results: Overall ophthalmic improvement was more common using 7.47 g (52%) than 4.98 g (35%; $P = 0.03$) or 2.25 g (28%; $P = 0.01$). Compared with lower doses, the high-dose regimen led to the most improvement in objective measurement of ocular motility and in the Clinical Activity Score. The Clinical Activity Score decreased in all groups and to the least extent with 2.25 g. Quality of life improved most in the 7.47-g group, although not reaching statistical significance. No significant differences occurred in exophthalmos, palpebral aperture, soft tissue changes, and subjective diplopia score. Dysthyroid optic neuropathy developed in several patients in all groups. Because of this, differences among the three groups were no longer apparent at the exploratory 24-wk visit. Major adverse events were slightly more frequent using the highest dose but occurred also using the lowest dose. Among patients whose GO improved at 12 wk, 33% in the 7.47-group, 21% in the 4.98-group, and 40% in the 2.25-group had relapsing orbitopathy after glucocorticoid withdrawal at the exploratory 24-wk visit.

Conclusions: The 7.47-g dose provides short-term advantages over lower doses. However, this benefit is transient and associated with slightly greater toxicity. The use of a cumulative dose of 7.47 g of methylprednisolone provides short-term advantage over lower doses. This may suggest that an intermediate-dose regimen be used in most cases and the high-dose regimen be reserved to most severe cases of GO. **(*J Clin Endocrinol Metab* 97: 4454–4463, 2012)**

Graves' orbitopathy (GO) is an orbital autoimmune disorder (1, 2) closely linked to thyroid autoimmunity, mainly Graves' disease (3). After an initial progressive inflammatory period (active phase), GO stabilizes and eventually subsides (inactive phase) (3). Immunosuppressive treatment is effective when GO is active (3). GO is invalidating and disfiguring, profoundly impairing the quality of life (QoL) (4). Unfortunately, the majority of patients are dissatisfied with the outcomes of medical treatment (4, 5), and rehabilitative surgery is frequently needed for residual exophthalmos, ocular motility impairment, and/or eyelid malposition (6).

Highly effective treatments with no/minimal side effects are not available. Targeted biological therapies are

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Abbreviations: CAS, Clinical Activity Score; DON, dysthyroid optic neuropathy; EUGOGO, European Group on Graves' Orbitopathy; GC, glucocorticoid; GO, Graves' orbitopathy; HD, high dose group; LD, low dose group; MD, middle dose group; MP, methylprednisolone; QoL, quality of life; RCT, randomized clinical trial; TRAb, autoantibody to the TSH receptor.

under evaluation (7), but evidence is lacking concerning their efficacy and safety (8). Thus, glucocorticoids (GCs) still represent the first-line treatment (9, 10). The iv route is more effective and better tolerated than the oral route (11–13). However, the optimal treatment regimen is still undefined (14). A common protocol uses a 4.5-g cumulative dose of methylprednisolone (MP) subdivided into 12 weekly infusions (12). No study has so far investigated the efficacy and safety of different cumulative doses of iv GCs.

To address this issue, the European Group on Graves' Orbitopathy (EUGOGO) undertook a multicenter, double-blind, randomized clinical trial (RCT) comparing three different cumulative doses of iv MP (2.25, 4.98, 7.47 g) in a large series of patients with moderate to severe and active GO.

Patients and Methods

Patients and study design

From December 2005 to December 2010, patients with moderate to severe and active GO, defined according to the EUGOGO consensus statement (9), seen at eight EUGOGO centers (Amsterdam, The Netherlands; Brussels, Belgium; Lyon, France; Milan, Italy; Olten, Switzerland; Pisa, Italy; Thessaloniki, Greece; and Varese, Italy) were invited to participate in the study if they met inclusion criteria (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Enrolled patients were randomized (using sealed envelopes in blocks of six) to receive iv MP (Solumedrol; Pfizer, Karlsruhe, Germany) to a cumulative dose of 2.25 g [low dose (LD) group], 4.98 g [middle dose (MD) group], or 7.47 g [high dose (HD) group], subdivided in 12 weekly infusions. In each group the starting dose (250 mg in the LD group, 540 mg in the MD group, 830 mg in the HD group) was maintained for the first six infusions and then halved (125 mg in the LD group, 290 mg in the MD group, 415 mg in the HD group) for the remaining six infusions. The highest dose was dictated by what is currently believed to be safe, at least in terms of hepatotoxicity (9); the others were chosen to cover the range likely to be associated with some efficacy. The precise dose (to a decimal point) was selected to make the infusion calculations easy for administration. The regimen did not include the use of oral GCs in decreasing doses after finishing the iv therapy. Both ophthalmologists and patients were blinded to treatment assignments. Patients were treated by endocrinologists and received gastric protection and, in most cases, oral bisphosphonates. The study was approved by the institutional review boards of the participating centers. Written informed consent was obtained from all participants.

