CLINICAL STUDY

Fatal and non-fatal adverse events of glucocorticoid therapy for Graves' orbitopathy: a questionnaire survey among members of the European Thyroid Association

Claudio Marcocci, Torquil Watt¹, Maria Antonietta Altea, Ase Krogh Rasmussen¹, Ulla Feldt-Rasmussen¹, Jacques Orgiazzi², Luigi Bartalena³ and for the European Group of Graves' Orbitopathy (EUGOGO)

Department of Endocrinology and Metabolism, University of Pisa, Via Paradisa 2, 56124 Pisa, Italy, ¹Department of Medical Endocrinology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, ²Department of Endocrinology and Metabolism, Hopital Lyon Sud, and Claude Bernard University, Lyon, France, and ³Department of Clinical Medicine, University of Insubria, Varese, Italy

(Correspondence should be addressed to C Marcocci; Email: claudio.marcocci@med.unipi.it)

Abstract

Objective: The objective of this study was to investigate the side effects of glucocorticoid (GC) therapy observed by European thyroidologists during the treatment of Graves' orbitopathy (GO).

Design: A questionnaire-based survey among members of the European Thyroid Association (ETA) who treat GO.

Results: A response was obtained from 128 ETA members of which 115 used GC therapy for GO. The majority of respondents (83/115, 72%) used intravenous (i.v.) GC, with a relatively wide variety of therapeutic regimens. The cumulative dose of methylprednisolone ranged between 0.5 and 12 g (median 4.5 g) for i.v.GC and between 1.0 and 4.9 g (median 2.4 g) for oral GC. Adverse events were often reported during oral GCs (26/32, 81%); most side effects were non-severe, but ten respondents reported severe adverse events (hepatic, cardiovascular, and cerebrovascular complications), including two fatal cases, both receiving a total of 2.3 g prednisone. Adverse events were less common in i.v.GC (32/83 respondents, 39%), but mostly consisted of severe events, including seven fatal cases. All but one fatal event occurred in cumulative i.v.GC doses (> 8 g) higher than those currently recommended.

Conclusions: GCs are preferentially administered i.v. for the treatment of GO in Europe. Both oral and i.v.GC may be associated with severe adverse effects, including fatal cases, which are more frequently reported in daily or alternate day i.v.GC. IvGC therapy should be undertaken in centers with appropriate expertise. Patients should be carefully examined for risk factors before treatment and monitored for side effects, which may be asymptomatic, both during and after treatment.

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Introduction

Glucocorticoids (GC), associated with or without orbital radiotherapy, represent the first-line treatment for moderate-to-severe and active Graves' orbitopathy (GO) (1). In clinical practice, it is still undefined whether clinicians in Europe utilize the i.v., oral, or local (subconjunctival or parabulbar) routes.

Randomized clinical trials (2, 3, 4, 5, 6) and two recent meta-analyses (7, 8) have demonstrated a greater efficacy of the i.v. pulse treatment over oral GC. Indeed, in the last 10 years, the i.v. pulse route has gained wide acceptance, particularly in Europe, and is presently considered the treatment of choice for moderate-to-severe and active GO (1). Evidence-based demonstration of the optimal therapeutic regimen, however, is still lacking.

Although usually better tolerated than oral GC, i.v.GC treatment was associated with fatal acute liver

failure and cardiovascular and cerebrovascular events (9, 10, 11, 12, 13). In a workshop held at the 2007 Annual Meeting of European Thyroid Association (ETA) on this issue, more clinicians than expected reported severe complications of i.v.GC. For this reason, a group of members of the ETA and the European Group on Graves' Orbitopathy (EUGOGO) were assigned the task of further addressing this issue by developing a specific questionnaire and distributing it among the ETA members.

The aims of this questionnaire were to gather information on the choice of GC treatment in clinical practice for moderate-to-severe and active GO and, in particular, to evaluate its side effects. Members were instructed to report their actual practice, without considering the EUGOGO consensus statement on the management of GO that was published shortly before the survey was launched.

Materials and methods

The format of the questionnaire was established by a group of experienced clinicians, all members of the ETA. It covered basic background information about the participating clinicians, including whether the respondents treated patients with GO, the approximate number of patients treated every year, the treatment of choice for moderate-to-severe and active GO, details about the treatment (e.g. dosing regimen, use of concomitant treatments, etc.), side effects of GC treatment, including fatalities, and information about the use of bone anti-resorptive therapy. Details concerning adverse events were collected initially by the questionnaire. Additional information about severe adverse events was then gathered by further e-mails.

