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REVIEW

Exacerbation of myasthenia gravis following corticosteroid treatment: what is the evidence? A systematic review

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Abstract

Corticosteroids (CS) are among the most widely- used immunosuppressive agents for immune-mediated conditions, including myasthenia gravis (MG). While their effectiveness in MG is documented and supported in the clinical practice over several decades, one of the main drawbacks of treatment results from the notion that MG patients may experience symptom worsening following CS treatment initiation. This may lead to the administration of lower than necessary doses of CS for the disorder, or even avoiding them altogether. As a consequence, some patients may not receive the optimal treatment to control their disease. In the present review, we analyzed 27 relevant publications and determined the prevalence of clinical exacerbation following CS treatment, its' severity and relation to the type and dose of CS. The rate of MG exacerbation is highest with the administration of cortisone, intermediate with prednisone, and lowest with methylprednisolone. High dose daily or alternate-day prednisone is associated with exacerbation more frequently than low-dose treatment, but most exacerbations are of mild to moderate severity. Other factors related to increased risk of an initial exacerbation include older age, generalized MG, bulbar symptoms, disease severity, presence of thymoma, and thymectomy. However, the current information is based mostly on heterogeneous studies of low quality, and prospective clinical trials designed to compare between the various agents and doses and assess the rate and severity of the exacerbation by a unified scale are warranted.

Keywords Myasthenia gravis · Corticosteroids · Initial exacerbation · Prednisone · Cortisone · Methylprednisolone

Introduction

Myasthenia gravis (MG) is an autoimmune disease characterized by impairment of the neuromuscular transmission, with resulting clinical weakness and fatigability of the skeletal and extraocular muscles [1]. The most common autoantibody associated with the pathogenesis of MG is directed against the nicotinic acetylcholine receptor (AChR). Less prevalent antibodies causing similar clinical and electrophysiological features include the anti- muscle-specific tyrosine kinase (MuSK), the anti-LRP4, and the anti-Agrin antibodies [2–5]. In about 10% of patients, none of these antibodies is detected, but the clinical and electrophysiological data enable the diagnosis of seronegative MG [6–8].

Treatment strategies of MG include symptomatic treatment, namely the applications of cholinesterase inhibitors aiming to improve muscle weakness by increasing the concentration of acetylcholine at the neuromuscular junction (NMJ), and immunosuppressive agents that decrease the immune-mediated attack, thereby aiming to induce clinical remission. Corticosteroids (CS) are considered the mainstay of the immunotherapies of MG [9–13].

Documentation of the beneficial effect of CS for MG can be dated to the 1940s and the 1950s, where the administration of the adrenocorticotrophic hormone (ACTH) was reported to improve muscle strengths in myasthenic patients [14–18]. However, this improvement was preceded by a decrease in muscle strengths during the initial therapeutic protocol in a significant proportion of patients. Namba et al. reported their experience in 64 treatment courses of ACTH in 22 myasthenic patients and summarized the experience of others in 251 courses in 166 patients [19]. An early reduction in muscle strength was observed in 54–96% of initial

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ACTH courses and during 62–98% of all treatment protocols. Four deaths due to respiratory failure were associated with corticotropin treatment, leading the authors to conclude that CS treatment should be administered only in the intensive care unit.

During the 1950s, several publications reported the use of cortisone in MG [17, 18, 20–22]. In some, a decrease in muscle strength was observed [17, 21, 22], and both treatments (ACTH and cortisone) have been gradually abandoned.

With the abandonment of ACTH and cortisone, the use of prednisone and methylprednisolone has gained a significant place as a first-line treatment for generalized MG. Although CS are considered as first-line treatment for MG, the evidence for their efficacy in MG is, for the most, based on relatively small, retrospective, and anecdotal studies, using different therapeutic regimens, while prospective, randomized clinical trials are scarce [23]. The lack of uniformity in the studies using CS treatment is related to early reports of MG exacerbation following high-dose treatment regimens. Therefore, taking into consideration the notion that daily administration of CS may be harmful, some authors recommended the usage of alternate-day high-dose oral CS [24–26], while others developed an alternative regime of gradual increase doses [27]. Yet, the initial worsening of symptoms has been reported despite slowly increasing alternate doses [28–31]. As clinical improvement may begin earlier with high dose CS [28, 32], some authors still recommend high doses at treatment initiation, either orally [28, 33] or intravenously [34, 35], possibly in conjunction with intravenous immunoglobulins (IVIg) or plasmapheresis to prevent exacerbation [34, 36]. Thus, almost a century after the first report of their use for the treatment of MG, there is still no accepted treatment protocol or guidelines to CS treatment of MG in the clinical practice [23, 37].

This review summarizes the available data regarding the initial deterioration of MG following CS treatment. We aim to determine the rate and characterize the mode of onset and the severity of such an event, as well as analyze whether the initial exacerbation is associated with certain disease- or-drug-related predisposing factors. This information may guide clinicians to the best approach to usage of CS in MG.