Primary objectives

There were two primary objectives at 12 wk: efficacy and safety. Efficacy comprised the overall ophthalmic assessment, and the subjective patient's GO-QoL questionnaire. The overall response to treatment was rated as improvement, no change, or deterioration (Supplemental Table 1). Adverse events were defined as major and minor, as indicated in Table 1.

Study procedures

Patients were evaluated at baseline and at 6, 12, and 24 wk. Eye examinations were performed using a modified EUGOGO case record form and the Color Atlas (www.eugogo.eu) (15). At baseline and at follow-up visits, the same ophthalmologist at each center evaluated patients and recorded palpebral aperture (in millimeters) in primary position, soft tissue involvement, exophthalmos (in millimeters), involvement of extraocular muscles (ductions measured in degrees), and visual acuity (in decimals using the Snellen chart) (Supplemental Table 1). Also, the 7-point Clinical Activity Score (CAS) (spontaneous retrobulbar pain, pain on attempted eye movements, conjuctival hyperemia, eyelid redness, chemosis, swelling of the caruncle, swelling of the eyelids) (16) and the diplopia score of Bahn and Gorman (17) were assessed (Supplemental Table 1). QoL was evaluated with the validated disease-specific GO-QoL questionnaire (www.eugogo.eu) (Supplemental Table 1) (18). Blood samples were obtained at all visits to assess thyroid function (serum free T_4, total or free T_3, and TSH) and autoantibodies against thyroid peroxidase and the TSH receptor. Adverse events were recorded at all visits.

Full assessments were done at baseline, and at 6, 12, and 24 wk. Outcomes for purposes of the primary objectives were assessed at 12 wk. Assessment at 24 wk was exploratory to evaluate maintenance of the response at 12 wk.

Statistical analysis

The sample size was based on the results of previous RCTs (11, 12), assuming a response rate of 80% in the HD group, 65% in the MD group, and 55% in the LD group. To detect such a difference with 80% power and a significance level of $P = 0.05$, each study group was designed to comprise 53 patients. Patients withdrawn from the study prematurely for any reason were included in the analysis if the 6-wk evaluation was available; results of their last assessment were carried forward and evaluated as the last visit. Patients lost to follow-up before the 6-wk visit were excluded and replaced.

Baseline characteristics of the three groups were expressed as means (±SD) or prevalence, as appropriate. The treatment

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TABLE 1. Baseline characteristics of the patients

	LD	MD	HD	*P* value
Demographic characteristics				
n	53	54	52	
Age (yr)	54 (10)	50 (9)	56 (11)	0.01
Sex (female)	37 (70%)	31 (57%)	42 (81%)	0.03
Weight (kg)	70 (13)	74 (14)	70 (12)	0.22
BMI	25.2 (3.7)	26.0 (4.1)	25.5 (3.5)	0.53
Systolic blood pressure (mm Hg)	126 (12)	126 (16)	126 (11)	0.98
Diastolic blood pressure (mm Hg)	79 (6)	80 (9)	77 (8)	0.24
Smoking history				
Current smoker	22 (41%)	29 (54%)	16 (31%)	0.21
Ex-smoker	12 (23%)	11 (20%)	15 (29%)	
Never-smoker	19 (36%)	14 (26%)	21 (40%)	
History of thyroid disease				
Graves' hyperthyroidism	52 (98%)	51 (94%)	52 (100%)	0.41[a]
Euthyroid Graves' disease	0 (0%)	1 (2%)	0 (0%)	
Primary hypothyroidism	1 (2%)	2 (4%)	0 (0%)	
Previous antithyroid treatments				
Antithyroid drugs	37 (70%)	40 (74%)	40 (77%)	
Radioiodine	8 (15%)	5 (9%)	6 (11.5%)	
Thyroidectomy	8 (15%)	6 (11%)	6 (11.5%)	0.95
Current thyroid treatments				
Levothyroxine and methimazole	13 (24%)	17 (31%)	14 (27%)	0.99
Levothyroxine only	9 (17%)	9 (17%)	9 (17%)	
Methimazole only	28 (53%)	25 (46%)	27 (52%)	
None	3 (6%)	3 (6%)	2 (4%)	
Duration of eye symptoms (months)	10 (8.6)	12.4 (13)	18.3 (32.5)	0.11
Biochemical characteristics				
TSH (mU/liter)	1.7 (0.4, 2.4)	1.1 (0.1, 3.2)	0.5 (0.1, 1.5)	0.07[b]
TRAb (U/liter)	6.2 (3.5, 16.5)	7.3 (2.5, 20.1)	9.3 (4.1, 20.7)	0.40[b]
TRAb positive	53 (100%)	54 (100%)	51 (98%)	0.36
TPOAb positive	39 (74%)	42 (78%)	36 (71%)	0.70
Eye symptoms and signs				
Proptosis (mm)	23.3 (3.2)	22.2 (3)	22.5 (2.8)	0.11
Eyelid width (mm)	12.7 (2.3)	12.4 (2.3)	12.8 (2.3)	0.82
Soft tissue involvements				
Minimal	11 (21%)	7 (13%)	10 (19%)	0.09
Moderate	26 (49%)	40 (74%)	33 (64%)	
Marked	16 (30%)	7 (13%)	9 (17%)	
Diplopia (Bahn and Gorman's score)				
Constant	9 (17%)	9 (17%)	12 (23%)	0.92
Inconstant	16 (30%)	20 (37%)	14 (27%)	
Intermittent	11 (21%)	11 (20%)	11 (21%)	
Absent	17 (32%)	14 (26%)	15 (29%)	
CAS	4 (4, 6)	4 (4, 5)	5 (4, 6)	0.21[b]

