Intravenous Glucocorticoids for Graves' Orbitopathy: Efficacy and Morbidity

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Context: The administration of iv glucocorticoid pulses has been advocated as a treatment approach for patients with inflammatory and moderate to severe Graves' orbitopathy (GO). This review offers an update on this controversial regimen.

Evidence Acquisition: PubMed and the MeSH-Database were searched (with no temporal limit) for the following topics: management of active and severe GO; glucocorticoid therapy of GO; iv glucocorticoid administration; mechanism and pharmacokinetics of iv glucocorticoids; and adverse events, morbidity, and mortality of iv glucocorticoids. The articles were evaluated according to their setting and study design.

Evidence Synthesis: All randomized and uncontrolled trials, consensus statement, systematic reviews, and meta-analyses dealing with the efficacy and morbidity of iv glucocorticoids in GO were identified.

Conclusions: The current first-line treatment for active, moderate-to-severe GO is a 12-wk course of high-dose iv glucocorticoid pulses. The response rate of this regimen is approximately 80%. Intravenous glucocorticoids have a statistically significant advantage over oral treatment and cause significantly fewer adverse events. However, major side effects related to preexisting diseases, administered dose, and treatment schedule have been reported. The morbidity and mortality of iv glucocorticoid therapy are 6.5 and 0.6%, respectively. Thus, careful patient selection is warranted. Before iv glucocorticoid administration, patients should be screened for recent hepatitis, liver dysfunction, cardiovascular morbidity, severe hypertension, inadequately managed diabetes, and glaucoma. The cumulative dose should not exceed 8 g, and with the exception of sight-threatening GO the single doses preferably should not be administered on consecutive days. Monthly monitoring during subsequent treatment is warranted. **(*J Clin Endocrinol Metab* 96: 320–332, 2011)**

Immunosuppression in Graves' Orbitopathy: the Notion of Clinical Activity

The aim of immunosuppressive treatment in Graves' orbitopathy (GO) is to decrease inflammation and congestion of the orbital tissue, thereby trying to prevent clinical progression of the autoimmune disease (1–4). Thus, the first step before starting therapy is to establish whether GO is clinically severe and whether there is active inflammation (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) (5–10). The concept of disease activity in GO may explain why as many as 20–25% of patients do not respond to immunosuppressive treatment because only patients in the active stage of disease are expected to respond (11). Indeed, a beneficial response is observed in only 75–80% of patients, regardless of the modality applied. What are the reasons for this consistent rate of nonresponders? First, it may be that we need stronger immu-

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Abbreviations: CAS, Clinical activity score; CI, confidence interval; GO, Graves' orbitopathy.

nosuppressive regimens to increase the response rate. A second explanation is the *selection* of patients. Many physicians will use medical treatment in patients with severe GO regardless of the signs of activity. In other words, patients are selected on the basis of the disease severity only. However, severe GO can also be present in patients with inactive disease, who are not likely to respond to immunosuppression. If these patients with inactive, but severe and fibrotic, disease are included in studies, the response rate will be decreased considerably. Multivariate analyses have shown that soft tissue involvement and imaging signs of orbital tissue inflammation are significant predictors of a response to conservative therapy (12–14). Thus, clinical disease activity should determine which kind of treatment is used.

Glucocorticoids for GO

Since the 1950s, glucocorticoids have been the most common immunosuppressants used in the treatment of active and severe GO (15–17). Glucocorticoids serve in multiple capacities by decreasing inflammation and suppressing immune function by interfering with the function of T and B lymphocytes, reducing the recruitment of monocytes and macrophages, inhibiting the function of immunocompetent cells (18), inhibiting the release of inflammatory mediators (cytokines, prostaglandins), and decreasing glycosaminoglycan synthesis and secretion by activated orbital fibroblasts (19). Systemic glucocorticoids often improve acute symptoms of GO and health-related quality of life (20–27). Steroids are effective when given early in the active phase of the disease and have a beneficial effect on soft tissue swelling, visual acuity, and ocular motility, with a limited effect on proptosis. Glucocorticoids are also the first-line treatment for patients with sight-threatening GO (28, 29). Cigarette smoking decreases the efficacy of glucocorticoid treatment (30).

Intravenous administration of high-dose glucocorticoid pulses has been advocated as an alternative treatment in patients with active GO (31). Numerous randomized trials have demonstrated the advantages, in terms of effectiveness and possible side effects, of iv over oral administration. One advantage of the iv regimen is the rapidity of response in responsive patients. Early response to iv glucocorticoids predicts treatment outcome, and treatment response is inversely related to disease duration (32). In a survey, 91% of the responding members of the European Thyroid Association indicated that they would treat an index patient having active and severe GO with glucocorticoids, and 71% would immediately start with iv glucocorticoids (33). In a similar situation, 58% of the responding Latin-American thyroidologists administer iv glucocorticoids (34).

Methods and Results

PubMed and the MeSH-Database were searched (with no temporal limit) for the following topics: conservative management of GO; treatment of active and severe GO; glucocorticoid therapy of GO; iv glucocorticoid administration; mechanism and pharmacokinetics of iv glucocorticoids; and adverse events, morbidity, and mortality of iv glucocorticoids. All trials, regardless of publication status and language, were included. All full articles were obtained and independently inspected by the three authors. All articles were checked for quality by evaluating their setting and methods. Systematic reviews, meta-analyses, and randomized and nonrandomized trials were identified. S.Z. and G.J.K. extracted data from all the trials and again assessed the studies for methodological quality. Ophthalmic parameters and outcomes were evaluated by an independent ophthalmologist (K.A.P.). Data on exclusions after randomization and on whether the primary analysis was performed according to the intention-to-treat principle or per protocol were collected. Safety outcomes were obtained for all adverse events, serious adverse events leading to treatment discontinuation, and life-threatening events. Finally, we prospectively defined the following comparisons: iv steroids *vs.* placebo or control and iv *vs.* oral steroids.