The questionnaire was designed as an online survey with skip-patterns, using Esurveyspro.com (www.esurveyspro.com). The questionnaire consisted of 1–24 items, depending on the response pattern (e.g. respondents answering 'No' to the first item concerning whether he/she was treating patients with GO were not administered any additional items). After the initial survey development, a pretest was performed on five potential respondents and subsequent refinements were implemented. The full questionnaire is available upon request from the authors.

In June 2009, an invitation to participate in the survey containing a tagged link to the online survey was sent to all ordinary ETA members (i.e. those whose residence or place of work is in Europe or any country bordering the Mediterranean sea) whose e-mail address was available ($n=349$). Two reminders were sent to non-responders.

On completion of the survey in October 2009, the response database was downloaded and analyzed using SAS 9.1 (14). Results were subsequently exported to Excel spreadsheets for reporting. Results are expressed as percent of answers, unless otherwise indicated.

Results

Two hundred and forty-five of the 349 invited ETA members (70.2%) linked into the survey website, but only 148 gave a positive answer to the first question (Do you treat patients with GO in your clinic?). The remaining 97 members who linked into the website survey were not treating patients with GO (they were likely basic scientists). Of the 148 ETA members who replied positively to the first question, only 128 used GC in the treatment of patients with GO (subsequently termed 'treating clinicians'). Most responses came from Italy ($n=18$) and Denmark ($n=14$), followed by Germany ($n=9$), Greece ($n=9$), Turkey ($n=9$), UK ($n=7$), Sweden ($n=7$), Bulgaria ($n=6$), Poland ($n=6$), and Serbia ($n=5$).

Fifty of the treating clinicians (39%) treated one to ten GO patients each year, 41 (32%) treated 11–20 patients, and 37 (29%) treated more than 20 patients. Of the 128 respondents treating patients with moderate-to-severe GO, 115 (90%) used GC: 83 (72%) used the i.v. route and 32 (28%) the oral route and were the respective denominators for the following calculations. The remaining 13 respondents used other treatment modalities (e.g. orbital radiotherapy, etc.).

Oral route

Among the 32 ETA members who used oral GC, 29 (91%) used a fixed initial dose and three (9%) an initial dose based on body weight. The fixed initial dose was 20–40 mg prednisone (or prednisone equivalent) in seven, 40–75 mg in 16, and >75 mg in six cases. In most cases, the initial dose was continued for at least 2 weeks and then tapered off at 2-week intervals. The duration of treatment was longer than 3 months in most cases. The total dose ranged between 1 and 4.9 g, median 2.4 g.

Twenty-six out of the 32 respondents (81%) using oral GC reported adverse events. Ten respondents reported severe adverse events (cardiovascular ($n=1$), cerebrovascular ($n=3$), and increase (greater than fourfold upper normal limit) in liver enzymes ($n=6$)) and 17 reported mild/moderate adverse events. One respondent reported both severe and mild-to-moderate adverse events. The latter included hyperglycemia, gain in body weight, depression, and cushingoid features. Detailed data were obtained from four patients with severe adverse events. Two patients died during oral GC therapy due to cerebrovascular events (Table 1). One of them was also treated for congestive heart failure. The total dose administered at the time of the fatal event was 2.3 g prednisone in both cases. One of the two patients with serious, but non-fatal, adverse events had pulmonary embolism and the other a greater than fourfold increase in liver enzymes.

I.v. route

The treatment schedules used by the 83 ETA members using i.v.GC are shown in Fig. 1. Sixty-eight (82%) members used a fixed starting dose of equivalent methylprednisolone (ten members (15%), <0.5 g; 50 members (73%), 0.5–1 g; and eight members (12%): >1 g). Treatment schedules were as follows: once weekly (58%), twice weekly (14%), three times weekly (18%), twice a week on alternate weeks (1%), or other schedule (10%). Oral GC was administered either in the interpulse period by 16 or after the end of treatment in gradually tapered doses by 29 of these 83 ETA members. The cumulative dose of i.v.GC ranged between 0.5 and 12 g, median 4.5 g.

Thirty-two of the 83 ETA members using i.v.GC (39%) reported adverse events. Of these 32 respondents,

Table 1 Characteristics of the nine reported patients with fatal adverse events to treatment with oral or intravenous (i.v.) glucocorticoid (GC).