Patients were recruited at the following EUGOGO centers: Thessaloniki, Greece (35 patients); Varese, Italy (28 patients); Amsterdam, The Netherlands (25 patients), Pisa, Italy (24 patients); Milan, Italy (23 patients); Brussels, Belgium (11 patients); Lyon, France (8 patients); Olten, Switzerland (5 patients). Unless otherwise stated, data are means (SD) or numbers (proportions) or median (25th to 75th percentiles). *P* values: one-way ANOVA F test for continuous variables, and χ^2 test for proportions. BMI, Body mass index; TPOAb, autoantibody to thyroid peroxidase.

[a] Fisher's exact test.

[b] Kruskal-Wallis test.

groups were slightly unbalanced by age and gender, with the MD group being on average younger and with a greater prevalence of men. For the two primary outcomes of efficacy, a two-level outcome (improvement *vs.* no improvement, the latter defined as no change or deterioration) was determined (Supplemental Table 1); the overall dose effect as well as pairwise differences in the probability of improvement between doses were tested by age- and gender-adjusted Wald χ^2 tests from logistic regression model. As secondary end points, we considered the individual eye parameters as well as the Go-Qol subscales. The effect of dose on the probability of improvement, no change/deterioration was tested by means of a generalized logistic model; for parameters expressed on a continuous scale, we estimated a 12-wk trend over time within groups through repeated-measures linear regression models. Due to the discrete nature of the CAS, time trends and differences at 6 and 12 wk were tested with a nonparametric approach (Jonckheere-Terpstra test and Kruskall-Wallis test, respectively). Differences in the safety score were analyzed by analysis of covariance F test, with age and gender as covariates, considering both the total safety scores and major adverse events alone. All analyses were done using the Statistical Analysis System (SAS) Software for Windows, version 9.2 (SAS Institute Inc., Cary, NC).

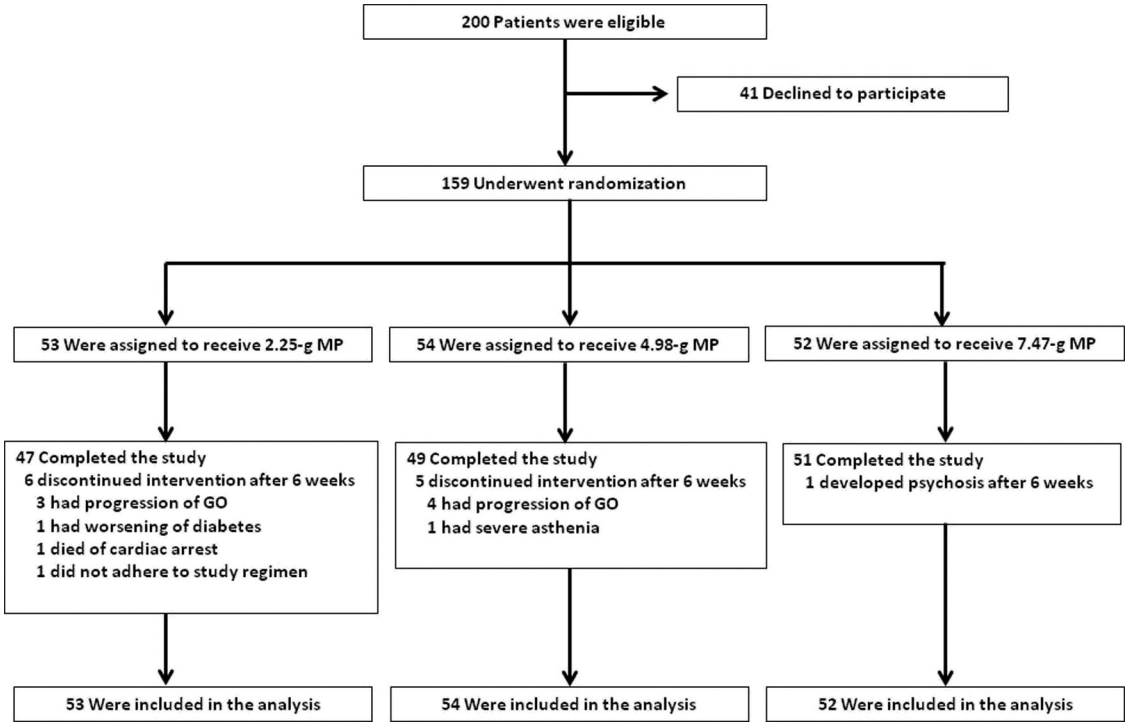

FIG. 1. Enrollment, randomization, and follow-up of study patients.

