• Meta-Analysis •

Intravenous glucocorticoids therapy in the treatment of Graves' ophthalmopathy: a systematic review and Meta-analysis

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Abstract

• AIM: To evaluate the benefit and harms of high-dose intravenous glucocorticoids (IVGC) as first-line treatment for Graves' ophthalmopathy (GO).

• METHODS: A systematic review and Meta-analysis of randomized clinical trials (RCTs) comparing IVGC for the treatment of GO, with placebo or other treatments, were conducted. Electronic databases were searched, and standard methodological guidance of Cochrane Handbook for Systematic Reviews of Interventions was used. The primary outcome was overall response, and secondary outcomes included the improvement and change in clinical activity score (CAS), and adverse events.

• RESULTS: Ten RCTs were included in the Meta-analysis. Low quality evidence (one trial) showed that participants receiving IVGC achieved significantly higher response compared to participants receiving placebo [risk ratio (RR) 7.50, 95% confidence interval (CI) 1.14 to 49.26]. Moderate quality evidence (four trials) support appreciable benefit of IVGC in response compared with oral glucocorticoids (OGC), with of RR being 1.51 (95%CI 1.25 to 1.83). There was low quality evidence (one trial) compatible with appreciable benefit for IVGC plus orbital radiotherapy in response (RR 1.38, 95%CI 1.07 to 1.79), compared with OGC plus orbital radiotherapy. One IVGC versus rituximab trial provided moderate quality evidence suggesting that participants using IVGC achieved significantly lower response compared to participants using rituximab (RR 0.70, 95%CI 0.50 to 0.98). One IVGC versus mycophenolate mofetil (MMF) trial provided moderate quality evidence suggesting that participants using IVGC achieved significantly lower response compared to participants using MMF (RR 0.74, 95%CI 0.63 to 0.88). Very low quality evidence (one trial) showed that participants with dysthyroid optic neuropathy (DON) receiving IVGC were more likely to achieve response compared to participants receiving orbital decompression (RR 3.33, 95%CI 0.51 to 21.89).

• CONCLUSION: The current evidence is moderate quality, which is sufficient to support IVGC to be as the first-line treatment for moderate-to-severe GO, and the use of rituximab or MMF to be the second-line treatment instead of IVGC. However, the evidence is very low quality, which is insufficient to support the use of IVGC or orbital decompression as the first-line treatment of DON.

• KEYWORDS: glucocorticoids; Graves' ophthalmopathy; Meta-analysis

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INTRODUCTION

Graves' ophthalmopathy (GO) is an autoimmune disorder that has puzzled physicians and scientists for nearly two centuries, which generally occurs in the patients with hyperthyroidism, and sometimes occurring in patients with hypothyroidism or euthyroid[1-4]. Recently, the European Group on Graves' Orbitopathy (EUGOGO) published the first guideline for the management of GO, which recommend high-dose intravenous glucocorticoids (IVGC) as the first-line treatment for active and moderate-to-severe GO and the immediate treatment for dysthyroid optic neuropathy (DON)[5]. Since the 1950s, glucocorticoids have been the most common immunosuppressive agents used in the treatment of active and moderate-to-severe GO[6], and more and more randomized trials and Meta-analyses have proven the beneficial effect of high-dose IVGC in GO[7-10]. However, the efficacy and

safety of IVGC were not accurately estimated. Moreover, the rigorous and detailed use of IVGC has not been established. Hence, an evidence-based approach might need to evaluate the benefit and harms, and the present study was conducted as a systematic review and Meta-analysis of all published randomized clinical trials comparing IVGC for the treatment of GO, with placebo or other treatments.

METHODS

This Meta-analysis was performed using the standard methodological guidance of Cochrane Handbook for Systematic Reviews of Interventions, and also conformed to the PRISMA statement[11-13].