The literature search identified a total of 35 reports, case series, and trials of iv treatment published between 1987 and 2009, which included 1844 patients with active and moderate to severe GO. In detail, 13 nonrandomized (retrospective and prospective) and nine randomized clinical trials, eight reports on adverse events, two systematic reviews and meta-analyses, and one consensus statement of the European Group on Graves' Orbitopathy were analyzed.

Immunological and Genomic Mechanisms of Intravenous Glucocorticoids

Intravenous glucocorticoids have been successfully administered in patients with chronic obstructive pulmonary disease for decades (35–37), and a large trial (73,765 patients) has demonstrated the efficacy and safety of high-dose iv glucocorticoid pulses (38). In GO, by comparison, iv glucocorticoids significantly decreased serum TSH-receptor autoantibody levels in patients with Graves' disease (39), and this marked effect was maintained for 24 months. Furthermore, the levels of detected serum eye muscle autoantibodies significantly decrease after iv steroid pulses (40). Additionally, a significant increase in pe-

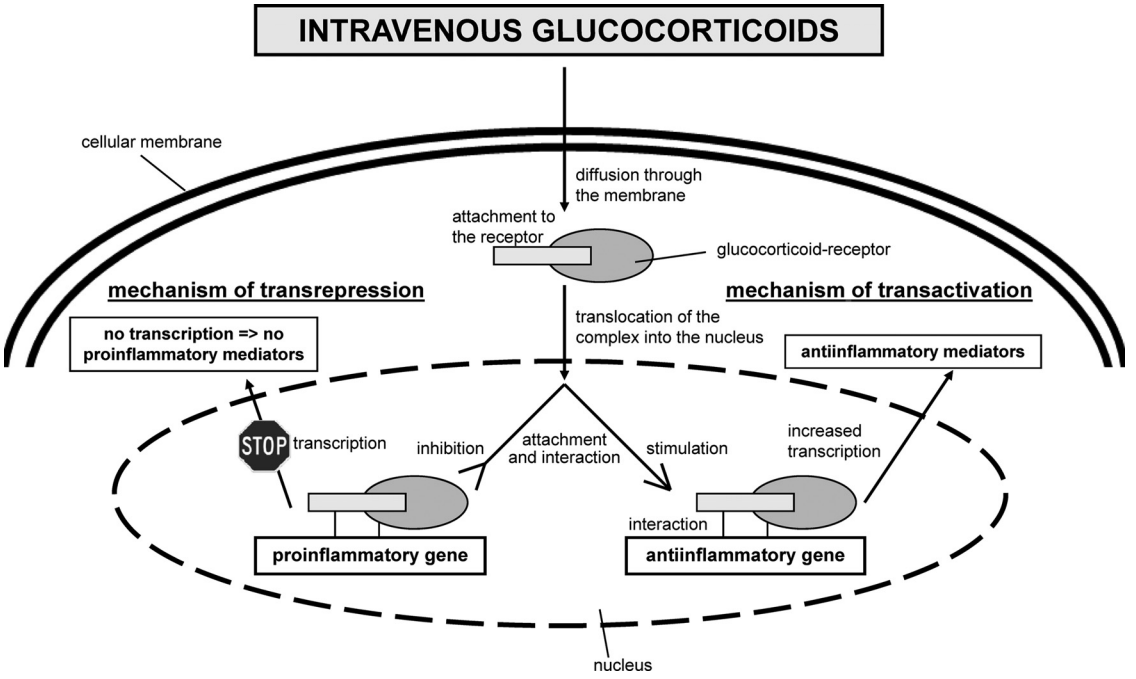

FIG. 1. Genomic mechanism of iv glucocorticoids. Glucocorticoid binding to its receptor may have a dual effect on gene activation such as activation of transcription (transactivation) or a suppression of transcription (transrepression) by interacting with nuclear factor (NF)-κB (45). After diffusing into the cell, the lipophilic glucocorticoids attach to their receptor. The activated glucocorticoid-receptor complex is then transported to the cell nucleus where it dissociates and directly intervenes in the transcription process of several genes. The production of antiinflammatory proteins is increased (transactivation), whereas the inflammatory ones are diminished (transrepression). The process of transactivation contains the function of the activated glucocorticoid receptor as a ligand-controlled transcription factor interacting with the DNA. The consequence for the inflammation process is an increased transcription of lipocortin-1 (annexin-1) inhibiting phospholipase A2 (46). Glucocorticoids do encroach very early into the inflammatory cascade by suppressing a few key inflammatory mediators. The transrepression process is based on protein-protein interactions. The glucocorticoid receptor reacts with the NF-κB protein, which is involved in the activation of several genes regulating the immunological activities, such as cytokines or chemoattractant cytokines. By inhibiting NF-κB, these genes are transrepressed, and therefore the synthesis of proinflammatory factors is prohibited. Apart from the protein-protein interaction, an alternative way of transrepressing NF-κB by activating IκBα, which again inhibits activation of NF-κB, has been reported (47).

ripheral blood CD4+CD45RA+ cells has been observed after iv glucocorticoids. Increased numbers of CD11-CD8+ cells and decreased numbers of CD11+CD82+ cells have been found before treatment and were normalized after pulse therapy.