Materials and methods

We performed a systematic search of all available studies reporting the therapeutic effect of corticosteroids in MG, using Pubmed, Embase (Ovid), and Web of Science databases. The following search keywords were used: corticosteroids; glucocorticoids; prednisone; prednisolone; cortisone; methylprednisolone; dexamethasone; myasthenia gravis; treatment; therapy; exacerbation; deterioration; worsening; flare-up.

The terms adrenocorticotropic hormone, ACTH, mineralocorticoids, aldosterone, and deoxycorticosterone acetate were defined as exclusion terms.

This review aims to document the harmful effects of CS on MG course. Therefore, only studies that reported worsening of symptoms during CS treatment, or mentioned that such exacerbation was not observed, were included. Publications in which no reference to the presence or absence of clinical worsening was made, were excluded. When more than 1 study reported the results of the same cohort, only the one that was first published was included. The search was performed through May 2020 and was limited to English language results only. The initial search resulted in 535 abstracts. When duplicate citations were removed, the results were reduced to 161 abstracts. Of these 161 abstracts, 108 were excluded due to lack of information regarding initial exacerbation, and 53 were chosen for full-text screening. Of these, 26 were excluded because they contained information on the same cohorts of patients ($n=4$), reported results from previously reported studies ($n=5$), and from studies conducted on animal models ($n=17$). 27 references were selected for final inclusion.

Figure 1 illustrates a flow chart of the selection process of publications for this review.

Results

A total of 27 studies were included in this analysis. Of these, five reported initial exacerbation of MG following treatment with cortisone [16–18, 21, 22], 15 with prednisone [24, 27–30, 32, 33, 38–45], and 7 with methylprednisolone [34, 46–51].

For all types of CS, most of the data concerning the rate of initial clinical deterioration following treatment were reported retrospectively, in case reports and relatively small case series, where CS were given as an open-label treatment. However, initial exacerbation following treatment with prednisone was reported in 2 prospective trials-: one randomized, double-blind trial of prednisone Vs. Placebo comprising 13 patients [43], and one open-label trial of 55 patients [44]. In addition, the other two prospective trials report the occurrence of initial clinical deterioration after treatment with methylprednisolone: one double-blind trial of methylprednisolone Vs. Placebo comprising 19 patients [51], and one open-label trial of 6 patients [49].

A summary of the available data on initial exacerbation following treatment with cortisone, prednisone, and methylprednisolone is provided in Tables 1, 2, and 3, respectively.