Results

Patients

Two hundred eligible patients were invited to participate (Fig. 1). Due to stringent inclusion and exclusion criteria, including no previous treatment for GO and the lack of dysthyroid optic neuropathy (DON), eligible patients constituted approximately 15% of referred patients. Of the 200 eligible patients, 159 were randomly assigned to the LD group (53 patients), the MD group (54 patients), or the HD group (52 patients). Six patients left the study before the 6-wk evaluation after withdrawing consent (five patients) or suspected (but not confirmed) pulmonary infection (one patient in the MD group) and were replaced. Consent withdrawal was due to personal reasons and not related to intolerance to treatment. All 159 randomized patients underwent at least the 6-wk evaluation and were included in the final 12-wk analysis (Fig. 1). Twelve patients withdrew prematurely after the 6-wk visit. Early withdrawal was due to the occurrence of DON (n = 6, three in the LD group and three in the MD group); further deterioration of GO requiring other treatments (one patient in the MD group); worsening of diabetes mellitus (one patient in the LD group) or severe asthenia (one patient in the MD group) requiring GC withdrawal; psychosis (one patient in the HD group); death due to myocardial infarction 1 wk after the sixth infusion (one patient in the LD group); and one patient was lost to follow-up for unknown reasons. The baseline characteristics of the patients are shown in Table 1. Because of differences in age and gender distribution, results were age and gender adjusted. This adjustment did not, however, affect the significance of the results. Almost all patients were euthyroid, and only a few patients needed minor adjustments of antithyroid drugs or levothyroxine. Serum free thyroid hormone levels did not change during the study. Serum autoantibodies to thyroid peroxidase and the TSH receptor decreased significantly in all groups, with no differences among groups.

Outcomes of treatment

An improvement in the QoL occurred at 12 wk in 35 of 52 HD patients (67%), 26 of 54 MD patients (48%), and 26 of 53 LD patients (51%) (P values: HD *vs.* LD, $P = 0.10$; HD *vs.* MD, $P = 0.07$; MD *vs.* LD, $P = 0.80$; Fig. 2A). The visual functioning subscale was more affected by treatment dose than the appearance subscale (Table 2).

The rate of overall ophthalmic improvement at 12 wk was significantly higher in the HD group (27 of 52 patients, 52%) than in the other groups (MD: 19 of 54 patients, 35%; $P = 0.03$; LD: 15 of 53 patients, 28%; $P = 0.01$, Fig. 2B). Differences among groups maintained the same significance if only patients with CAS of 4 or higher (n = 44 in the LD group, n = 44 in the MD group, n = 46 in the HD group) were considered (data not shown). Deterioration at 12 wk occurred in four HD patients (8%), six MD patients (11%), and six LD patients (11%).

CAS improved by at least two points in 81% of the HD patients and 83% of the MD patients but in a significantly

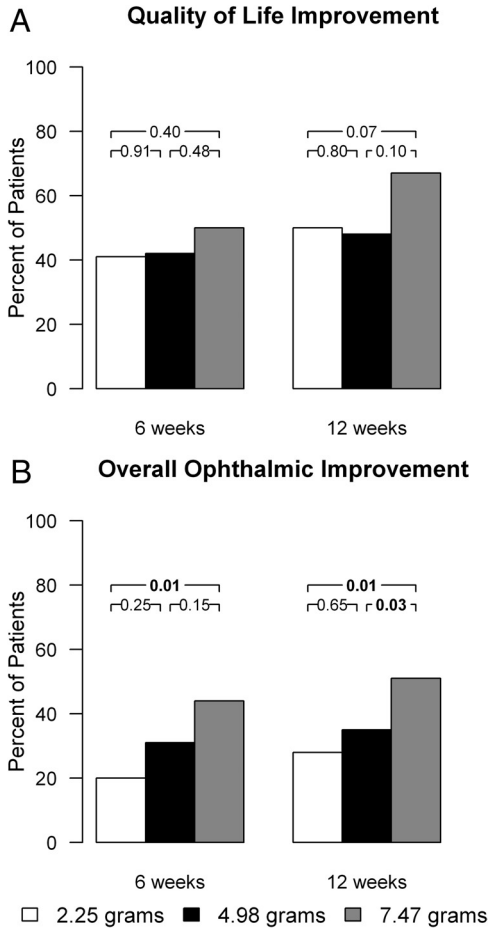

FIG. 2. Primary objectives. Panel A shows the improvement at 6 and 12 wk in the score on the GO-QoL. The questionnaire measures limitations in visual functioning (as a consequence of diplopia, decreased visual acuity, or both) and in psychosocial functioning (as a consequence of a changed appearance). The quality of life and the overall ophthalmic evaluations were considered to be improved according to predefined criteria. Panel B shows the improvement at 6 and 12 wk in overall results of the ophthalmic evaluation performed by an ophthalmologist who was unaware of the treatment assignments.