Intravenous glucocorticoids have inhibitory effects on plasma cells and abrogate circulating dendritic cells (41). All dendritic cells completely disappeared after iv treatment and reached their pretreatment level again 8 d after iv administration. The homing of dendritic cells to lymphoid organs or peripheral tissue, or a decrease in production and differentiation of dendritic progenitor cells, or initiation of apoptosis may be responsible (42). By comparison, T-lymphocyte adhesion molecule expression, circulating T-cell subset distribution, and TNF-α concentration were successfully modulated by iv methylprednisolone in patients with an exacerbation of multiple sclerosis (43). Pharmacologically, iv glucocorticoids increased the area under the plasma concentration-time curve compared with the oral administration, but no differences between the two administration schemes in volume of distribution, disposition, and bioavailability were noted (44).

A simplified genomic mechanism based on Refs. 45–47 is shown in Fig. 1. The nongenomic pathway (48) can be divided into two different paths: 1) a mechanism involving receptor-mediated actions, in which signals to membrane-bound glucocorticoid receptors are responsible for rapid effects a few minutes after application; and 2) physiochemical actions induced by high concentrations of iv glucocorticoids. The latter mechanism stabilizes the cellular membrane, preventing sodium and calcium from crossing, which decreases ATP (used for ion cycling over cellular and mitochondrial membranes) and finally disturbs the physiological course in affected cells.

Nonrandomized Trials of Intravenous Glucocorticoids for GO

Thirteen trials (32, 40, 49–59) encompassing a total of 346 patients (Table 1) and a study of nine patients receiving prophylactic iv glucocorticoids during radioiodine therapy (60) were evaluated. Treatment with iv glucocorticoids was safe and effective (response rate, 82.6%) and was associated with both a lower recurrence rate and less

TABLE 1. Nonrandomized trials of iv glucocorticoid therapy for GO

First author, year (Ref.)	iv group n[a]	Design	Dosage and treatment protocol	Comparison group	iv group response rate (%)	Patients with side effects (%)
Nagayama, 1987 (49)	5	Prospective	1 g/d iv methylprednisolone sodium succinate for 3 consecutive days, repeated weekly for 3 to 7 wk. Cumulative dose not mentioned.	Only one group	4 (80%)	Adverse events not mentioned in the study (elevated blood glucose in two patients during pulse therapy)
Kendall-Taylor, 1988 (50)	11	Prospective	0.5 g iv methylprednisolone repeated once after 48 h, followed by tapering dose of oral prednisolone. Cumulative dose not mentioned.	Only one group	8 (72.7%)	Exact number of patients with side effects not mentioned (7 minor adverse events)
Hiromatsu, 1993 (40)	15	Prospective	1 g/d iv methylprednisolone for 3 consecutive days repeated weekly for 3–5 wk, followed by tapering dose of oral prednisolone. Cumulative dose not mentioned.	Only one group	No overall response rate mentioned. Improvement of eye motility, 12/15 (80%); diplopia, 9/15 (60%); periorbital edema, 9/15 (60%)	Exact number of patients with side effects not mentioned (6 moderate adverse events, no major adverse events)
Tagami, 1996 (51)	27	Prospective	1 g/d iv methylprednisolone sodium succinate for 3 consecutive days repeated once weekly until ophthalmopathy improved (up to 4 wk), followed by tapering dose of oral prednisolone. Cumulative dose, variable.	Only one group	No overall response rate mentioned. Improvement of diplopia, 21/27 (77.8%); proptosis, 15/27 (55.6%); visual acuity, 9/27 (33.3%)	Exact number of patients with side effects not mentioned (2 minor, 5 moderate, and 1 major adverse event)
Matejka, 1998 (52)	8	Prospective	12.5 mg/kg BW iv methylprednisolone once monthly for 3–6 months, oral prednisone administered between the pulses and tapered down after the last pulse. Cumulative dose variable.	Only one group	7 (87.5%)	Adverse events not mentioned in the study
Ohtsuka, 2002 (53)	41	Prospective	1 g/d iv methylprednisolone for 3 consecutive days, repeated once weekly over 3 wk, followed by oral prednisone. Cumulative dose not mentioned.	Only one group	No overall response rate mentioned. Improvement of eye motility, 15/41 (36.6%)	Adverse events not mentioned in the study
Ohtsuka, 2003 (54)	20	Prospective	1 g/d iv methylprednisolone for 3 consecutive days repeated once weekly over 3 wk, oral prednisone administered between the pulses and tapered down after the last pulse. Cumulative dose not mentioned.	1 g/d iv methylprednisolone for 3 consecutive days repeated once weekly over 3 wk, oral prednisone administered during radiation and tapered down after radiotherapy. Cumulative dose not mentioned. + Orbital irradiation with a cumulative dose of 24 Gray	No overall response rate mentioned (immediate improvement of extraocular muscle hypertrophy, minimal improvement of proptosis)	Adverse events not mentioned in the study
Hart, 2005 (32)	18	Prospective	0.5 g/d iv methylprednisolone for 3 consecutive days, followed by oral prednisolone. Cumulative dose, 1.5 g.	Only one group	12 (66%)	1 (5.6%) (only 1 minor adverse event documented)
Sánchez-Ortiga, 2009 (56)	13	Retrospective	6 doses of 0.5 g/wk iv methylprednisolone followed by 6 doses of 0.25 g/wk iv methylprednisolone. Cumulative dose, 4.5 g.	4 cycles 15 mg/kg BW iv methylprednisolone, then 4 cycles 7.5 mg/kg BW iv methylprednisolone. Cumulative dose, 90 mg/kg BW	12 (92%)	2 (15.4%) (1 minor and 1 major adverse event)
	11	Retrospective	4 cycles 15 mg/kg BW iv methylprednisolone, then 4 cycles 7.5 mg/kg BW iv methylprednisolone. Cumulative dose, 90 mg/kg BW.	6 doses of 0.5 g/wk iv methylprednisolone followed by 6 doses of 0.25 g/wk iv methylprednisolone. Cumulative dose, 4.5 g	11 (100%)	2 (18.2%) (1 minor and 1 moderate adverse event)
Mensah, 2009 (57)	28	Retrospective	0.5–0.75 g/d iv methylprednisolone for 3 d, followed by tapering dose of oral glucocorticoids.	Only one group	21 (75%)	Adverse events not mentioned in the study

