LITERATURE REVIEW

Outcome and Safety of Different Cumulative Doses and Protocols of Intravenous Methylprednisolone in Moderate to Severe and Active Graves' Ophthalmopathy

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ABSTRACT

Background: Graves' ophthalmopathy (GO), also known as Graves' orbitopathy or thyroid eye disease, has a potential sight-threatening complications. The activity and severity are important determinants in GO and are implications for treatment. Intravenous Glucocorticoid (GC) was associated with significantly greater efficacy and was better tolerated than oral route in the treatment of patients with moderate to severe and active GO. Intravenous GC has a variation cumulative dose and protocols; meanwhile the optimal treatment is still undefined. The aim of this literature review was to analyze the outcome and safety of different cumulative doses and protocols of intravenous methylprednisolone of patients with moderate to severe and active GO.
Methods: The literature search was conducted from Google Scholar and Pubmed for journal articles that were published and related to the use of IVGC in moderate to severe and active GO
Results: From the keywords mentioned, titles were screened for eligibility and seventeen articles were found. After being checked for the duplication, the articles were screened based on the abstracts and/or full texts. As many as eight articles met the inclusion criteria, others were excluded.
Conclusion: Intravenous GC therapy in moderate to severe and active GO provide effect in reducing CAS, decreasing lid aperture size, decreasing proptosis size, and disappearing diplopia. A protocol uses a low cumulative doses (<5 g) of methylprednisolone weekly for 6 weeks and then halved dose weekly for another 6 weeks are preferred due to higher response in clinical outcome and safety profile.

Keywords: Graves' ophthalmopathy, thyroid eye disease, Graves' orbitopathy, glucocorticoid, intravenous methylprednisolone

Graves' ophthalmopathy (GO) also known as Graves' orbitopathy or thyroid eye disease, is part of an autoimmune disorders that can affect the orbital and periorbital tissue. It is occasionally associated with hypothyroid, euthyroid and Graves' hyperthyroidism. The clinical signs are characterized by eye lid retraction, lid lag, proptosis, restrictive extraocular myopathy and optic neuropathy. Graves' ophthalmopathy is usually bilateral, although it may be asymmetric or unilateral in 15% of patients.[1] The disease has potential sight threatening complications.[2]

The insidence of GO in Neuroophthalmology division Kirana Cipto Mangunkusumo Hospital between January 2013 to December 2014 was 68 patients, with the peak incidence aged between 40 and 60 years old.[3] In Denmark, the incidence of moderate to severe and very severe GO is 16.1 per million per year in the general population, primarily effects women. Tanda et al reported, over an 8-year period of prospective study, 5.8% of patients had moderate to severe GO.[4]

The pathophysiology of GO is caused by retro-orbital inflammation. Orbital fibroblast activation is a key contributor. These fibroblasts express the TSH receptor and produce extracellular matrix components and pro-inflammatory molecules. Further, there is an infiltration of immuno-competent T helper cells, B cells, macrophages and mast cells. Inflammation of the extraocular muscles, retrobulbar fat and connective tissue can lead to restricted eye movements and proptosis. The optic nerve can be compressed which can cause optic neuropathy resulting in permanent visual loss. Similar changes affect the eyelids and anterior periorbital tissues. These changes, combined with the local production of cytokines and other mediators of inflammation, result in pain, periorbital edema, conjunctival injection, and chemosis.[2]

Graves' opthalmopathy commences with active (inflammatory) phase with rapidly worsening signs and symptoms, reaching a point of maximum severity which then improves to a static plateau but does not resolve to baseline (inactive phase). This is known as Rundle's curve.[5,6] Activity is measured by the Clinical Activity Score (CAS). Severity of GO is classified into mild, moderate to severe and very severe (sight threatening).[7]

The activity and severity are important determinations in GO and have implications for treatment. Management for GO are divided into non surgical and surgical treatment. The non surgical treatments are conservative (ocular lubrication, sunglass wear), steroid and radiotherapy. Initiation of immunosupressive therapy is most efficacious during the active phase of the disease. Surgery is usually reserved for inactive phase with persistent proptosis and/or eyelid changes.[8]

Glucocorticoid (GC) have been used for treatment of moderate to severe GO due to their anti-inflammatory and immunosuppressive actions during the active phase of GO. It can be administered orally and intravenously. Intravenous GC was associated with significantly greater efficacy and was better tolerated than oral route in the treatment of patients with moderate to severe and active GO.[8] Intravenous GC has a variation cumulative dose and protocols, meanwhile the optimal treatment is still undefined. Lack of study investigated treatment effect and safety of different cumulative doses and also there were less research about protocols of IVGC for moderate to severe and active GO.