lower proportion (58%) of the LD patients (Fig. 3). CAS significantly decreased in all three groups during the treatment period (Table 2); differences in the rate of decrease were significant only between the HD and the LD group ($P = 0.004$ at 6 wk and $P = 0.01$ at 12 wk, respectively; Table 3). At the end of intervention, GO was inactive (CAS ≤ 2) in 60% of the HD patients, 65% of the MD patients, and 45% of the LD patients (LD *vs.* MD, $P = 0.06$; LD *vs.* HD, $P = 0.13$; MD *vs.* HD, $P = 0.71$). Soft tissue changes improved in approximately half of the HD patients and to a lower, nonsignificant, extent in the other groups (Fig. 3); palpebral aperture and exophthalmos decreased significantly in a minority of patients, with no differences between the groups (Table 3 and Fig. 3). Objective eye motility (particularly elevation and abduction) significantly improved in the HD group but not in the MD and LD groups ($P = 0.01$ *vs.* the LD group, $P = 0.05$ *vs.* the MD group; Fig. 3); changes in subjective diplopia [Bahn and Gorman score (19)] did not differ in the three groups (Table 2). In a multivariate analysis, age, gender, smoking habits, autoantibody to the TSH receptor (TRAb) levels, or the duration of GO were not related to treatment efficacy.

DON developed between 6 and 12 wk of treatment in six patients, three (6%) in the MD and three (6%) in the LD groups, as well as after completion of treatment (12–24 wk) in four patients, three (6%) in the HD and one (2%) in the MD groups. The latter four patients had not improved during MP treatment. Because of the occurrence of DON after the 12-wk visit, overall ophthalmic improvement at the exploratory follow-up visit at 24 wk did not significantly differ among groups (HD: 43%, MD: 40%, LD: 34%). Among patients whose GO had improved at 12 wk, nine of 27 patients in the HD group (33%), four of 19 patients in the MD group (21%), and six of 15 patients in the LD group (40%) showed progression of GO at the exploratory 24-wk visit, with no significant differences among groups. After completion of treatment, a second nonsurgical treatment (second course of iv GCs with or without orbital radiotherapy; oral steroids; cyclosporine associated with oral steroids) was required in eight patients in the HD group, 11 patients in the MD group, and eight patients in the LD group. Urgent decompression was needed in two patients of each group because of DON. Some kind of rehabilitative surgery (orbital decompression and/or squint surgery and/or eyelid surgery) was in the long term performed in 10 patients in the HD group, 15 patients in the MD group, and 14 patients in the LD group, with no significant differences among groups.

Adverse events

Mild adverse events were observed in 12 of 52 HD patients (21%), 18 of 54 MD patients (30%), and 14 of 53 HD patients (26%), with no significant differences among groups. Minor adverse events included frequent skin flushes during infusion, mild cushingoid features (six patients), mild increase in blood pressure not requiring therapy (three patients), mild gastric symptoms controlled by omeprazole (one patient), and mild weight gain (two patients).

Major adverse events occurred in 10 patients (five in the HD group, three in the MD group, two in the LD group), and one patient in the HD group had two major adverse events (Table 3). No patient had relevant hepatotoxicity, defined as a 4-fold or greater increase in serum liver enzymes. One patient in the LD group, who had preexisting chronic obstructive pulmonary disease, died of myocardial infarction 1 wk after the sixth infusion. There was no significant difference among groups in the safety score

TABLE 2. GO-QoL score, CAS, and eye evaluation at baseline and at 6- and 12-wk evaluation