(*Continued*)

TABLE 1. Continued

First author, year (Ref.)	iv group n	Design	Dosage and treatment protocol	Comparison group	iv group response rate (%)	Patients with side effects (%)
Koshiyama, 1994 (58)	8	Prospective	1 g/d iv methylprednisolone sodium succinate for 3 consecutive days, repeated once weekly until diplopia improved, followed by oral prednisolone. Cumulative dose variable. + 2 Gray/d orbital irradiation over a 2-wk period., Cumulative dose, 20 Gray.	Only one group	No overall response rate mentioned. Improvement of diplopia, 5/8 (62.5%); eye motility, 1/8 (12.5%)	Exact number of patients with side effects not mentioned (minor adverse events only)
Ohtsuka, 2003 (54)	19	Prospective	1 g/d iv methylprednisolone for 3 consecutive days repeated once weekly over 3 wk, oral prednisone administered during radiation and tapered down after radiotherapy. Cumulative dose not mentioned. + Orbital irradiation with a cumulative dose of 24 Gray.	1 g/d iv methylprednisolone for 3 consecutive days repeated once weekly over 3 wk, oral prednisone administered between the pulses and tapered down after the last pulse. Cumulative dose not mentioned	No overall response rate mentioned (immediate improvement of extraocular muscle hypertrophy, minimal improvement of proptosis)	Adverse events not mentioned in the study
Kulig, 2009 (55)	101	Prospective	1 g/d on 3 consecutive days for 3 to 6–7 pulses, followed by tapering dose of prednisone. Cumulative dose, variable. + 10 daily doses of 200 cGy to each eye between the 2nd and 4th iv pulses.	Only one group	No overall response rate mentioned. Improvement of diplopia, 85/101 (84.2%)	Adverse events not mentioned in the study
Sterker, 2009 (59)	21	Retrospective	0.5 g/wk iv methylprednisolone for 6 consecutive wk followed by 0.25 g/wk for 6 wk. Cumulative dose not mentioned. + Orbital irradiation with a cumulative dose of 13 Gray.	Only one group	15 (71.4%). Improvement of driving competency, 10/21 (47.6%); diplopia, 6/21 (28.6%)	2 (9.5%) (two moderate adverse events)
Total	346[a]				90 of 109 (82.6%)[b]	7 of 63 documented cases (11%)

n, Number of patients in the iv glucocorticoid-treated group. BW, Body weight.

[a] This table does not include the nine patients receiving prophylactic iv glucocorticoids during radioactive iodine treatment (60).

[b] Based on studies with exactly documented overall response rates or number of adverse events only.

frequent side effects compared with oral regimens. In patients with active and severe GO, enlarged eye muscles significantly reduced in size after iv treatment (40). Post-radioiodine-thyroid-ablation-induced GO activation occurred in 47.6% of patients treated with oral glucocorticoids but none of the patients treated with iv glucocorticoids ($P = 0.0001$) (60). However, a recent paper (61) showed that low doses of oral prednisone also exert a protective effect after radioiodine treatment.

Randomized Controlled Trials of Intravenous Glucocorticoids for GO

In a single-blind trial (62), 70 consecutive subjects with active and severe GO were randomly assigned to receive either 500 mg of methylprednisolone iv once weekly for 6 wk and then 250 mg/wk for 6 wk (a total of 4.5 g) or 100 mg/d of prednisolone orally for 1 wk, after which the dose was reduced by 10 mg/d at weekly intervals and stopped after 12 wk (a total of 4 g). Among the patients who received iv methylprednisolone, 27 (77%) responded to treatment, compared with 18 (51%) who received oral prednisolone. Quality of life improved for patients in the iv group. During the 6-month follow-up period, optic neuropathy developed in four patients of the oral group, and more patients in this group underwent orbital surgery. There were fewer manifestations of Cushing's syndrome and fewer adverse events in the iv group. An identical protocol was applied in patients with untreated active and moderately severe GO (63). Similar success rates (72 *vs.* 49%; $P < 0.001$, in the iv and oral groups, respectively) and higher efficacy of the iv regimen confirmed the data reported above. Additionally, the iv schedule was better tolerated than the oral one (side effects in 56 *vs.* 81%; $P < 0.01$). Intravenous glucocorticoids achieved a more rapid and significant improvement than oral glucocorticoids as measured by clinical activity score (CAS) ($P < 0.01$), proptosis ($P < 0.038$), lid fissure width ($P < 0.0001$), extraocular muscle changes ($P < 0.02$), optic neuropathy ($P < 0.001$), intraocular pressure ($P < 0.04$), visual acuity ($P <$

0.03), quality of life ($P < 0.0001$), and treatment response ($P < 0.001$; Table 2).