To address this issue, the aim of this literature review was to analyze the outcome and safety of different cumulative doses and protocols of intravenous methylprednisolone of patients with moderate to severe and active GO.

Table 1. Oxford Center for Evidence-Based Medicine Levels of Evidence

Level of Evidence	Therapy/ Prevention Studies
I	Systematic review of randomized trials or n-of-1 trials
II	Randomized trial or observational study with dramatic effect
III	Non-randomized controlled cohort/follow-up study
IV	Case-series, case-control studies, or historically controlled studies
V	Mechanism-based reasoning

MATERIAL AND METHOD

The literature search was conducted from Google Scholar and Pubmed for journal articles that were published and related to the use of IVGC in moderate to severe and active GO, using the keywords: Graves' ophthalmopathy, thyroid eye disease, Graves' orbitopathy, glucocorticoid, intravenous methylprednisolone. Only articles written in English were selected. Reference lists from the included studies were also checked for potentially relevant articles.

Initial screening was performed by reviewing abstracts to choose articles related to the study purpose from achieved articles based on keywords. Complete studies related to the accepted abstracts were then screened based on the inclusion and exclusion criteria.

Inclusion criteria were all studies (interventional and observational) that reported the use of intravenous methylprednisolone on moderate to severe and active Graves' ophthalmopathy, which emphasized on the outcome and side effects. Outcome variables was based on four variables, such as Clinical activity score (CAS), eyelid aperture, proptosis, and diplopia. Safety was based on the side effects. Publication date was set between year 2005 to 2016. Studies were excluded if the full text could not be accessed.

All studies that met the inclusion criteria were rated according to the level of evidence developed by Oxford Center for Evidence-Based Medicine (Table 1).[9]

All articles that fulfilled the inclusion and exclusion criteria were thoroughly examined for data available. Author use a previously made form to record data regar-ding baseline characteristic (author, year of published, level of evidence, study design, duration of follow up, total subject, subject's age and gender patients), outcome parameters and safety, using Microsoft Excel.

Moderate to severe of GO was the severity of GO that assessed according to the criteria of NOSPECS (Table 2): marked soft tissue swelling (2c by NOSPECS), and/or proptosis > 18 mm in females, > 20 mm in males (3a or more by NOS¬PECS), and/or inconstant/ constant diplopia in primary or reading (4b by NOS¬PECS), and/or punctuate staining of cornea, without any optic nerve involvement.

Table 2. GO severity assessment according to NOSPECS classification[11]

Grade		Symptoms/sign	
0		No symptoms, no signs	
1		Only signs	
2		Soft tissue involvement : swelling/redness of the eyes	
	0	Absent	
	A	Mild	
	B	Moderate	
	C	Marked	
3		Female	Male
	0	<17	<20
	A	18-19	21-22
	B	20-22	23-25
	C	>23	≥26
4		Extraocular muscle (EOM) involvement	Diplopia
	0	Absent	Absent
	A	In extremes of gaze	Intermittent
	B	In primary or reading position	Inconstant
	C	Frozen eye	Constant
5		Corneal involvement	
	0	Absent	
	A	Stippling of cornea	
	B	Ulceration	
	C	Clouding, necrosis and perforation	
6		Sight loss (visual acuity)*	
	0	>0.67	
	A	0.67-0.33	
	B	0.33-0.10	
	C	<0.10	

*Expressed as decimal, normal vision 20/20=1

Table 3. Clinical Activity Score (CAS).[7]

Clinical Activity Score (CAS)	
Spontaneous retrobulbar pain	1
Pain on eye movement (upward or downward gaze)	1
Eyelid erythema	1
Conjungtival injection	1
Chemosis	1
Swelling of the caruncula or plica	1
Swelling of eyelid	1

In active GO = CAS < 3
Active GO = CAS ≥ 3

Or according to EUGOGO (European Group on Graves' Orbitopathy): 7 Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients with moderate to severe GO usually have any two or more of the following: lid retraction > 2 mm, moderate or severe soft tissue involvement, exophthalmos > 3 mm above normal for race and gender, inconstant or constant diplopia. Activity of GO was defined with clinical activity score (CAS) > 3 points (Table 3).[7]