Outcome Measures The primary outcome of efficacy was overall response. "Response" to treatment was defined as an improvement in composite outcome, single sign such as visual function, or symptoms. The secondary efficacy outcomes included the improvement in clinical activity score (CAS), and the change in CAS. Adverse outcomes were also assessed, including total adverse events and Cushingoid symptoms, weight gain, gastrointestinal events, hypertension, hyperglycaemia.

Search Strategy Published randomized clinical trials were identified through a comprehensive search of PubMed, EMBASE, and CENTRAL (which contains the Cochrane Eyes and Vision Trials Register). The keywords for the interventions were methylprednisolone, glucocorticoid, corticosteroid, or steroid. The keywords for the disease were Graves' ophthalmopathy, Graves' orbitopathy, Graves' eye disease, thyroid associated ophthalmopathy, thyroid associated orbitopathy, thyroid ophthalmopathy, thyroid eye disease, thyroid orbitopathy, endocrine ophthalmopathy, endocrine eye disease, or endocrine orbitopathy. The limit for article types was clinical trial. Language restriction was not used in the electronic searches. The last search was performed on 31 December 2017. The reference lists of all identified full articles were also retrieved for the additional studies.

Study Selection Published studies were selected, which were based on pre-determined selection criteria. 1) Study type: randomized clinical trials, including placebo- or active-controlled. 2) Population: patients with the diagnosis of GO. 3) Intervention: intravenous corticosteroid therapy, with or without the combined therapy, versus placebo or other interventions. 4) Outcome variables: one or more of the outcome variables be covered, including response, the improvement in CAS, and the change in CAS.

The electronic searches and trial eligibility were conducted independently by two reviewers (Cheng JW and Zhao LQ). First, the title and abstract of all obtained articles from the comprehensive searches were screened to determine their relevance. Then, if the title and abstract were definite or ambiguous to identify, full articles were scrutinized.

Data Extraction Data extraction was performed according to the customized protocol, independently by two reviewers (Cheng JW and Zhao LQ) and in duplicate. If there was any disagreement, it was resolved by discussion. For each included study, a customized form of data was extracted, as follows, 1) Method: randomization method, allocation concealment, blinding (participants, investigators, examiners), loss to follow-up, compliance, intention-to-treat or per protocol analysis, and location. 2) Participants: inclusion and exclusion criteria, sample size, patient age, sex, activity and severity of GO. 3) Interventions: dose, route, and duration of interventions, comparison interventions, and co-interventions. 4) Outcomes: efficacy outcomes (overall response, the improvement and change in CAS), adverse outcomes, assessment times, and length of follow-up. 5) Notes: general information such as article title, authors and source, published year, and published language.

Quality Assessment The methodological quality of each included study was independently assessed by two authors (Cheng JW and Zhao LQ), using the Cochrane Collaboration's tool for assessing risk of bias. The parameters of the Cochrane Collaboration's tool included random sequence generation and allocation concealment for assessing selection bias, blinding of participants and personnel for assessing performance bias, blinding of outcome assessment for assessing detection bias, incomplete outcome data for assessing attrition bias, selective reporting for assessing reporting bias, and other sources of bias, such as stopping early for benefit.

We assessed each parameter of Cochrane Collaboration's tool and graded it as low risk of bias, unclear risk of bias, and high risk of bias. If any parameter of any trial graded as high risk of bias, a sensitivity analysis was used to assess the effect of the trials on the results of Meta-analysis.

Statistical Analysis The statistical analysis was performed using the Review Manager software version 5.3 from the Cochrane Collaboration. For efficacy outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes, and standardized mean difference (SMD) with 95%CIs for continuous outcomes were calculated. For safety outcomes, odds ratios with 95%CIs for adverse events were calculated.

The statistical heterogeneity was stated using the Cochran's Q statistic and I^2 metrics. If no heterogeneity was identified, when a P value >0.1 and I^2 value <50%, the fixed effects model was used to Meta-analyses. Otherwise, if heterogeneity was identified, the random effects model was used, and also heterogeneity was explored by conducting subgroup analyses[14-15].