A double-blind trial comparing iv methylprednisolone to saline infusion demonstrated the efficacy of this regimen (64). The treatment was successful in five of six patients (83%) receiving methylprednisolone and in one of nine (11%) given placebo [relative risk = 7.5; 95% confidence interval (CI), 1.1–49.3; $P = 0.005$). Intravenous glucocorticoids were also more effective than orbital decompression surgery in patients with

TABLE 2. Randomized trials of iv glucocorticoid therapy for GO

First author, year (Ref.)	Number of patients in the iv group n	Dosage and treatment protocol	Comparison group	Response rate in the iv group (%)	Patients with side effects (%) (documented side effects: minor/ moderate/major)
Macchia, 2001 (65)	25	1 g/wk iv methylprednisolone for 6 wk. Cumulative dose, 12 g.	60–80 mg/d oral prednisone, reduced every second week for a total duration of 4–6 months	21 (84%)	Exact number of patients with side effects not mentioned (17 minor and 18 moderate adverse events)
Kauppinen-Mäkelin, 2002 (66)	18	2 × 0.5 g (1 g/48 h) iv methylprednisolone repeated after 1 wk, oral prednisone administered between the pulses and tapered down after the last pulse. Cumulative dose, 2 g.	60 mg/d oral prednisone, reduced over 15 wk to 5 mg every other day for one more final week. Cumulative dose, 2990 mg	16 (89%)	Exact number of patients with side effects not mentioned
Kahaly, 2005 (62)	35	0.5 g/wk iv methylprednisolone, then 0.25 g/wk iv methylprednisolone (6 wk each). Cumulative dose, 4.5 g.	100 mg/d oral prednisolone tapered by 10 mg/wk over a total of 12 wk. Cumulative dose, 4 g	27 (77%)	6 (17%) (8 minor adverse events, no major adverse events)
Ng, 2005 (69)	7	0.5 g iv methylprednisolone for 3 consecutive days, followed by tapering dose of oral prednisolone. Cumulative dose, 4.46 g.	0.5 g iv methylprednisolone for 3 consecutive days. + 2 Gray/d orbital irradiation over 2 wk. Cumulative dose, 20 Gray.	2 (29%) improvement (soft tissue swelling and ocular motility)	Exact number of patients with side effects not mentioned (14 minor and 10 moderate adverse events)
Wakelkamp, 2005 (28)	9	1 g/d iv methylprednisolone for three consecutive days repeated after 1 wk, followed by tapering dose of oral prednisone. Cumulative dose, 6 g.	Orbital surgery (three wall coronal decompression)	5 (56%)	Exact number of patients with side effects not mentioned
Aktaran, 2007 (63)	25	0.5 g/wk iv methylprednisolone, then 0.25 g/wk iv methylprednisolone (6 wk each). Cumulative dose, 4.5 g.	72 mg/d oral methylprednisolone tapered by 8 mg/wk for a total of 12 wk. Cumulative dose, 4 g.	18 (72%)	14 (56%) (9 minor and 4 moderate adverse events)
Menconi, 2007 (67)[a]	60	Two iv infusions of methylprednisolone acetate on alternate days each week: 15 mg/kg BW for the first four infusions, and 7.5 mg/kg BW for the last eight infusions. Cumulative dose, 6–10 g.	Patients were divided in two groups: 1) near-total thyroidectomy, and 2) near-total thyroidectomy and radioactive iodine. Both groups received the same treatment schedule of iv glucocorticoids	50 (83%)	Exact number of patients with side effects not mentioned (no major adverse events)
van Geest, 2008 (64)	6	0.5 g iv methylprednisolone for 3 consecutive days. Cumulative dose, 6 g.	Placebo-controlled study	5 (83%)	Exact number of patients with side effects not mentioned (6 minor and 3 moderate adverse events)
Marcocci, 2001 (68)	41	iv methylprednisolone acetate, 15 mg/kg BW for 4 cycles, then 7.5 mg/kg BW for 4 cycles. Cumulative dose, 9–12 g. + 2 Gray/d (4 meV linear accelerator). Cumulative dose, 20 Gray.	100 mg/d oral prednisone reduced weekly over 22 wk. Cumulative dose, 6 g + 2 Gray/d (4 meV linear accelerator). Cumulative dose, 20 Gray.	36 (88%)	23 (56%) (14 minor, 14 moderate and 2 major adverse events (transient hepatitis, depression))
Ng, 2005 (69)	8	0.5 g iv methylprednisolone for 3 consecutive days. Cumulative dose, 4.243 g. + 2 Gray/d orbital irradiation over 2 wk. Cumulative dose, 20 Gray.	0.5 g iv methylprednisolone for 3 consecutive days, followed by tapering dose of oral prednisolone	7 (87.5%)	Exact number of patients with side effects not mentioned (only moderate adverse events)

(*Continued*)

TABLE 2. Continued

First author, year (Ref.)	Number of patients in the iv group n	Dosage and treatment protocol	Comparison group	Response rate in the iv group (%)	Patients with side effects (%) (documented side effects: minor/moderate/major)
Total	234			187 of 234 (79.9%)[b]	Total no. of patients with side effects: 43 of 101 documented cases (43%) Total no. of documented side effects: 68 minor, 49 moderate, 2 major

BW, Body weight.

[a] In the study by Menconi *et al*. (67), all patients had thyroid surgery, and 30 of 60 also received radioactive iodine after surgery.

[b] The overall response rate (n = 187/234, 79.9%) includes both iv glucocorticoid monotherapy (n = 144/185, 77.8%) and the combination iv glucocorticoids plus orbital irradiation (n = 43/49, 87.8%).

sight-threatening GO (28). In another study (65), all patients showed a significant improvement of orbital inflammation, proptosis, and diplopia. Relevant side effects were reported from patients receiving oral but not iv glucocorticoids. In a further trial (66), the iv group required less additional therapy at 3 months than the oral group. Furthermore, 60 patients with moderate GO (67) who were treated with iv glucocorticoids were randomized as follows: group 1, near-total thyroidectomy; and group 2, thyroidectomy plus radioiodine ablation. The distribution of GO outcome at 9 months was more favorable in group 2 ($P = 0.0014$).