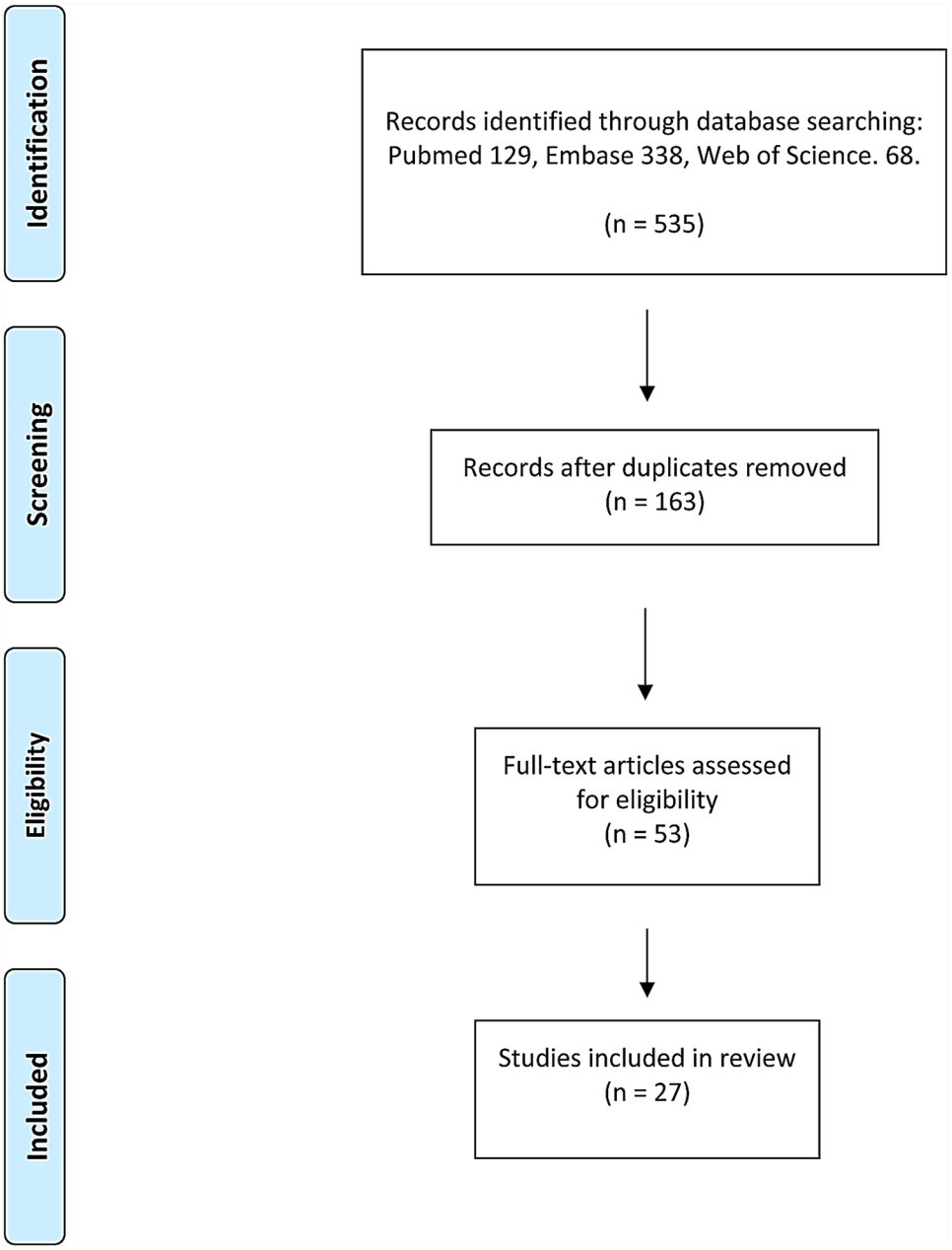

Fig. 1 Flow chart of the paper selection process

I. Baseline classification and severity of MG in patients treated with corticosteroids,

Most of the patients treated with CS in the studies reporting initial deterioration had generalized MG: 13 studies included only generalized MG patients, comprising 269 patients [16–18, 22, 24, 27, 34, 40, 43, 44, 46, 47, 51]; 9 studies included both generalized and ocular MG patients, comprising 369 patients with generalized MG and 44 patients with ocular MG [28–30, 32, 33, 38, 42, 49, 50]; 2 studies included only ocular MG patients, comprising 26 patients [39, 48]: and in 3 studies involving 73 patients, the MG classification was not reported [21, 41, 45]. Overall, 638 patients (84.5%) had generalized MG, 44 patients (6%) had ocular MG, and in 73 patients (9.5%), the MG classification was not reported.

Disease severity of generalized MG before CS treatment is reported in 21 studies: in nine, disease severity was defined according to the Osserman scale[52], or the modified Osserman and Genkins classification[53]; in three, the severity was defined according to the myasthenia gravis foundation of America (MGFA) score [54]; in one, the Oosterhuis classification was used [55], in one, a modification of the scale reported by Besinger was used [56], in seven, a descriptive definition of severity without

Table 1 initial exacerbation of MG following treatment with cortisone

Author (year); reference number	Study design	Patient Number, gender & age	MG classification and severity	Treatment dose	Prior and concomitant treatments	Rate and severity of MG deterioration	Definition of MG deterioration
Shy et al. [22]	Retrospective	One male, 29 years old	Marked weakness of facial, masticatory, and pharyngeal musculature; marked weakness of the neck muscles and the muscles of the shoulder girdle	Not reported	AChEI	1/1	The patient became worse by cortisone but returned to his previous status on therapy discontinuation
Milikan et al. [16]	Retrospective	3 2 Females, one male Ages 30, 36, 40 years old	Generalized MG One patient had a severe bulbar and peripheral weakness;	100 mg/day	AChEI	3/3	Two patients died, one had decreased ability to squat, rise, and lift his arms and was unable to swallow, returned to pretreatment state after discontinuation
McEachern [21]	Retrospective	1	Not reported	Not reported	Not reported	1/1	Severe increase of symptoms
Shlezinger [18]	Retrospective	1 Female age not reported	Ptosis, multiple extraocular muscle paresis, myasthenic facies	900 mg	AChEI	1/1	Possible aggravation of ophthalmoplegic manifestations
Grob and Harvey [17]	Retrospective	3 Females, ages 12, 25, 32 years	Two patients had a mild bulbar and moderate peripheral weakness; 1 patient had a moderate bulbar and very severe peripheral weakness	150–200 mg/day	AChEI	3/3	One patient became slightly weaker; two patients became moderately weaker