The sensitivity analyses were performed, as the studies at high risk of bias in one or more domains were excluded. Subgroup

analyses were also conducted, based on the activity of disease (active, and inactive), the severity of disease (mild, moderate to severe, and sight threatening), the type of outcome criteria, the protocols of interventions (daily, weekly, and monthly), and the type of comparison interventions [placebo, oral glucocorticoids (OGC), surgery, rituximab, and so on]. Standard funnel plots were also constructed to investigate the potential of publication bias, by examining visually the asymmetry[16].

The 'Summary of findings' table of primary outcome (overall response) was created using GRADEproGDT software. The GRADE approach, were used to assess the quality of clinical evidence, which might be downgraded depending on five considerations, including study limitations (high risk of bias), publication bias, imprecision (wide CIs), unexplained heterogeneity or inconsistency, and indirectness of evidence[17].

RESULTS

The selection flow chart is shown in Figure 1. A total of 275 articles were identified across the electronic searches, and then 90 duplicates were removed. We reviewed the remaining 185 abstract reports, and 20 full-text articles potentially met the selection criteria were scrutinized. Finally, 10 eligible randomized clinical trials included in the systematic review[18-27].

Trials Characteristics The characteristics of 10 eligible randomized controlled trials are shown in Table 1. Overall, 569 participants were evaluated, with the mean age of 45y, and involving 411 females and 158 males. Eight trials reported participants with the activity categorized as the active phase, and two reported participants as both active and inactive. One trial reported participants with the severity rated as sight threatening (DON); seven reported participants as moderate to severe; and two reported participants as mild to moderate. The follow-up periods ranged from 12wk to 2y.

One study compared IVGC with placebo; five compared IVGC with OGC; one compared IVGC plus orbital radiotherapy (IVGC+OR) with OGC plus orbital radiotherapy (OGC+OR); one compared IVGC with rituximab; one compared IVGC with mycophenolate mofetil (MMF); and one compared IVGC with surgical decompression.

Risk of Bias and Publication Bias All trials had a prospective, parallel design. One trial had a high risk of bias in four domains; one trial had a high risk of bias in three domains; two trials had a high risk of bias in two domains of performance bias and detection bias; and four trials had a high risk of bias in one domain of performance bias. Two trials were found with low risk of bias (Figure 2).

Funnel plot for the response of IVGC (with or without orbital radiotherapy) versus placebo or other interventions is qualitatively symmetrical, indicating low probability of publication bias (Figure 3).

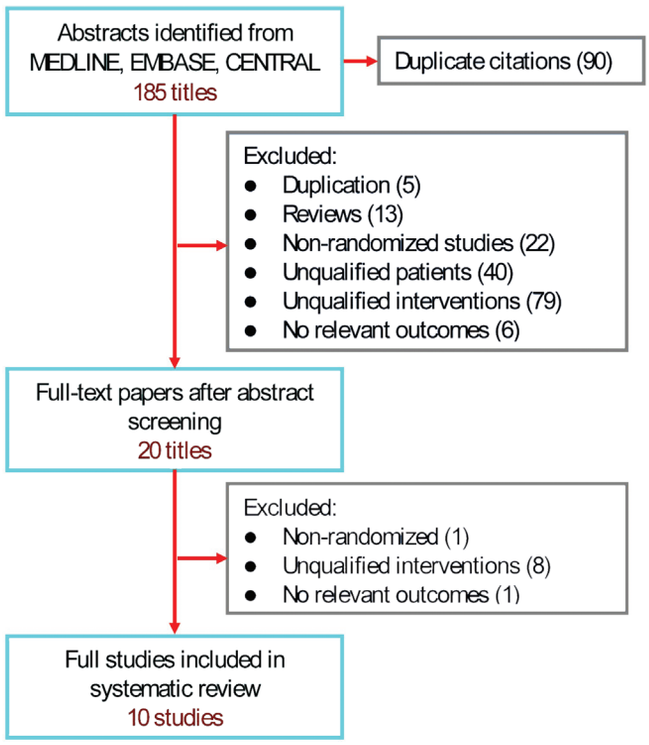

Figure 1 Flow diagram of study selection.