The effect of orbital irradiation was evaluated with iv or oral glucocorticoids (68). The CAS decreased significantly more in the iv group. By self-assessment evaluation, 85% of the iv patients and 73% of the oral patients reported an improvement in ocular conditions, and responders were more common in the iv group (88%) than in the oral group (63%). Side effects occurred in 56% of the iv and 85% of the oral patients. Cushingoid features developed in five of the iv and 35 of the oral glucocorticoid subjects. However, one iv patient had severe hepatitis at the end of glucocorticoid treatment, followed by spontaneous recovery. Similar results were reported in a study (69) that claimed a high response rate (88%) for a combination of orbital irradiation and iv glucocorticoids. By contrast, the addition of 20 Gray to iv prednisolone had no extra benefit in a Japanese study (54). However, due to the absence of randomized controlled trials, a synergistic effect of radiotherapy with iv glucocorticoids cannot be excluded.

Effect of Intravenous Glucocorticoids on Clinically Relevant Issues

Eye symptoms and/or subjective outcomes

The effect of iv glucocorticoids on eye symptoms and/or subjective outcomes was evaluated in six randomized (n = 147) and three nonrandomized (n = 47) studies. Intravenous treatment improved subjective symptoms in 92 of 117 (69%), remained unchanged in eight of 72 (11%), and worsened in four of 72 (6%) reported cases. The satisfaction rate was 80% after iv therapy ($P < 0.007$). As many as 77% considered their quality of life to be poor before glucocorticoids, but only 11% did so after iv therapy ($P < 0.001$) (62). The self-assessment score decreased from 3.1 to 2.2 ($P = 0.0001$) in the iv group. In another randomized trial, 85.3% of the iv glucocorticoid patients reported an improvement in ocular condition by self-assessment evaluation (68), whereas the nonrandomized trials showed an improvement in 29 of the 31 reported cases (94%).

Soft tissue features

Soft tissue features were evaluated in eight randomized (n = 174) and eight nonrandomized (n = 229) studies. Average decreases in CAS of 2.5 and 3.5 points were registered in the randomized and nonrandomized trials, respectively. Inactivation of GO according to CAS was noted in 59 and 89% of the reported cases in randomized and nonrandomized studies, respectively. The percentage of subjects with chemosis and conjunctivitis decreased by 61 and 52%, respectively, after iv therapy (62).

Proptosis

A reduction in proptosis of 1.6 mm ($P < 0.0001$) and a decrease of 1.5 mm in lid width ($P < 0.001$) were noted after iv treatment (68). In another randomized trial, 60% had a decrease in proptosis of at least 2 mm ($P < 0.02$). Additionally, 63% showed a decrease in lid width of 2 mm ($P < 0.01$) (62). In eight randomized (n = 174) and nine nonrandomized (n = 175) studies, the mean decreases in proptosis were 1.14 and 1.58 mm, respectively.

Ocular motility, diplopia, and dysthyroid optic neuropathy

A total of seven randomized (n = 149) and eight nonrandomized (n = 136) studies evaluated the changes in ocular motility and diplopia after iv treatment. In the randomized trials, ocular motility improved in 12 of 21 (57%), did not change in five of 15 (33%), and worsened in one of seven (14%) reported cases, whereas diplopia disappeared in 23 of 64 (36%), improved in 17 of 61 (28%), and did not change in 23 of 53 (43%) reported cases after iv treatment. In the nonrandomized trials, diplopia disappeared in 26 of 105 (25%), improved in 40 of 116 (35%), and did not change in 10 of 30 (33%) reported cases. An improvement in one-gaze eye muscle motility of 10 degrees was noted in 46% after iv treatment ($P < 0.01$) (62). Finally, dysthyroid optic neuropathy improved in 77% of the reported cases in the randomized trials, whereas visual acuity improved in 67% in the nonrandomized trials.

Comparison of Intravenous *vs.* Oral Glucocorticoids

A comparison of iv *vs.* oral administration is reported in five randomized trials. The overall response rate was 82% (118 of 144) and 53.4% (63 of 118) in the iv and oral groups, respectively, whereas 43 of 101 (42.6%) and 75 of 103 (72.8%) GO patients complained of side effects. The use of oral prednisone between pulses and its use in the tapering after iv glucocorticoids did not increase the response rate, according to the results of both randomized (response rate, 82% without *vs.* 68% with oral prednisone) and nonrandomized (response rate, 84% without *vs.* 74% with oral prednisone) trials.

Evaluation of both therapeutic modalities on clinically relevant issues showed the following: eye symptoms improved in 102 of 123 (83%), remained stable in 12 of 98 (12%), and worsened in five of 98 (5%) iv-treated subjects. By comparison, in the oral group, 80 of 125 (64%) improved, 28 of 98 (29%) remained stable, and 10 of 98 (10%) worsened. Regarding soft tissue features and proptosis, the average decreases in the CAS were 2.4 and 1.8 points, and the decreases in proptosis were 1.3 and 1.1 mm in the iv and oral groups, respectively. With respect to ocular motility, diplopia disappeared in 23 of 64 (36%) and improved in 15 of 57 (26%) patients in the iv group and disappeared in 16 of 46 (35%) and improved in six of 34 (18%) patients in the oral group. Finally, a dramatic improvement in optic neuropathy occurred during iv treatment in 21 of 25 cases (84%), whereas severe eye signs improved in three of eight orally treated subjects (38%). Additionally, visual acuity significantly improved in the iv group and remained almost stable in the orally treated subjects.