AChEIs acetylcholinesterase inhibitors

Table 2 Initial exacerbation of MG following treatment with prednisone

Author (year); reference number	Study design	Patient Number, gender and age	MG classification and severity	Treatment dose	Prior and concomitant treatments	Rate and severity of MG deterioration	Definition of MG deterioration
Kjær [45]	Retrospective	7 (3 Females, four males), mean age 63, range 50–74	Not reported	45 mg/day for 7 days, then tapered gradually to 7.5–15 mg/day	AChEIs	None	
Warmolts et al. [24]	Retrospective	5 (2 Men, 3 wome), ages 19–68 years	Generalized MG (1 mild, 1 moderate, 1 marked, 2 not reported)	100 mg\day on alternate day	1 Patient -none; 1—AchEIs-; 3 -AChEIs + thymectomy	None	
Jenkins [29]		9 (2 Males, seven females) mean age 41.1 years, range 21–56 years	One ocular, eight generalized, severity not reported	100 mg/day on alternate days	AChEIs; 5 patients had a thymectomy	2/9 (22.2%) Severity not reported	Not reported
Seybold et al. [27]		12	Generalized MG (7 patients Osserman class IV, 5 class IIB)	25 mg/day on alternate days, increased by 12.5 mg every 3rd dose until a maximal dose of 100 mg/day on an alternate day or an optimal response at a lower dose	AChEIs	None	
Pinelli et al. [30]	Retrospective	15 (10 Males, 5 females), mean age 49.5, range 15–71	Ossermans class I-1 patient; class IIB-6 patients; class IIB-III- 1 patient; class III- 3 patients; class IV- 3 patients; class V- 1 patient	100 mg/day on an alternate day for 3 months, then gradually tapered	Most patients received AChEIs; 9 patients had thymectomy, One patient, in the IVMP group reported moderate initial deterioration after treat	4/15 (26.6%; 1 Mild, 1 moderate, 2 severe)	Mild- slight deterioration without respiratory involvement; moderate- artificial respiration required for < 24 h; severe- required prolonged artificial respiration
Fischer et al. [39]	Retrospective	8 (3 Males, five females), mean age 54.9, range 5–83 years)	Ocular MG (1 patient had mild neck flexor weakness)	25–100 mg/day on alternate day	AChEIs	None	
Mann et al. [38]	Retrospective	30 patients (45 incidents of therapy) 14 males, 16 females; Mean age 45, range 13–81	Osserman class I-2 patients; class II- 4 patients; class III-V-24 patients	Mean initial dose of 59 mg/day (range 10–100)	AChEIs; four patients had a thymectomy	20/45 Incidents of therapy (44.4%; mild in 11, moderate in 5, severe in 4)	Severe- marked increase in muscle weakness requiring brief periods of respiratory support

Table 2 (continued)

Author (year); reference number	Study design	Patient Number, gender and age	MG classification and severity	Treatment dose	Prior and concomitant treatments	Rate and severity of MG deterioration	Definition of MG deterioration
Howard et al. [43]	Prospective, randomized (patients initially randomized to prednisone and placebo; patients in the placebo group with severe disability were switched to the active drug after 6 months)	13 (9 males, four females), mean age 59.5 (range 36–72) *Overall, ten patients received prednisone	Osserman class II- 1 patient; class III-12 patients	100 mg/day on alternate days	AChEIs *Patients who were previously treated with steroids and patients who had thymectomy were excluded	Although a few patients showed some increase in weakness during the first 3 weeks of prednisone therapy, especially on the off-prednisone day, this effect was usually mild *Exact number not reported	Not reported
Johns T.R [42] *2 separate series, series A identical to Mann et al. 1976	Retrospective	22)4 males, 18 females), mean age 43.5 years, range 14–81 years	Osserman class I- 2 patients; class IIA- 3 patients; class IIB- 4 patients; class III- 12 patients; class IV- 1 patient	120 mg/day on an alternate day	AChEIs	10/22 (45%) 7 mild, 3 moderate	Not reported
Scoppetta et al. [41]	Retrospective	65 Patients	Not reported	75–100 mg/day daily- 12 patients; 75–115 mg/day on alternate day- 36 patients; 25–50 mg/day daily- 5 patients; 25–50 mg/day on alternate day- 12 patients	Not reported	17/65 (26%) Severity not reported	Not reported
Pascuzzi et al. [33]	Retrospective	116 (41 Males, 75 females), mean age 45 (range 8–82 years)	Osserman class I-2 patients; class II-18 patients; class III-18 patients; class IV-60 patients; class V-18 patients ACh R-Ab positive in 33 of 35 patients with available studies	60–80 mg/day until sustained improvement then changed to an equivalent alternate-dose schedule	AChEIs used early during treatment with prednisone; dosage was reduced as rapidly as tolerated	56/116 Patients (48%); severe in 10 patients, moderate in 9, mild in 37	Severe- usually required intubation or assisted ventilation

Table 2 (continued)