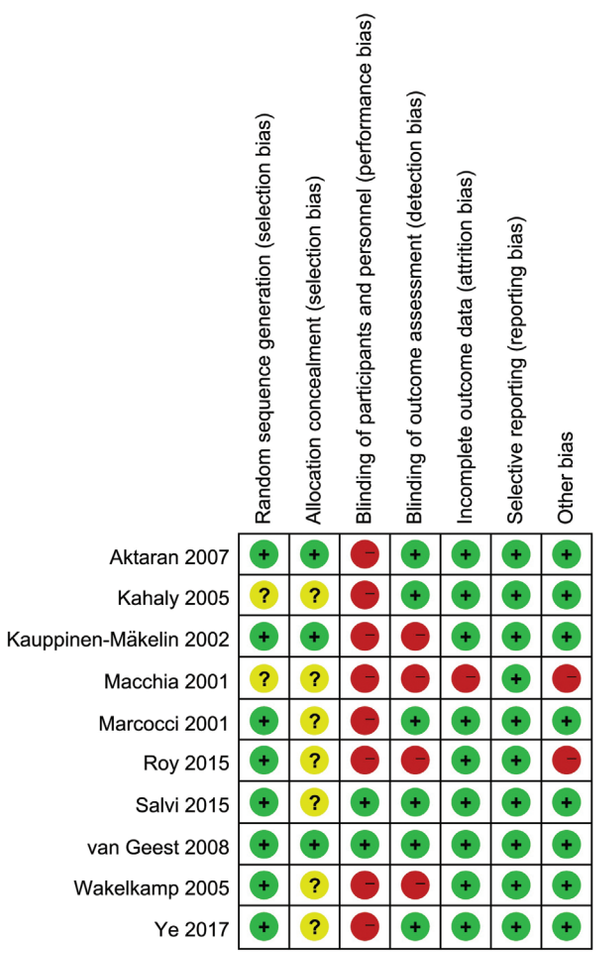

Figure 2 Risk of bias of included studies.

Efficacy: response The forest plot of response compared IVGC with control is shown in Figure 4, and the 'summary of findings' table is shown in Table 2.

Table 1 Baseline characteristics of eligible randomized clinical trials

Study	Location	Patients (*n*)	Mean age (y)	Sex (M/F)	Disease activity (CAS)	Disease severity	Intervention			Comparison interventions			Combination	Follow-up	Response definition
							Treatment	Dose	Route	Treatment	Dose	Route			
Aktaran *et al*[18]	Turkey	52	43	24/28	Active (4-6/10)	Moderately severe	iv methylprednisolone	Total 4.5 g	Weekly (12wk)	PO methylprednisolone	Total 3.9 g	Daily (12wk)	None	12wk	Composite outcome improvement
Kahaly *et al*[19]	Germany	70	50	21/49	Active (3-7/7)	Moderately severe	iv methylprednisolone	Total 4.5 g	Weekly (12wk)	PO prednisolone	Total 4.0 g	Daily (12wk)	None	6mo	Composite outcome improvement
Kauppinen-Mäkelin *et al*[20]	Finland	33	46	2/31	All (0-6/6)	Mild to moderate	iv followed by PO methylprednisolone	Total 4.16 g	Daily (14wk)	PO prednisolone	Total 2.99 g	Daily (16wk)	None	12mo	No
Macchia *et al*[21]	Italy	51	44	11/40	All (3.52/7)	Mild to moderate	iv methylprednisolone	Total 12 g	Weekly (6wk)	PO prednisolone	60-80 mg·d by tapered	Daily (4-6mo)	None	2y	Symptoms improvement
Marcocci *et al*[22]	Italy	82	49	14/68	Active (4.35/7)	Moderate to severe	iv methylprednisolone	Total 9-12 g	Weekly (14wk)	PO prednisolone	Total 6 g	Daily (22wk)	Radiotherapy (20 Gy, 2wk)	12mo	Composite outcome improvement
Roy *et al*[23]	India	62	37	24/38	Active (4.35/7)	Moderate to severe	iv methylprednisolone	Total 6 g	Monthly (4mo)	PO prednisolone	1 mg/kg·d by tapered	Daily	None	1y	Composite outcome improvement
Salvi *et al*[24]	Italy	31	51	5/26	Active (4.6/10)	Moderate to severe	iv methylprednisolone	Total 7.5 g	Weekly (14wk)	iv rituximab	Total 2000 or 500 mg	Weekly (2wk)	None	76wk	Disease inactivation (CAS<3)
van Geest *et al*[25]	Netherlands	15	47	3/12	Active (4-8/10)	Moderately severe	iv methylprednisolone	Total 6 g	Daily (4mo)	iv placebo	-	Daily (4mo)	None	48wk	Composite outcome improvement
Wakelkamp *et al*[26]	Netherlands	15	52	2/13	Active (6/7)	DON	iv methylprednisolone	Total 6 g	Daily (2wk)	Orbital decompression	-	-	None	26wk	Visual improvement
Ye *et al*[27]	China	158	41	52/106	Active (5.25/10)	Moderate to severe	iv methylprednisolone followed by PO prednisone	Total 3 g, 60 mg/d by tapered	Daily (24wk)	PO MMF	1000 mg/d	Daily (24wk)	None	24wk	Composite outcome improvement