Systematic Reviews, Meta-Analyses, and Consensus Statement

In a quantitative review (21), 14 studies were identified and included in the final analysis five cohort and nine randomized. A total of 813 patients were evaluated. The authors stated that glucocorticoids are an effective treatment for GO compared with the other treatments currently available and that the combination of oral glucocorticoids and orbital radiotherapy is more effective than either modality alone (pooled relative reduction in risk of failure, 70%). The number of patients needed to treat with the combination of oral glucocorticoids and radiotherapy to prevent a single failure is between three and eight. Additionally, evidence from the studies suggested that iv glucocorticoids have the best documented efficacy, similar to or greater than the combination of oral glucocorticoids and radiotherapy. The side effects of oral glucocorticoids can also be minimized by the use of iv glucocorticoid pulse therapy. A second systematic review and meta-analysis of randomized trials comparing treatment modalities for GO *vs.* placebo was recently published (70). The primary outcome was the CAS. Thirty-three trials, evaluating 1367 patients, fulfilled the inclusion criteria. This systematic review also stated that in patients with moderate to severe GO, iv pulses were significantly better than oral glucocorticoids in reducing the CAS (standardized mean difference, −0.64; 95% CI, −1.11 to −0.17; χ^2, 7.91; I^2, 62% random effect). This advantage was mostly due to the results in the patients with severe GO (standardized mean difference, −86; 95% CI, −1.24 to −49). In patients receiving oral glucocorticoids, there were significantly more adverse events than in the iv group (odds ratio, 0.12; 95% CI, 0.05–0.26). Patients in the oral group had a high rate of steroid-related adverse events, mostly weight gain (26%), hypertension (8%), and Cushingoid features (7%). Adverse events in the iv group included lower rates of steroid-related events (3–4%) and common mild symptoms occurring during infusion or within 24 h of treatment, which consisted of palpitations (8%), flushes (20%), and transient dyspepsia (15%). Treatment was discontinued in four patients in the oral group and in none of the patients in the iv group. Finally, in their recently published consensus statement (9, 10), the European Group on Graves' Orbitopathy did recommend the use of iv glucocorticoids as first-line treatment for patients with ac-

tive and severe GO. The iv treatment should preferably be administered in centers with the appropriate expertise. Bisphosphonates are recommended when long-term glucocorticoid therapy is used, but only in the case of oral treatment with an average dose of 5 mg/d prednisone (or equivalent) for more than 3 months. In comparison, during short-term administration of iv steroids, bisphosphonates are not required (9, 10).

TABLE 3. Morbidity and mortality of iv glucocorticoid therapy in GO

First author, year (Ref.)	n	Dosage and treatment protocol	Morbidity		Mortality
			Cardiovascular	Hepatic	
Weissel, 2000 (74)	1	Five cycles of 1 g/d iv methylprednisolone for 3 consecutive days. Documented received dose, 15 g.	Not mentioned	See mortality	Fatal liver failure, n = 1
Marino, 2004 (75)	800	1 g/d iv methylprednisolone acetate for 3 consecutive days per week for 8 wk. Cumulative dose, 24 g.	Not mentioned	See mortality	Acute liver failure, n = 1
		Eight, 12, or 16 cycles of two injections of 7.5–15 mg/kg BW iv methylprednisolone acetate on alternate days every second week. Cumulative dose, 3–15 g.	Not mentioned	Acute liver damage, n = 4	Acute liver failure, n = 1; kidney complications after liver transplantation, n = 1
Salvi, 2004 (76)	1	Eight cycles of two infusions (7.5 mg/kg BW) iv methylprednisolone on two alternate days every second week. Cumulative dose, 5.5 g.	Not mentioned	Increase of serum aminotransferases (up to 1200 U/liter) and antinuclear antibodies, n = 1	None
Marino, 2005 (77)	1	Documented received dose, 4.7 g iv methylprednisolone acetate	Not mentioned	Acute autoimmune hepatitis, n = 1	None
Gursoy, 2006 (71)	1	Cycle of two infusions of 1 g/d iv methylprednisolone on alternate days every second week. Documented received dose, 2 g.	Acute pulmonary edema and hypertension, n = 1	Not mentioned	None
Owecki, 2006 (72)	1	3 d 1 g/d iv methylprednisolone, followed by 4 d pause. Documented received dose, 5 g.	Severe hypertension, myocardial infarction on the fifth day of treatment, n = 1	Not mentioned	None
Le Moli, 2007 (78)	13	1 g/d iv methylprednisolone on 3 consecutive days in the first and the second week. Cumulative dose, 8.45 g.	Cardiac palpitations during infusion, n = 1	Increase of liver enzymes, n = 6	None
	14	0.5 g/wk iv methylprednisolone for 6 wk followed by 0.25 g/wk for another 6 wk. Cumulative dose, 4.5 g		Increase of liver enzymes, n = 1	None
Lendorf, 2009 (73)	49	1 g/d iv methylprednisolone for 5 consecutive days. Cumulative dose, 5 g.	Coronary thrombosis and angina, n = 1; coronary angina, n = 1	Not mentioned	Stroke, n = 1; pulmonary embolism, n = 1
Total	881		18 (2%)		6 (0.68%)
Randomized trials (62, 63, 68)[a]	101	See Table 2	43 (43%) with minor, moderate or major adverse events		

(*Continued*)

TABLE 3. Continued

First author, year (Ref.)	n	Dosage and treatment protocol	Morbidity		Mortality
			Cardiovascular	Hepatic	
Nonrandomized trials (32, 56, 59)[a]	63	See Table 1	7 (11%) with minor, moderate or major adverse events		
Grand total	1045		68 (6.5%)[b]		6 (0.57%)

BW, Body weight.

[a] Six randomized and nonrandomized trials (32, 56, 59, 62, 63, 68) only reported the exact number of patients with side effects.

[b] Grand total of morbidity and mortality calculated according to the exactly documented number of patients with minor, moderate and major side effects (14 studies including 1045 patients receiving iv glucocorticoids).

Morbidity and Mortality of Intravenous Glucocorticoids

There are numerous case-series reports on the potential serious cardiovascular and hepatic risks of the iv glucocorticoid administration modality (71–78). Of a total of 1461 iv-treated patients, complete data were present in only 1045. The calculated morbidity and mortality of these fully documented patients receiving iv glucocorticoids approached 6.5 and 0.6%, respectively (Table 3). Serious adverse events occurred only in patients receiving daily and/or alternate single doses higher than 0.5 g. Severe complications were reported in five of these GO patients, of whom two died due to cardio- and cerebrovascular complications (73). In the three surviving patients, coronary thrombosis and an increase in specific cardiac enzymes were registered. All five patients received continuous doses of 1 g of iv glucocorticoids for 5 consecutive days.