Variable	LD (n = 53)	MD (n = 54)	HD (n = 52)	*P* value		
				HD *vs.* LD	HD *vs.* MD	MD *vs.* LD
GO-Qol score						
Visual functioning						
At baseline	59 ± 30	55 ± 29	51 ± 29			
Change at 6 wk	2.1 (−3.4; 7.6)	4.7 (−0.7; 10.2)	7.3 (1.8; 12.9)	0.19	0.51	0.51
Change at 12 wk	5.8 (0.3; 11.3)	10.1 (4.7; 15.5)	12.8 (7.2; 18.3)	0.08	0.49	0.27
P value, trend over time	0.11	0.001	<0.0001			
Appearance						
At baseline	62 ± 25	70 ± 18	62 ± 23			
Change at 6 wk	5.2 (0.7; 9.6)	1.9 (−2.5; 6.3)	3.8 (−0–7; 8.2)	0.67	0.55	0.30
Change at 12 wk	7.6 (3.2; 12)	3.3 (−1.1; 7.6)	9.0 (4.5; 13.5)	0.66	0.07	0.17
P value, trend over time	0.003	0.3	<0.0001			
CAS						
Baseline						
Median	4	4	5			
Interquartile range	(4, 6)	(4, 5)	(4, 6)			
Change at 6 wk	−1.4 ± 1.1	−1.7 ± 1.5	−2.1 ± 1.3	0.004	0.13	0.31
Change at 12 wk	−1.8 ± 1.6	−2.3 ± 1.4	−2.7 ± 1.5	0.01	0.15	0.13
P value, trend over time	<0.0001	<0.0001	<0.0001			
Ophthalmic evaluation						
Palpebral aperture (n, %)						
At 6 wk						
Improved	8 (15)	6 (11)	10 (19)	0.49	0.50	0.45
Unchanged	43 (81)	44 (82)	37 (71)			
Deteriorated	2 (4)	4 (7)	5 (10)			
At 12 wk						
Improved	12 (23)	10 (19)	10 (19)	0.63	0.26	0.56
Unchanged	37 (70)	37 (69)	40 (77)			
Deteriorated	4 (7)	7 (12)	2 (4)			
At baseline (mm)	12.7 ± 2.3	12.4 ± 2.3	12.8 ± 2.3			
Change at 6 wk	−0.5 (−1; 0.1)	−0.4 (−0.9; 0.1)	−0.8 (−1.3; −0.3)	0.38	0.30	0.88
Change at 12 wk	−0.5 (−1; 0)	−0.3 (−0.8; 0.3)	−0.8 (−1.3; −0.2)	0.51	0.52	0.19
P value, trend over time	0.1	0.3	0.004			
Soft tissue signs (n, %)						
At 6 wk						
Improved	12 (23)	21 (39)	16 (31)	0.33	0.49	0.09
Unchanged	41 (77)	33 (61)	36 (69)			
Deteriorated	0 (0)	0 (0)	0 (0)			
At 12 wk						
Improved	16 (30)	18 (33)	25 (48)	0.06	0.11	0.78
Unchanged	37 (70)	36 (67)	27 (52)			
Deteriorated	0 (0)	0 (0)	0 (0)			
Exophthalmos (n, %)						
At 6 wk						
Improved	12 (23)	10 (19)	9 (17)	0.76	0.27	0.29
Unchanged	40 (75)	39 (72)	42 (81)			
Deteriorated	1 (2)	5 (9)	1 (2)			
At 12 wk						
Improved	17 (32)	11 (20)	11 (21)	0.25	0.86	0.12
Unchanged	34 (64)	36 (67)	35 (67)			
Deteriorated	2 (4)	7 (13)	6 (12)			
At baseline (mm)	23.3 ± 3.2	22.2 ± 3.0	22.5 ± 2.8			
Change at 6 wk	−0.6 (−1; −0.2)	−0.3 (−0.6; 0.1)	−0.5 (−0.8; −0.1)	0.61	0.23	0.49
Change at 12 wk	−0.8 (−1.2; −0.4)	−0.4 (−0.8; 0)	−0.6 (−1; −0.2)	0.38	0.50	0.12
P value, trend over time	0.001	0.1	0.01			
Ocular motility (n, %)						
At 6 wk						
Improved	5 (9)	11 (20)	17 (33)	0.01	0.08	0.20
Unchanged	34 (64)	28 (52)	29 (56)			
Deteriorated	14 (27)	15 (28)	6 (11)			
At 12 wk						
Improved	11 (21)	14 (26)	24 (46)	0.01	0.05	0.8
Unchanged	24 (45)	25 (46)	21 (40)			
Deteriorated	18 (34)	18 (34)	7 (14)			

Parameters on a quantitative scale: Change at 6 and 12 wk: average change from baseline at wk 6 and 12 (95% confidence interval). Reported *P* values for pairwise comparisons are for the null hypothesis of equal change from baseline between treatment groups. Improvement/no change/deterioration outcome: Wald χ^2 test testing the hypothesis of equal distribution between groups.