Table 4. Characteristic data of reviewed studies

No	Author	Year	Level of evidence	Study design	Follow up	Total subject	Age (year)	Gender	
								Male	Female
1	Kahaly et al1[7]	2005	II	Randomized controlled trial	12 weeks	35	52(31-72)	10	25
2	Aktaran et al[10]	2007	II	Randomized controlled trial	12 weeks	25	44,3 ± 11	11	14
3	Van Geerst et al1[8]	2008	II	Randomized controlled trial	12 months	6	50.7 (11.5)	0	6
4	Bartalena (A) et al1[9]	2012	II	Randomized controlled trial	12 weeks	53	54 (10)	16	37
	Bartalena (B)et al[16]	2012	II	Randomized controlled trial	12 weeks	54	50 (9)	23	31
	Bartalena (C) et al[16]	2012	II	Randomized controlled trial	12 weeks	52	56 (11)	10	42
5	Philip et al2[0]	2013	II	Randomized controlled trial	12 weeks	10	39.5	2	8
6	Beleslin et al2[1]	2013	IV	Retrospective analysis	6 months	50	48± 10	13	37
7	Zhu (A) et al2[2]	2014	II	Randomized controlled trial	12 weeks	39	45.30± 11.2	15	24
	Zhu (B) et al[19]	2014	II	Randomized controlled trial	12 weeks	39	48.23± 8.88	18	21
8	Roy et al[11]	2015	II	Randomized controlled trial	6 to 12 months	31	37.6 ± 6.31	9	22

RESULT

From the keywords mentioned, titles were screened for eligibility and seventeen articles were found. After duplication was checked, the articles were screened based on the abstracts and/or full texts. As many as eight articles met the inclusion criteria, others were excluded. Flowchart of the study selection is summarized in Figure 1.

The baseline characteristic data of the reviewed articles are presented in Table 4. The literature search identified a total of 8 articles, published between 2005 until 2016, including a total of 394 patients (267 female), suffering from moderate to severe and active Graves' ophthalmopathy.

All of the patients were treated with IV methylprednisolone. Most of studies' methods are prospective randomized clinical trial and one article is retrospective analysis. The mean age of the subjects varied from 31 to 72 years old. The shortest period of follow up was 12 weeks while the longest were up to 12 months after initial intervention.

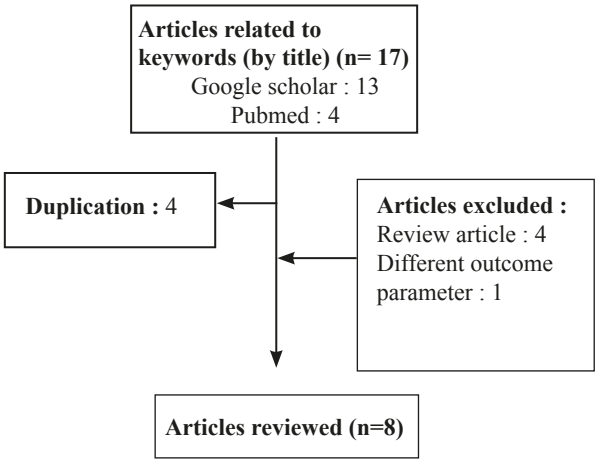

Fig 1. Flowchart showing screening process of articles included in this review

There are four protocols in this review, the most common was protocol I. Throughout all protocols, single dose of 0.5 g per day was found most frequently administered, the doses given ranging from 0.25-0.83 g per day.

There are three cumulative doses, ranging between 2.25 g to 10.2 g. The most frequent cumulative dose was 4.5 g (Table 5).

Table 5. Protocols (P) and cumulative dose of intravenous methylprednisolone administration