Patient no.	Age (years)	Sex (M/F)	Cause of death	GC route	GC schedule ^a	Total GC dose (g)	Days after starting GC	Time of event	Comorbidities
1	68	M	Cerebrovascular	Oral	50 mg/die	2.3	45	During GC	Ischemic heart disease and arterial hypertension
2	32	F	Cerebrovascular	Oral	60 mg/die	2.3	60	During GC	None
3	45	F	Cerebrovascular	I.v.	800 mg daily for 3 days every 2 weeks	11.8	45	After GC	Atrial fibrillation and diabetes mellitus
4 ^b	24	F	Cerebrovascular	I.v.	1 g daily for 5 days	5	9	After GC	None
5 ^b	71	F	Pulmonary embolism	I.v.	1 g daily for 5 days	8	4 (2nd cycle of GC)	During GC	Atrial fibrillation
6 ^c	71	F	Acute liver failure	I.v.	1 g daily for 3 days every 2 weeks	15	90	After GC	None
7 ^d	47	F	Acute liver failure	I.v.	15 mg/kg BW on alternate days every 2 weeks for two cycles and 7.5 mg/kg BW on alternate days every 2 weeks for six cycles	8.3	120	After GC	None
8 ^d	63	F	Acute liver failure	I.v.	15 mg/kg BW on alternate days every 2 weeks for two cycles and 7.5 mg/kg BW on alternate days every 2 weeks for six cycles	9.3	60	During GC	Atrial fibrillation and arterial hypertension
9 ^d	56	F	Acute liver failure	I.v.	1 g daily for 3 days weekly	15	60	During GC	None

^aGC doses are prednisone equivalent for oral GC and methylprednisolone for i.v.GC; BW, body weight.^bReported by Lendorf *et al.* (6).^cReported by Weisel *et al.* (4).^dReported by Marino *et al.* (5).

27 reported severe adverse events (cardiovascular ($n=10$), cerebrovascular ($n=5$), acute liver failure ($n=3$), autoimmune encephalitis ($n=1$) and increase (greater than fourfold upper normal limit) in liver enzymes ($n=8$)), and 14 reported mild-to-moderate adverse events. Nine respondents reported both mild-to-moderate and severe adverse events. Detailed data were available for 32 patients with non-fatal severe adverse events (Table 2) and seven with fatal adverse events (Table 1). All fatal adverse events occurred in females. Three patients died during the i.v.GC treatment period and four after completion of treatment. Three patients had relevant cardiovascular comorbidities. One patient died the day after the last infusion of a treatment course with 1 g i.v.GC daily for five consecutive days. With the exception of the latter patient, all other patients received a total dose of i.v.GC of at least 8 g (range 8–15 g).

Severe non-fatal adverse events, mostly a greater than fourfold increase in liver enzymes ($n=20$) and cardiovascular events ($n=8$), occurred in 32 patients (Table 2). Relevant comorbidities were reported in half of them. In three of the 20 patients with increased liver enzymes, receiving GC on alternate days every other week, a diagnosis of autoimmune hepatitis was made. All patients stopped i.v.GC and recovered after oral GC therapy. In the majority of cases, the adverse events occurred during GC treatment. The median i.v.GC dose received at the time of the event was 6 g (range 1–22 g).

Discussion

The purpose of this study was to gather information on the clinical practice of GC treatment for moderate-to-severe and active GO and, particularly, to evaluate its side effects. A substantial proportion of the ETA members who linked into the survey without providing a response (97/245, 39.6%) is likely to be those who were not involved in the treatment of GO patients. As a matter of fact, several of the ETA membership includes basic scientists who are not involved in patient care.

The present survey confirms that GC represents, among endocrinologists, the first-line treatment for GO in Europe. Although there is a wide heterogeneity in the treatment modality, the i.v. route is the most common (7, 8). This is in keeping with the notion that i.v.GCs are more effective than oral GCs (average response rates ~80 and 50% respectively). Indeed, five randomized clinical trials have compared i.v. and oral routes, and all but one showed a greater effectiveness of the former treatment, using a total dose of i.v.GC ranging between 4.2 and 12 g (2, 3, 4, 5, 6). Interestingly, about one-third of physicians treating GO still prefer oral GC.

The survey showed that usual starting dose of i.v.GC was between 0.5 and 1 g, which was maintained for four to six infusions. The most common schedule is based on one weekly infusion, with administration of oral GC in

Figure 1 Treatment schedules of i.v.GC therapy used by the 83 European Thyroid Association members.

the interpulse period used by a minority of physicians. The cumulative dose ranged from 0.5 to 12 g methylprednisolone. The marked heterogeneity of the i.v.GC regimens used by ETA members reflects the present lack of evidence of the superiority of one schedule over others. A wide heterogeneity also exists among oral GC regimens in Europe. The most commonly employed starting dose is between 40 and 75 mg, maintained for at least 2 weeks and then gradually tapered down until withdrawal after 3 or more months.