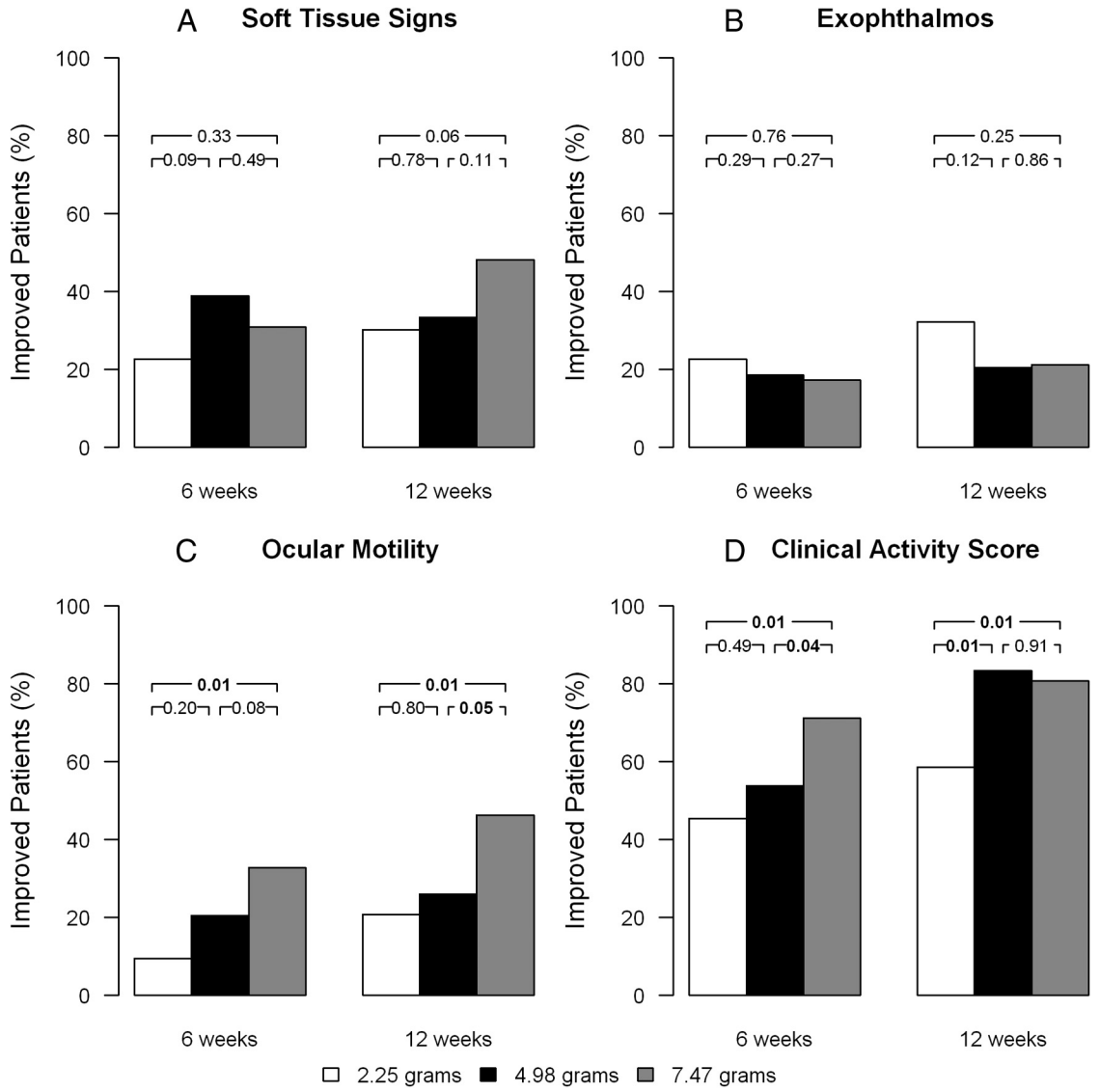

FIG. 3. Improvement at 6 and 12 wk in soft tissue signs (A), exophthalmos (B), ocular motility (C), and CAS (D) in the three treatment groups. Improvement was defined according to predefined criteria. *Numbers about the bars* represent the *P* values.

(Supplemental Table 1) when either all adverse events (minor and major) or only major adverse events were considered.

Discussion

Medical treatment of GO is challenging (19). Prevention is partially possible by controlling risk factors (smoking, thyroid dysfunction) (20). Selenium improves mild GO and prevents progression (21). For moderate to severe, active GO, GCs still are the first-line treatment (9). Intravenous GCs are associated with higher response rates than oral GCs (11–13, 22). Because RCTs are scarce, uncertainty remains concerning the optimal regimen for effectiveness and safety. Adverse events are a major concern of iv GC therapy (22–24), with morbidity and mortality rates of 6.5 and 0.6%, respectively (22).

In this large RCT, three different cumulative doses of iv MP were evaluated (HD: 7.47 g; MD: 4.98 g; LD: 2.25 g). Improvement of GO occurred in a significantly higher proportion of HD patients. However, improvement was lower than in two previous major RCTs (77–88%) (11, 12) and in a recent review (22). This difference may be due to several factors. Higher MP doses (9–12 g) combined with orbital radiotherapy were used in one study (11). Although the greater efficacy of this combined treatment has been proven only using oral GCs (25, 26), the combination of iv GCs with orbital radiotherapy may be more effective than iv GCs alone. In the other study (MP as monotherapy, cumulative dose: 4.5 g), the duration of GO was shorter (median 4 months) and the disease more se-

TABLE 3. Major adverse events

Adverse event	Treatment group	Time of occurrence
Occurrence of DM requiring therapy	LD	Between 1 and 6 wk
Death due to myocardial infarction	LD	Between 6 and 12 wk
Major depression	MD	Between 1 and 6 wk
Occurrence of DM requiring therapy	MD	Between 6 and 12 wk
Profound muscle weakness	MD	Between 6 and 12 wk
Occurrence of DM requiring therapy[a]	HD	Between 1 and 6 wk
Occurrence of DM requiring therapy	HD	Between 1 and 6 wk
Severe infection requiring hospitalization[a]	HD	Between 6 and 12 wk
Psychosis	HD	Between 1 and 6 wk
Major depression	HD	Between 6 and 12 wk
Major depression	HD	Between 6 and 12 wk

DM, Diabetes mellitus.