P	Treatment	Cumulative Dose	Author
I	Intravenous methylprednisolone 500 mg weekly for 6 weeks and 250 mg weekly for next 6 weeks.	4.5 g	Kahaly et al[14]
		4.5 g	Aktaran et al[10]
		4.5 g	Philip et al[17]
		4.5 g	Zhu (A) et al[19]
	Intravenous methylprednisolone 250 mg in the first six infusion and then 125 mg for remaining six infusion	2.25 g	Bartalena (A) et al[16]
	Intravenous methylprednisolone 540 mg in the first six infusion and then 290 mg for remaining six infusion.	4.98 g	Bartalena (B) et al[16]
	Intravenous methylprednisolone 830 mg in the first six infusion and then 415 mg for remaining six infusion	7.47 g	Bartalena (C) et al[16]
II	Intravenous methylprednisolone 500 mg for three consecutive days, in four cycles at 4 weekly intervals.	6 g	Van Geerst et al[15]
		6 g	Roy et al[11]
III	Intravenous methylprednisolone 500 mg in 500 ml of physiologic saline. Infusion was repeated after 48 hours and then followed by tappering doses of oral prednisone (40 mg/day for the first week,30 mg/day for the second week, 20 mg/day for the third week, 10 mg/day for the fourth week). Repeated each month for the next 5 months	10.2 g	Beleslin et al[18]
IV	Intravenous methylprednisolone 500 mg daily for 3 consecutive days per week for 2 weeks,followed by 250 mg daily for 3 consecutive days per weeks for 2 weeks and tappering oral prednisone	4.5 g	Zhu (B) et al[19]

Table 6. Response of IVGC in reducing CAS (%), lid aperture (%), decreasing proptosis size (%), disappearing diplopia (%)

Cumulative dose	P	Reducing CAS (%)	Lid aperture(%)	Decreasing proptosis size(%)	Disappearing diplopia(%)
Low dose (LD)					
- Kahaly et al[14]	I	60%*	15%*	8%*	25%*
- Aktaran et al[10]	I	60%*	16%*	5%*	22%*
- Philip et al[17]	I	78%*	N/A*	3%*	20%*
- Bartalena (A) et al[16]	I	45%*	4%*	3%*	N/A
- Bartalena (B) et al[16]	I	58%*	2%*	2%*	N/A
- Zhu (A) et al[19]	I	50%*	4%*	6%*	3%*
- Zhu (B) et al[19]	IV	25%*	2%*	0.5%*	13%*
Moderate dose (MD)					
- Bartalena (C)et al[16]	I	54%*	6%*	3%*	N/A
- Roy et al[11]	II	88% **-83%***	13% **-14%***	7%** - 9%***	67%** -67%***
- Van Geerst et al[15]	II	58%***	12%***	6%***	50%***
High dose (HD)					
- Beleslin et al	III	56%**	15%**	Up 0.4%**	27%

*= 12 weeks follow up
**= 6 months follow up
*** = 12 months follow up
P = Protocol
N/A = Not Available

In the 12 weeks follow up, protocol I with LD group have 45-78% response in decreasing CAS, 2 to 16% response in decreasing lid aperture size, 2 to 8% response in decreasing proptosis size and 3-25% response in disappearing diplopia (Table 6).

In the 6 months follow up, protocol II with MD group showed higher response compare to protocol III with HD in decreasing CAS (88%), decreasing proptosis size (7%), and disappearing diplopia (67%) (Table 6).

Safety of IVGC therapy was classified into major and minor side effects (Table 7). The major side effects were diabetes/hyperglicemi, hypertension, elevation of ALT, depression, psychosis, death due to myocardial infarction and serious infection. The most common minor side effects were weight gain, cushingoid features, hirsutism, gastrointestinal discomfort and hypokalemia.

Table 7. Safety of IVGC therapy

Side effects		Cumulative dose		
		Low	Moderate	High
Major	Diabetes/Hyperglycemia	0-12%*	3-100%***	N/A
	Hypertension	0*	6-50%***	22%**
	Elevation of ALT	5-20%*	0***	2%**
	Depression	0-2%*	4-6%***	6%**
	Psychosis	N/A	2%***	N/A
	Death to myocardial infarction	2%*	N/A	N/A
	Serious infection	N/A	2%***	4%**
	Weight gain > 3 kg	3-50%*	19-33%***	64%**
Minor	Cushingoid habitus	4%*	10-50%***	N/A
	Hirsutism	N/A	N/A	42%**
	Gastrointesinal discomfort	3-8%	3-33%***	14%**
	Hypokalemia	18/28%*	N/A	N/A

*=12 weeks follow up
N/A= Not Available
**= 6 months follow up
***= 12 months follow up

DISCUSSION

Glucocorticoid therapy is a well-established treatment of moderate to severe and active GO, owing to its anti-inflammatory and immunosuppressive actions. Cytokine release and glycosaminoglycan secretion by orbital fibroblast are inhibited by GC.