Severe liver damage was reported after iv pulses; it resulted in fatal acute liver failure in four patients with GO (74–76). The cumulative doses were 10–24 g. Another study (77) reported an acute autoimmune hepatitis in a patient without history of liver disease. Liver enzymes increased subsequent to administration of a cumulative prednisolone dose of 4.7 g, leading to the immediate discontinuation of the iv pulses. Because liver enzymes remained elevated and reached a peak after 45 d, immunosuppression with oral glucocorticoids was started and led to a normalization of the liver enzymes. The assumption was that the autoimmune disorder did rebound during an interpulse period.

Sequential sampling of patients with severe GO (59) showed better liver tolerability for a weekly regimen encompassing six doses of 0.5 g iv prednisolone per week followed by six doses of 0.25 g/wk (cumulative dose, 4.5 g) *vs.* a regimen of four cycles of 15 mg/kg, followed by four cycles of 7.5 mg/kg (cumulative dose, 90 mg/kg; range, 4.9–7.4 g). Thus, iv glucocorticoids may exert a direct toxic effect on hepatocytes, and the extent and outcome of severe liver damage seems to be dose dependent (78). Pretreatment liver steatosis and/or diabetes are not related to liver damage, but preexistent viral hepatitis B is a risk factor. By contrast, cases of hepatitis and liver failure have not been reported in patients treated with high doses of oral glucocorticoids, which may be related to the gradual withdrawal of the oral dose. Another explanation could be an underestimation of the problem. Patients given iv glucocorticoids are usually more carefully (and frequently) followed with respect to possible increases in liver enzymes. These increases may be totally asymptomatic and therefore may be missed if not looked for carefully. Thus, the abrupt withdrawal of iv glucocorticoids, after prolonged immunosuppression, may cause a reexacerbation of an underlying autoimmune liver disease process, which may result in liver damage. Although a direct relation between iv glucocorticoids and severe liver damage has yet to be proven, these individual reports prompt a strict selection and careful monitoring of patients to be subjected to iv therapy. Accordingly, restrictive measures have been recommended, such as limiting the cumulative dose of iv glucocorticoids to 6–8 g, assessment of liver morphology by sonography, virus markers and autoantibodies before iv treatment, and exclusion of patients at risk (*i.e.* those with liver dysfunc-

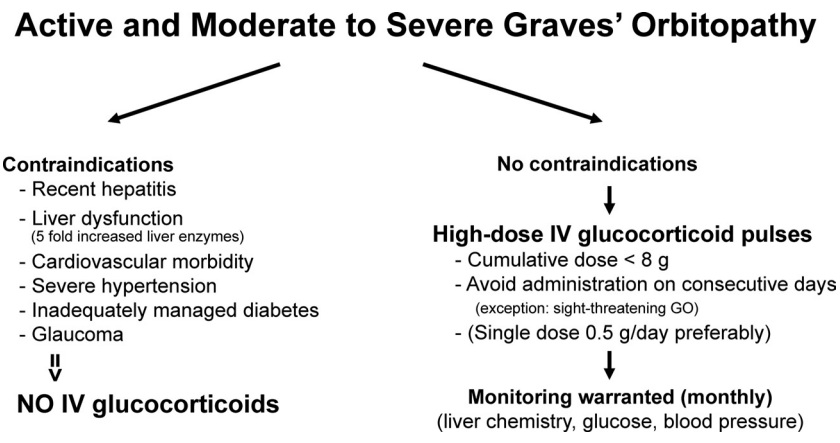

FIG. 2. Algorithm for the iv glucocorticoid treatment in active and severe GO.

tion, severe cardiovascular morbidity, severe hypertension, inadequately managed diabetes, and glaucoma). The dosing schedule seems relevant, and an alternate weekly schedule with single doses not surpassing 0.5 g/d should be safer (with the exception of cases of sight-threatening GO). Finally, monitoring liver function (monthly) during iv treatment is warranted. Accordingly, a recommended algorithm is presented in Fig. 2.

Conclusion

Numerous randomized trials and meta-analyses (9, 10, 21, 70, 79) have proven the beneficial effect of glucocorticoids in GO. Systemic glucocorticoids are strongly recommended based on evidence, primarily in the clinically active inflammatory stage of the disease, and are actually regarded worldwide as the first-line treatment. Oral glucocorticoids are effective and widely used, and they represent a valid, but probably less effective, alternative to iv glucocorticoids. Current evidence demonstrates the efficacy of iv pulses in decreasing disease activity in patients with active and severe GO. The response rate of this therapeutic regimen is approximately 80%. Intravenous glucocorticoids have a statistically significant advantage over oral treatment and cause significantly fewer adverse events. Intravenous glucocorticoids should preferably be administered in centers with appropriate expertise. The currently recommended treatment for patients with active and moderate to severe GO (9, 10, 17) is a course of 0.5 g of methylprednisolone iv once weekly for 6 wk, followed by 0.25 g/wk for 6 wk (cumulative dose, 4.5 g). If there is negative clinical response, iv glucocorticoid treatment may be stopped after 6 wk of 0.5 g/wk dosing. Although effective, this treatment may be accompanied with major side effects related to preexisting diseases, dose, and treatment schedule. Thus, careful patient selection and monthly monitoring during treatment are necessary. The total cumulative dose of iv glucocorticoids should not exceed 8 g, and single doses should preferably not be administered on consecutive days.

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