[a] Same patient.

vere than reported here (12). DON was present in the two studies in 14 of 41 patients (46%) (11) and five of 35 patients (14%) (12), respectively: in both studies iv GC treatment was highly effective on DON (79 and 100%, respectively). Finally, in previous studies, response was defined by different criteria. Thus, the lower response rate in this study is likely due to selection of patients with relatively longer duration (10 months in the LD group, 12 months in the MD group, and, particularly, 18 months in the HD group) and less severe GO.

Although palpebral aperture and exophthalmos showed marginal changes in all three groups, soft tissue changes and, particularly, eye motility (elevation and abduction) ameliorated significantly in the HD group but insufficiently to influence the Bahn's and Gorman's diplopia score, which is a subjective score with categorical variables sensitive to gross changes. The latter was selected because it reflects the patient's daily experience. Nevertheless, lesser motility improvements, such as those measured by excursions, could still be highly significant for the patient. They have the potential to improve the efficacy of subsequent strabismus surgery and provide a significantly better final outcome. Hence, both assessment methods are relevant. CAS significantly decreased in all three groups but to a greater degree in the MD and HD groups, and it occurred earlier in the HD group. At the end of intervention, GO was inactive (CAS $\leq$ 2) in 60% of the HD, 65% of the MD, and 45% of the LD patients. This underscores the high antiinflammatory effect of iv GCs. The earlier inactivation of GO with the high and intermediate doses of MP is an important objective, making rehabilitative surgery (if needed) possible at an earlier stage.

Improvement in the QoL was not statistically different in the three groups, but there was a trend to a greater increase in GO-QoL scores in the HD group. This was evident in the visual functioning subscale, most likely due to improvement in motility but less so in the appearance subscale, consistent with marginal changes in palpebral aperture and/or exophthalmos.

Adverse events of high-dose iv GCs are a major concern, particularly acute liver damage and cardio- and cerebrovascular events (24, 27–30). No major hepatotoxicity has been documented using cumulative doses of MP less than 8 g (31, 32). No patient enrolled in our study had severe hepatotoxicity. It should be underscored that this adverse event is rare (0.6%) (27), and therefore, our study might be underpowered to detect it. Minor side effects were common, irrespective of the MP dose. Major adverse events (Table 3) were slightly more frequent in the HD group (five patients *vs.* three patients in the MD group and two patients in the LD group). There were three cases of major depression or psychosis in the HD group and one of major depression in the MD group. One LD patient died of a heart attack after 6 wk of treatment. Thus, although severe adverse events are more common using higher doses, low-dose therapy is not devoid of serious risks. Therefore, appropriate selection of patients and careful monitoring during and after treatment in specialized centers is warranted (2).

DON developed in six patients during treatment, three in the LD group and three in the MD group. However, in the exploratory period (12–24 wk), four additional patients, who failed to improve during the iv GC course, developed DON (three in the HD group). In addition, several patients in the three groups did not maintain the improvement observed during treatment. Both phenomena (progression of nonresponders to DON, relapse of GO after initial improvement) may be due to the abrupt GC withdrawal. In addition to tapering down GC treatment orally, other strategies might be applied to improve the results. The latter may include the early association of iv GCs with orbital radiotherapy or with other drugs, such as cyclosporine, rituximab, and mycophenolate. However, the evidence for the effectiveness of such a strategy is lack-

ing. The significant risk of progression of GO after GC withdrawal mandates close monitoring of patients, even after treatment completion.

The strength of the study is that it is the first, multicenter, double-blind RCT evaluating the efficacy and safety of three different doses of iv MP for GO. This is particularly relevant because enrollment of large numbers of patients with a rare disease is extremely difficult. A recent study from Denmark reported an incidence of moderate to severe and active GO of 15.5/million per year (33). Our study shows that both intermediate and high cumulative doses of MP reduce inflammation more effectively and earlier than low doses. High doses, at least in the short term, are more efficacious on eye motility. The fact that the duration of GO was slightly longer in the HD group may have underestimated differences between HD group and other groups. High doses carry a slightly higher risk of major adverse events, which are, however, also encountered with low doses. The risk of relapses, in particular the risk of DON, is not completely eliminated, even by high doses, despite the initial favorable response.

This study has also limitations. The response rates were lower than expected, and differences between the high and the intermediate doses were modest. This is possibly due to the exclusion of patients with very severe GO and the inclusion of some patients with relatively long duration of GO. Treatment arms were slightly unbalanced with respect to age and gender, possibly due to a low number of subjects enrolled in some centers in the context of a within-center, six-block randomization scheme. However, age and gender were considered as covariates in our main analysis, a strategy that offers some advantages, even in case of balanced arms (34).

In conclusion, the use of a cumulative dose of 7.47 g of MP provides a short-term advantage over lower doses. However, this benefit is transient and is associated with slightly greater toxicity, suggesting that an intermediate-dose regimen may be used in most cases and the high-dose regimen be reserved to most severe cases of GO. Efficacy may be further enhanced by selecting patients with a short duration of disease. Potential strategies to reduce the risk of relapse/progression of GO at the end of iv GC therapy need to be explored and implemented in RCTs.

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