The rationale for the use of pulse therapy is the observation, that GO is often characterized by a single flare of the autoimmune process. Also, there is evidence that in progressive autoimmune disorders, IVGC achieve a rapid and effective immune suppression.[5]

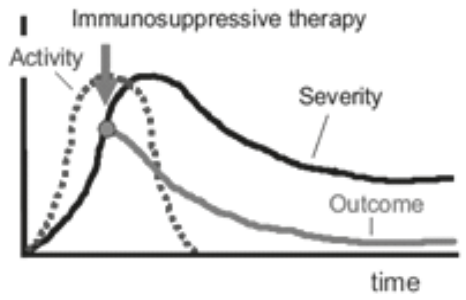

Fig 2. Administration of immunosuppressive therapy during the active phase of GO results in reduction of both the disease activity and severity.[1]

In this review, we found that IVGC provide positive effect in controlling acute inflammatory signs of GO. It showed the greatest response on soft tissue changes (incorporated in CAS) and disappearance of diplopia, whereas proptosis and lid aperture were less responsive.

Low cumulative dose in protocol I showed better response in decreasing CAS, lid aperture size, proptosis size and disappearance of diplopia, compare to other protocol group in 12 weeks follow up. Moderate cumulative dose in protocol II showed better response in decreasing CAS, diplopia and proptosis size than protocol III with HD in 6 months follow up. High dose in protocol III showed a better response in decreasing lid aperture compare to protocol II with MD in 6 months follow up. In 12 months follow up, protocol II with MD showed a 58-83% in decreasing CAS, 12-14% in decreasing lid aperture, 6-9% in decreasing proptosis size and 50-67% in disappearance of diplopia. Given the standar analysis for proptosis in this review, protocol III showed worsening of proptosis by 0.4%, although was not found to be statistically significant.[18]

Protocol I is the most common protocol for IVGC therapy. This weekly protocol also has been recommended by Zang et al.[17] The protocol was made for outpatient. However, practically, it was unfeasible to manage parenteral therapy

and examination in the same day. Beleslin et al[18] reported that their protocol (protocol III) were more convenient and feasible than weekly protocol, especially for patients who live far from a tertiary center and need several hours of travel. Zhu et al[19] showed that the weekly protocol (protocol I) was preferred because of the potential safety issues compare to the daily protocol. A fixed dosage in a longer duration of pulse IVGC therapy might lead to a better response. A weekly therapy is superior in terms of disease severity. There is also significantly fewer retreatment events and prolonged retreatment-free survival.[19]

Adverse events are major concern of IVGC therapy and it seems to be dose dependent. Since the benefit of IVGC has to outweigh the possible adverse events, the cumulative amount of GC must be high enough to show expected effects and low enough to prevent adversities.[18] The cumulative dose of GC in this literature review was ranged from 2.25 g to 10.2 g. Author found that low cumulative dose regimen may be used in most cases of GO meanwhile a higher dose regimen should be reserved for highly severe cases of GO. Bartalena et al[16] suggests that CAS was decreased in all three different cumulative dosage groups, but it occurred earlier in MD group. Early inactivation of GO is an important objective, making rehabilitative surgery (if needed) possible at earlier stage.

In this review, major side effects of IVGC were more frequent in the MD and HD group in 6 and 12 months follow up, respectively. Long-term follow up, at least 1 year, is needed after high dose IVGC administration. Although major side effects are more common using higher doses, low dose therapy is not devoid of serious risk. The possibilites of hepatotoxicity, serious cardiovascular disease, cerebrovascular disease, diabetes, psychiatric disorders and infection risks are concern when using high dose GC.[19]

Intravenous GC gives a direct toxic effect on hepatocytes and the severity of liver damage is dose dependent. Severe liver damage could lead to death with acute liver failure following IVGC pulse therapy using a cumulative dose of 10–24 g.[14] In this literature review, LD and HD showed an elevation of ALT, 5-20% and 2%, respectively. Protocol IV with LD showed 5% patient had impaired liver function. Protocol IV showed 2 % patient had a marked asymptomatic transitory increase in serum aminotransferase levels without relevant hepatoxicity.

Cardiovascular disease such as hypertension, heart failure and cardiac arrhythmias may occur in patient treated with IVGC.[13] Hypertension associated with IVGC therapy may be mild and may resolve spontaneously without additional treatment. In this review, we found blood pressure elevation in MD and HD group. Blood pressure was elevated temporarily during the trial in MD group.