Author (year); reference number	Study design	Patient Number, gender and age	MG classification and severity	Treatment dose	Prior and concomitant treatments	Rate and severity of MG deterioration	Definition of MG deterioration
Sghirlanzoni et al. [28]	Retrospective	60 (43 females, 17 males), age 17–71 years	Osserman class I- 2 patients; class IIA- 11 patients; class IIB- 22 patients; class III- 10 patients' class IV- 15 patients	Prednisone 10–75 mg/day on alternate days ($n=30$); prednisone 100 mg/day on alternate days ($n=20$); dexamethasone 20 mg/day ($n=10$); after 3–4 months gradually tapered to minimal effective dose	AChEIs; 17 patients had thymectomy before steroids	38% of patients given high doses, and 19% of patients given slowly increasing doses The severity of all patients not reported; 4 patients taking high-dose CS developed respiratory crisis	Not reported
Evoli et al. [32]	Retrospective	104 (59 Males, 45 females)	Osserman class !-14 patients; class IIA- 16 patients; class IIB- 47 patients; class III-IV- 27 patients; 92 patients positive for AChR-Ab	0.8–1.5 mg/kg/day	AChEIs (except a few patients with ocular MG); 45 patients had thymectomy before prednisone *No immunosuppressive therapies in the 6 months before steroids	22/104 (21%); Mild to moderate- 15 patients, severe- 7 patients)	Severe- requiring assisted ventilation
Seok Bae et al. [44]	Prospective	55 (20 Men, 35 women; mean age 45.8 ± 14.5	Osserman class II, AChR-Ab positive	40–80 mg/day	AChEIs(number of patients not reported); Thymectomy—30 patients	23/55 (42%). Severe in 10 patients	A decrease in MSS score by three or more points during the initial 4 weeks of prednisone use
Kanai et al. [40]	Retrospective	62 (26 Males, 36 females), Mean age 58.4 ± 16.9	Generalized, AChR-Ab positive MG MGFA class II- 49 patients; class III- 10 patients; class IV- 3 patients	17.6 ± 13.3 mg/day	Not reported	16/62 (26%;); Severe in 3 patients- 2 tubal feeding and one mechanical ventilation	Increment of three points in the Quantitative MG score within 2 weeks after the start of steroid treatment

MSS myasthenia severity scale, *AChEIs* acetylcholinesterase inhibitors, *AChR-Ab* acetylcholine receptor antibody, *MGFA* myasthenia gravis foundation of America

Table 3 initial exacerbation of MG following treatment with methylprednisolone

Author (year); reference number	Study design	Patient Number, gender and age	MG classification and severity	Treatment dose	Prior and concomitant treatments	Rate and severity of MG deterioration	Definition of MG deterioration
Brunner et al. [46]	Retrospective	9 (3 Males, six females), mean age 48.6 years, range 20–66 years *42 courses of treatment	All patients had very marked bulbar weakness, five patients had very marked peripheral weakness, four had marked peripheral weakness, and 1 had a moderate peripheral weakness	60 mg/day	Eight of the nine patients had 1 to 7 short, intensive courses of corticotropin for a total of 27 courses. Two patients had thymectomy before the study optimal doses of AChEIs were administered during MT treatment	30/42 Courses (71%); very marked or marked in 24 courses (57%), moderate or slight in 6 courses (14%)	Very marked or marked- requiring mechanical respiratory support
Arsura el al. [47]	Retrospective	15 (9 Females, six males), mean age 57 ± 18 years	Generalized, AChR-Ab positive MG patients hospitalized due to recent exacerbation (ten patients had a severe weakness that included the respiratory, bulbar, trunk, extremity, and oculofacial muscles. Five patients had mainly bulbar and oculofacial weakness)	2 g/day every 5 days (up to 3 courses)	6 Patients underwent thymectomy 3–96 months before MP treatment; AChEIs were adjusted to optimum levels before MP treatment	3/15 Patients (20%), mild decrease in strengths after infusion	Not reported
Lindberg et al. [51]	Prospective double-blind placebo-controlled	19 (9 Females, ten males; mean age ~ 52.4)	Generalized, AChR-Ab positive MG, Osterhuis class II- III	2 g/day for 2 consecutive days	AChEIs therapy was optimized immediately before the trial; Four patients had been on IVMP before the trial Two patients in the IVMP group were treated with azathioprine during the trial	One patient treated with IVMP reported moderate initial deterioration; None of the patients developed respiratory or other severe symptoms after treatment	Not reported

Table 3 (continued)