Our study also focused on the side effects of GC therapy. Previous studies comparing oral and i.v.GC have shown that the oral treatment is associated with a significantly higher rate of steroid-related adverse events, particularly weight gain, hypertension, and cushingoid features (7, 8). The i.v. route is generally better tolerated, even though some patients complain of palpitations and flushes during or shortly after the infusion (7). The cumulative higher rate of side effects observed using oral GC is supported by this survey, since 81% of the ETA respondents reported side effects using

oral GC and 39% using i.v.GC. However, severe (non-fatal and fatal) adverse events were more common in i.v.GC, mostly consisting of hepatic and cardiovascular events. Events were fatal in nine cases (seven treated with i.v.GC and two with oral GC). All but one occurred in females, likely reflecting the higher frequency of GO in women compared with men. We cannot estimate the true rate of fatal and non-fatal adverse events in this survey, since data on the total number of patients treated by each ETA member were not available. However, respondents who treated more than 20 patients per year mostly reported fatal events (data not shown). In addition, it seems conceivable that patients receiving i.v.GC are subject to tighter surveillance for side effects than patients receiving oral GC. Indeed, if one considers that, e.g. even serious hepatotoxicity associated with several-fold increases in liver enzymes may be totally asymptomatic, major (non-fatal) adverse events of oral GC may have been underreported or underestimated.

Zang *et al.* (8) have recently performed a meta-analysis in which the efficacy and morbidity of i.v.GC in GO have been reviewed. Data were largely derived from case-series reports and complete information on side effects was available for 1045 patients. The calculated morbidity and mortality rates were 6.5 and 0.6% respectively (8). Mild and moderate adverse events mostly accounted for the observed morbidity. The total morbidity rate is rather low when compared with that observed in randomized clinical trials (43%). In this regard, it is worth noting that the study that contributed the largest number of patients ($n=800$) did not mention mild-to-moderate side effects and only focused on acute liver damage (15). Zang *et al.* reported six cases of death related to i.v.GC and all occurred in patients receiving daily or alternate days injection of a large dose of methylprednisolone (1 g in four cases). Two single-center experiences on severe side effects of i.v.GC pulses have been reported. In a study of 101 patients from

Table 2 Characteristics of the 32 reported patients with non-fatal adverse events to treatment with i.v.GC.

Characteristic	Non-fatal adverse events				
	Greater than fourfold increase of liver enzymes	Cardiovascular	Autoimmune hepatitis	Autoimmune encephalitis	Others
<i>n</i>	19	7	3	1	2
Age (years, mean, and range)	50 (21–72)	59 (39–76)	41 (38–41)	24	60 (56–64)
Mean cumulative dose of i.v.GC (methylprednisolone (g))	11.5 (2–22)	2.7 (1–6)	4.8	3.0	6.0 (4.4–7.6)
Time of event				NA	
During GC	11	7	1		–
After GC	8	0	2		2
Comorbidities					
Cardiovascular	6	3	–	–	–
Metabolic	4	1	1	–	1
Not specified	3	4	–	–	–
None	9	0	1	1	1

NA, Not available.

Poland, no deaths occurred, but about half of the patients had non-fatal complications, mostly abnormalities of carbohydrate metabolism and infections (16). Among 800 patients from Italy, acute and severe liver hepatotoxicity occurred in eight patients (1%), three of whom (0.4%) died (15). Six of the nine fatal cases described in this questionnaire-based survey, all receiving i.v.GC, had already been reported in the literature (Table 1) (9, 10, 11). It is worth noting that all seven of the nine patients who died were given either daily or alternate day single doses of 1 g methylprednisolone. All but one had received a cumulative dose of 8 g GC or more when the fatal event occurred. The remaining patient received 1 g methylprednisolone for five consecutive days. Two patients died due to cerebrovascular events during oral GC therapy; in both patients, the total cumulative dose of GC was 2.3 g (Table 1).

Acute liver failure, either during or after completion of therapy, accounted for death in four out of the seven patients receiving i.v.GC (9, 10); the remaining three patients died due to cerebrovascular ($n=2$) or cardiovascular ($n=1$) events (11). Cardiovascular comorbidities were reported in four out of the five patients who died due to cerebrovascular or cardiovascular events. No history of liver dysfunction was reported in patients who developed fatal liver failure (9, 10).