Diabetes or glucose metabolism impairment (hyperglycemia) occurred in LD and MD dose.[13] There was no available data of patient that have diabetes or hyperglycemia in HD group. There were only a few studies assessing the influence of IVGC for GO patient on diabetes.

Psychosis disorders (depression and psychosis) can occur in patients treated with GC. The prevalence of psychiatric disorders was higher in patients treated with oral GC.[13] In this review, we found depression in all group of cumulative dose and psychosis in MD group.

Glucocorticoid are potent immuno-suppressive and anti inflammatory. Infections are common side effects.[13] In this review we found serious infection in MD and HD group (herpes zoster and pulmonary tuberculosis).

The low cumulative dose is preferred due to the potential safety. However, one patient in LD group, who had preexisting chronic obstructive pulmonary disease, died with myocardial infarction 1 week after the sixth infusion.

Minor side effects were common, irrespective of the cumulative GC dose. Weight gain, cushingoid habitus, hirsutism and gastrointestinal discomfort were the most common adverse effects. Hypokalemia (18-28%) was reported in LD group. Hypokalemia due to kaliuresis is a recognised side effect of glucocorticoid treatment, severe symptomatic glucocorticoid-induced hypokalemia is uncommon in routine clinical practice.[20]

The most frequently administered single doses in this review is 0.5 g per day, with doses ranged between 0.25 g to 0.83 g per day (table

3.2). Zang et al[12] reported that high-single dose-therapy-trials (1 g/day) was found to be slightly superior to the low-single dose-therapy (0.5 g/day) in decreasing CAS, proptosis and diplopia. However, high single dose implicated a higher number of side effects. Data on adverse events during IVGC showed that all cases of fatal adverse events also appeared in patients treated with 1 g/day, mostly on consecutive days and lead in to cumulative doses between 5 and 24 g. [12] The cumulative dose of 4.5 g is preferred because this dosage does not result in suppression of the hypothalamus-pituitary-adrenal axis. The 7.5 g is an option in severe cases with diplopia.[22]

Limiting the usage of total cumulative dose of GC, careful patient selection and monitoring the condition of patients during treatment are necessary. Patients at risk should be excluded (e.g. recent hepatitis, liver dysfunction, severe cardiovascular morbidity, severe hypertension, inadequately managed diabetes and glaucoma) before IVGC administration.[15]

There are several factors may influence on the GC outcome. Smoking, age, gender and long duration of GO, had become confounding factors. Smoking not only increases the chance of developing GO 7 to 8 fold, it also increases the severity and progression of GO with a lessening the beneficial effects of immunosuppressive therapy.[5] Xing et al[21] revealed that smoking, even past smoking, was associated with poor therapeutic response to 4.5 g IVGC in patients with moderate to severe and active GO. Therefore, patients must be encouraged to stop smoking.[23]

Patients younger than 50 years old and female subject responded better to steroid therapy, because old subjects and male subjects may show severe forms of GO.[14] Long duration of GO give higher risk of the disease become inactive and fibrotic, therefore immunosuppression will be less effective.[22]

To evaluate the effect of GC, subjective patient's GO-Quality of Life assessment and the risk of of relaps/ progression of GO are need to be explored. These two outcomes were not done in our study and it was a limitation of this review.

Other limitation in this review were various follow up durations and also limitation in using other protocols (protocol II, III and IV) that needed to compare each protocol directly. Prospective controlled randomized trial with a large number of patients to reach statistical power is recommended to find the optimal dose and protocol of IVGC in treating patients. Selection bias can be avoided with consideration of confounding factors.

CONCLUSION

Intravenous GC therapy in moderate to severe and active GO provide effect in reducing CAS, decreasing lid aperture size, decreasing proptosis size, and disappearing diplopia. We recommended a protocol uses a low cumulative doses (<5 g) of methylprednisolone weekly for 6 weeks and then halved dose weekly for another 6 weeks are preferred due to higher response in clinical outcome and safety profile.

Side effects in IVGC therapy seemed to be dose dependent. Although major side effects are more frequent in MD and HD group in 6 and 12 months follow up, LD therapy is not devoid of serious risk. High cumulative dose regimen should be reserved for the most severe cases of GO. Therefore, limiting the total cumulative dose of GC with careful patient selection and monitoring the condition of patients during treatment are necessary.

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