Author (year); reference number	Study design	Patient Number, gender and age	MG classification and severity	Treatment dose	Prior and concomitant treatments	Rate and severity of MG deterioration	Definition of MG deterioration
Komiyama et al. [49]	Prospective	6 (1 Male, five females), mean age 27.1 years, range 4–57	Generalized AChR-Ab positive MG ($n=3$) and ocular MG ($n=3$, 2 seronegative, 1 AChr-Ab positive) MG score (modified from Besinger)—15, 13, 9, 5, 4, 4	30 mg/kg/day (max 1 g/day) for 3 consecutive days, followed by 4th day infusion-free period. The course was repeated 3–5 times in patients with generalized MG and 2–3 times in patients with ocular MG	All patients with generalized myasthenia gravis had undergone extended thymectomy and plasmapheresis and received oral PSL (30 to 100 mg/alternate days) and azathioprine (75 to 100 mg/day) The three patients with ocular myasthenia gravis received oral PSL (30 to 60 mg/alternate days) with or without pyridostigmine	4/6 Patients (66.6%). Three patients with generalized MG required artificial ventilation	Increase in MG score
Nagane et al. [34]	Retrospective	71 (21 Males, 50 females), mean age ~ 53 years	MGFA classification class II-25 patients; class III-26 patients; class IV- 11 patients; class V-9 patients 49 AChR-Ab positive, 22 seronegative	MP 1 g/day for 3 days following each PLEX; oral PSL started at 10–20 mg/day and gradually increased by 5–10 mg/day every week, up to a maximum dose of 1 mg/kg/d	30 Patients underwent thymectomy	No MG crisis or severe initial worsening observed	
Ozawa et al. [48]	Retrospective	18 (14 Males, four females), mean age 64.4 years	Ocular, AChR-Ab positive MG	MP 1 g/day, repeated monthly till patients achieved minimal manifestations; PSL started at 5-10 mg/day, increased or decreased according to symptoms	No patient received immunotherapy at baseline; All patients were given AChEIs	No patient in either group experienced initial worsening of symptoms or developed generalized weakness	

Table 3 (continued)

Author (year); reference number	Study design	Patient Number, gender and age	MG classification and severity	Treatment dose	Prior and concomitant treatments	Rate and severity of MG deterioration	Definition of MG deterioration
Sugimoto et al. [50]	Retrospective	51 (32 Females, 19 males), mean age ~ 57	MGFA classification class I-18 patients; class II- 27 patients; class III- 3 patients; class IV- 1 patient; class V- 2 patients 46 patients positive for AChR-Abs, two positives for MUSK Abs, three double seronegative	250 mg-1 g/day for 3 days	15 Patients underwent thymectomy; 4 were treated with apheresis, four were treated with IVIG, 12 were treated with oral PSL, 38 were treated with AChEIs	26/51 (51%) Experienced initial deterioration in qualitative analysis, and 21/51 (41.2%) experienced initial deterioration in quantitative analysis *Severity not reported	Qualitative: appearance or aggravation of fatigue, muscle weakness, double vision, ptosis, dysarthria, feeling of difficulty swallowing, respiratory distress, dropped head, weakness in biting strength/difficulty chewing, and/or rhinolalia following high- dose IVMP; Quantitative: increase of 2 or more points on the MG-ADL scale after the start of IVMP

MP methylprednisolone, *PSL* prednisolone, *IA* immunoadsorption, *PLEX* plasma exchange, *AChEIs* acetylcholinesterase inhibitors, *MGFA* myasthenia gravis foundation of America, *MG-ADL* myasthenia gravis activities of daily living, *AChR* Abs acetylcholine receptor antibodies

reference to specific classification score was used [16–18, 22, 24, 46, 47]. In other four studies, disease severity was not reported [21, 29, 41, 45].

Of a total of 427 patients classified according to the Osserman classification, 23 patients were in class I, 192 patients were in class II (including IIa and IIb), 55 patients were in class III, 86 patients were in class IV, and 19 patients were in class V. One patient was defined as class II–III, 27 patients- class III–IV, and 24 patients- class III–V [27, 28, 30, 32, 33, 38, 42–44].

One hundred eighty-four patients were classified according to the MGFA classification. Of these, 18 were in class I, 101 were in class II, 39 in class III, 15 in class IV, and 11 were in class V [34, 40, 50]. The 19 patients classified according to the Oosterhuis classification were defined as class II–III [51], and the six patients classified according to the modifies Besinger scale had a score ranging between 4 and 15 [49].

In conclusion, disease severity before treatment was either not reported or evaluated by four different severity scales that do not enable any comparison or summation.

II. Definition of initial exacerbation of MG following CS treatment,

A clear definition of initial exacerbation following CS treatment, based on quantitative measures of disease severity, has been applied in only four studies in the following way: In one, the initial exacerbation was defined as a decrease in the myasthenia severity score (MSS) of 3 or more points during the initial 4 weeks of CS treatment [44]; in one, an exacerbation was defined as an increase of 3 points in the quantitative MG score within 2 weeks after the start of steroid treatment [40]; in one, Initial exacerbation was defined as any increase in MG score [49], and in the fourth study, both qualitative and quantitative measures were used to define deterioration [50]. In other four studies, a severe exacerbation was defined as a requirement of assisted ventilation [32, 33, 38, 46]. in one study, a mild exacerbation was defined as a slight deterioration without respiratory involvement, a moderate exacerbation was regarded as artificial respiration required for more than 24 h, and severe exacerbation as one requiring prolonged artificial respiration[30]. In twelve studies, a definition of disease exacerbation was not reported [16–18, 21, 22, 28, 29, 41–43, 47, 51].