An increase in serum liver enzymes, often asymptomatic, is the most common non-fatal adverse event, which may be related to a direct toxic effect of GC on hepatocytes and appears to be dose dependent (15, 17). We cannot exclude that in a minority of cases, an increase in liver enzymes could be due to uncommon liver complications of Graves' disease itself (i.e. transient increase during the thyrotoxic phase or anti-thyroid drug toxicity), even though we clearly requested in the questionnaire to report only adverse events attributed to GC therapy. Autoimmune hepatitis was reported in three patients treated with i.v.GC (15, 18). It is likely that a sudden reactivation of the immune system after the abrupt withdrawal of i.v.GC may be responsible for the liver damage. The use of low-dose oral GC therapy either in the interpulse period or after withdrawal of i.v.GC therapy has been advocated to decrease the likelihood of autoimmune hepatitis, particularly in high-risk patients (with positive tests for autoantibodies associated with autoimmune hepatitis) (15), but the evidence that this abolishes the risk of liver damage is unavailable.

High-dose i.v.GC pulse therapy is used in several disorders, including multiple sclerosis and systemic lupus erythematosus; severe cardiovascular adverse events, including death, have been reported in a few cases, mostly related to short infusion rate, ventricular arrhythmias, and/or myocardial infarction (19, 20, 21, 22). An increase in systolic and diastolic blood pressure and in fluid retention might account for the occurrence of severe cardiovascular and cerebrovascular events in patients treated with i.v.GC pulses (12).

A direct evidence-based relationship between high-dose oral or i.v.GC and severe fatal or non-fatal side effects remains to be proven. Evidence for the superiority of any of the different i.v.GC schedules is lacking. However, the use of a schedule administering a cumulative dose of 4.5 g methylprednisolone (0.5 g once weekly for 6 weeks, followed by 0.25 g once weekly for 6 weeks) has gained wide acceptance in recent years, in terms of risk/benefit balance (5). The current recommendation is, however, that the cumulative dose of i.v.GC should not exceed 8 g in each treatment course and that pulses should not be given on consecutive or alternate days, except in the case of dysthyroid optic neuropathy (1, 8). With the exception of dysthyroid optic neuropathy, which requires a very aggressive therapeutic regimen, the administration schedule may also be relevant and a weekly schedule using <1 g methylprednisolone per week is recommended (1, 8). Patients who are to be treated with high doses of GC should initially be screened for diabetes mellitus and liver dysfunction. To the latter purpose, in addition to liver enzymes, tests for hepatotropic virus markers and autoantibodies related to autoimmune hepatitis are recommended. The potential risk for cardiovascular complications should also be evaluated, by screening the patients for hypokalemia, cardiac arrhythmias, and uncontrolled severe hypertension (1, 8). In patients with relevant liver dysfunction (i.e. a greater than fourfold upper normal limit), severe cardiovascular morbidity, severe hypertension, uncontrolled diabetes mellitus and glaucoma, use of i.v.GC therapy should be avoided. When alternative treatments are not indicated, weekly pulses with doses lower than 250 mg appear to be less commonly associated with adverse events, in particular cardiac arrhythmias (20). A slow rate of i.v.GC infusion (60–90 min) should be used and pulse rate and rhythm should be recorded during the infusion. Patients should be carefully followed and monitored for side effects. ECG should be performed before each pulse; tests for liver enzymes should be prescribed every other week during treatment.

This study has several limitations: i) the questionnaire was not formally tested for coverage, applicability, and validity before its use; ii) due to the retrospective nature of the data recollection, the reported adverse events may have occurred over many years, possibly on GC regimens different from those used when the questionnaire was answered; and iii) multiple reporting as some respondents may practice in the same center as other respondents.

In conclusion, i.v.GC appears to be the most common treatment of moderate-to-severe GO among European endocrinologists, and its greater efficacy over oral GC has been proven in randomized clinical trials. As clearly shown also in this survey, this treatment is not devoid of serious side effects, including death. Therefore, in each patient, the potential risks of i.v.GC treatment must be weighed against its potential benefits. Alternative

therapies should be considered in selected cases, including the use of orbital radiotherapy or the association of low-dose oral GC and cyclosporine (23, 24). Moreover, i.v.GC therapy should only be undertaken in specialized GO centers where a multi-disciplinary approach allows the appropriate selection of patients who can benefit from this treatment, as well as facilitating the correct procedure of i.v.GC administration and monitoring of possible adverse events. A strict follow-up schedule should be applied to patients receiving high-dose oral or i.v.GC for the treatment of GO, in view of the often asymptomatic features of acute liver damage.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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