III. Rate of MG exacerbation following CS treatment,

Overall, 238 events of initial deterioration were reported among 715 patients treated with CS (33.3%) in 25 out of 27 studies [16–18, 21, 22, 24, 27, 29, 30, 32–34, 38–42, 44, 46–51, 57]. two studies did not report the exact number of exacerbations [28, 43].

out of nine patients following cortisone treatment. [16–18, 21, 22]. Of those treated with prednisone, 148 events of initial deterioration are reported among 421 treatments (35.1%). Howard et al. report some increase in weakness during the first weeks of prednisone treatment without mentioning the exact number of patients that experienced such event [43]; Sghirlanzoni et al. report initial deterioration in 38% of patients given high dose prednisone and 19% of patients given slowly increasing doses, but the number of patients in each group is not specified, and it was not possible to calculate the exact number of patients [28]. Finally, 51 events of initial deterioration were reported among 222 patients treated with methylprednisolone (23%).

IV. Degree of exacerbation and relation with type and dose of CS treatment,

As mentioned above, all nine patients who were treated with cortisone experienced an initial deterioration. Of these, three patients received a dose of 100 mg/day [16], three patients received a dose of 150–200 mg/day [17], one patient received a course of 900 mg (course duration or daily dose not reported) [18], and for two patients the treatment dose was not provided [21, 22].

Prednisone was administered in a high-dose alternate-day regimen in 5 studies [24, 29, 30, 42, 43], and in a high-dose daily regimen in 5 studies [32, 33, 38, 44, 45]. In four of the five studies where a high-dose alternate-day regimen was used, initial deteriorations were reported in sixteen out of fifty-one patients (31.4%); in one study, the exact number of initial exacerbations was not reported [43]. In the five studies using the high-dose daily regimen, a total of 121 incidents of initial worsening out of 327 treatments (37%) were reported. In the other five studies, different therapeutic protocols were applied: Seybold et al. applied an alternate-day, gradually increasing low dose protocol, reporting no initial deterioration in twelve out of twelve patients[27]; Fischer et al. used both low- and high- dose alternate-day protocols, reporting no exacerbations in eight out of eight patients[39]; Scoppetta et al. applied four different therapeutic regimens- daily high- dose, alternate-day high-dose, daily low-dose, and alternate-day low dose. Initial exacerbations occurred in seventeen of the sixty-five patients (26.1%), but stratification of the rate of exacerbations in the different treatment arms was not reported[41]; Sghirlanzoni et al. used alternate-day low dose prednisone, alternate-day high-dose prednisone, and daily high-dose dexa-

methasone regimens, reporting initial exacerbations in 38% of the patients given high-dose and 19% of the patients given low-dose CS [28]. Kanai et al. used a daily low-dose regimen, reporting initial exacerbations in 16 out of 62 patients (25.8%)[40].

Methylprednisolone was administered intramuscularly at a dose of 60 mg/day in one study [46], and intravenously at a dose of 1–2 g/day in 6 studies [34, 47–51]. The rate of initial exacerbations was higher among the patients who were treated with the intramuscular formulation, compared with the intravenous formulation (30/42 incidents (71%) Vs. 29/180 incidents (16.1%), respectively).

V. Severity of MG exacerbation following CS treatment,

The severity of initial exacerbation following CS treatment was reported in 10 studies, comprising a total of 334 patients [17, 21, 30, 32, 33, 38, 42, 46, 47, 51]. Of these, 60 (18% of the incidents with reported severity, 8.3% of the total events of exacerbation) were mild, 21 (6.3% of the total incidents with reported severity, 2.9% of the entire occurrences of aggravation) were moderate, 21 (6.3% of the total events with reported severity, 2.9% of the total incidents of exacerbation) were mild-moderate, and 24 (7.2% of the total incidents with reported severity, 3.4% of the entire episodes of exacerbation) were severe. In additional five studies, comprising a total of 184 patients, only the proportion of severe exacerbation was documented- Sghirlanzoni et al. reported severe exacerbation in 4 out of 60 patients[28], Bae et al. reported severe exacerbation in 10 out of 55 patients[44], Koniyama et al. 3 out of 6 patients[49], Kanai et al. 3 out of 62 patients[40], and McEachern – 1/1 patient [21]. In seven studies with 143 patients, the severity of initial exacerbation was not reported [16, 18, 22, 29, 41, 43, 50]. In one of these, two death attributed to CS treatment have been described [16].

VI. Time of onset and duration of initial exacerbation following CS treatment,

Information regarding the onset timing of initial exacerbation after CS treatment is available in only ten studies [30, 32, 33, 38, 40, 42, 46, 47, 49, 50]. The onset of symptoms exacerbation in these studies ranges from 12 h to 21 days from treatment initiation, with a mean time-to-onset ranging, in the majority of studies, between 4 and 6 days. Information on the duration of initial deterioration is available in only five studies [33, 42, 47, 49, 50], ranging between 1 h and 21 days from the onset of symptoms, with a mean duration of 3–6 days.

VII. Factors associated with the risk of initial exacerbation following CS treatment,

This issue has been addressed explicitly in only three studies: Bae et al. found an association between the rate of initial exacerbation and older age, predominant bulbar symptoms and disease severity [44]; Kanai et al. report an association of initial exacerbation with the presence of thymoma, upper limb weakness and a dose of prednisone of more than 40 mg/day [40]. Sugimoto et al. identified an association between thymectomy and disease severity before treatment and the rate of initial exacerbation [50]. Other than these, Koniyama et al. report severe initial exacerbation (requiring assisted ventilation) in all three patients with generalized MG who were treated with methylprednisolone compared to initial worsening in 1 out of 3 patients with ocular myasthenia, suggesting an association between generalized MG and the rate (and severity) of initial exacerbation [49].

Discussion

CS represent an important first-line treatment for MG. However, one of the main limitations of CS treatment in MG is the possible occurrence of acute clinical worsening following treatment initiation. The present review summarizes the available data regarding the occurrence of initial clinical exacerbation following treatment with the three most widely used CS in MG. Our goal was to seek evidence on which CS regimens and risk factors are associated with clinical exacerbation, to formulate the best CS therapeutic protocol in treating MG.

To meet the goal of the present analysis and evaluate the impact of CS on muscle strength and disease severity in MG, the severity scale of the disease upon entrance to the various studies, and the degree of clinical change should be measured by the same scale. Moreover, the CS compound in use should be of similar dosage and administration mode, and the increase in muscle weakness should be evaluated at identical time points following treatment initiation. Unfortunately, these requirements were not met, and the available data from the 27 reports do not contain the information that is mandatory to answer the simple question: do CS cause clinical exacerbation upon initial usage in MG, and if so, at what dosage? Nevertheless, the information may still be used to confront with some unresolved clinical dilemmas.

The first question when considering CS treatment in MG is what the risk of initial deterioration is, and whether it relates to a specific drug. The calculated overall rate of initial exacerbation for cortisone, prednisone, and methylprednisolone is 33.3%. Considering the data for each drug separately, the occurrence of such complications seems

significantly higher for cortisone (for which initial exacerbation is reported in all nine patients included for analysis), intermediate for prednisone (35.1%), and lower for methylprednisolone (23%). Thus, the current evidence suggests that initial CS therapy is more frequently associated with clinical deterioration following treatment with cortisone, followed by prednisone and methylprednisolone. However, it should be noted that the information regarding cortisone treatment is significantly limited, as there are only five case reports studies available, and this conclusion should be interpreted with caution.

The second question to consider is whether the risk of initial exacerbation is related to the dose of CS. Regarding the treatment of prednisone and the rate of initial exacerbation, there seem to be no significant differences between a daily high-dose and an alternate-day high-dose regimen, which are associated with the highest rate of exacerbation (31.4% and 37%, respectively), while the rates of exacerbation using a low-dose regimen are lower, ranging between 0 and 26%[27, 40]. However, it should be noted that a significantly higher number of patients were treated with higher doses of prednisone. Moreover, among the studies that are aimed to identify whether the dose of treatment is specifically related to the rate of exacerbation, such an association was found in only one study [40]. Hence, the information seems to suggest that the initial administration of high dose CS is more often associated with clinical deterioration. Still, the available data do not enable us to draw any final conclusion.

Other factors that were found to be associated with increased risk of initial deterioration include older age, bulbar symptoms, disease severity, presence of thymoma, and thymectomy [40, 44, 50]. The risk of initial exacerbation is higher in patients suffering from generalized MG, compared to those with purely ocular MG [39, 48].

The severity of initial exacerbation was reported for 334 out of 715 incidents (46.7%). For an additional 184 patients (25.7%), only the rate of severe exacerbations was reported. Based on this data, most incidents of initial worsening were mild to moderate (30.6% of the events with reported severity, and 14.1% of the total episodes of clinical worsening), while only 8.1% of the incidents with reported severe exacerbations and 5.9% of the total events decrease in muscle strength were severe.

In conclusion, this review confirms the possible occurrence of clinical exacerbation during the initial stages of CS treatment. However, the evidence of this complication is, for the most, based on studies of low quality, since there are no randomized control studies comparing CS agents, dosage, and mode of administration. Therefore, our analysis did not provide convincing evidence that initial high dose steroids are associated with a higher risk of disease exacerbation, and the issue of what, if at all, the dosage of CS agent is more harmful remains open.

Having said that, the information presented in this review suggests that for young patients with mild to moderate disease, the risk of initial deterioration with prednisone seems relatively low and that for older patients with prominent bulbar and generalized weakness, in whom a rapid response to treatment is desired, intravenous methylprednisolone followed with oral prednisone may reduce the risk of initial deterioration. A prospective clinical trial designed to assess these essential clinical considerations is warranted.

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