MMF: Mycophenolate mofetil; DON: Dysthyroid optic neuropathy; iv: Intravenous; PO: Oral administration.

Table 2 The summary of findings table of primary outcome (overall response)

Outcomes	Illustrative comparative risks (95%CI)		Relative effect (95%CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Intervention			
IVGC *vs* Placebo	110 per 1000	825 per 1000 (125 to 1000)	RR 7.50 (1.14 to 49.26)	15 (1)	Low[c]
IVGC *vs* OGC	530 per 1000	800 per 1000 (663 to 970)	RR 1.51 (1.25 to 1.83)	235 (4)	Moderate[a]
IVGC+OR *vs* OGC+OR	630 per 1000	869 per 1000 (674 to 1000)	RR 1.38 (1.07 to 1.79)	82 (1)	Low[a,b]
IVGC *vs* Rituximab	1000 per 1000	700 per 1000 (500 to 980)	RR 0.70 (0.50 to 0.98)	31 (1)	Moderate[b]
IVGC *vs* MMF	910 per 1000	673 per 1000 (573 to 801)	RR 0.74 (0.63 to 0.88)	158 (1)	Moderate[a]
IVGC *vs* Surgery	170 per 1000	566 per 1000 (87 to 1000)	RR 3.33 (0.51 to 21.89)	15 (1)	Very low[a,c]

IVGC: Intravenous glucocorticoids; OGC: Oral glucocorticoids; IVGC+OR: Intravenous glucocorticoids plus orbital radiotherapy; OGC+OR: Oral glucocorticoids plus orbital radiotherapy; CI: Confidence interval; RR: Risk ratio. [a]Downgraded because of high risk of bias in included studies (-1); [b]Downgraded because of serious imprecision (-1); [c]Downgraded because of very serious imprecision (-2).

Table 3 Subgroup analyses of response compared intravenous with OGC

Items	No. of trials	RR (95%CI)	Heterogeneity	Overall effect
Activity of disease				
Active phase	3	1.53 (1.22, 1.91)	P=0.97; I^2=0	Z=3.75; P=0.0002
Active and inactive phase	1	1.46 (1.00, 2.11)	Not applicable	Z=1.98; P=0.05
Severity of disease				
Mild to moderate	1	1.46 (1.00, 2.11)	Not applicable	Z=1.98; P=0.05
Moderate to severe	3	1.53 (1.22, 1.91)	P=0.97; I^2=0	Z=3.75; P=0.0002
Type of outcome criteria				
Composite outcome	1	1.46 (1.00, 2.11)	Not applicable	Z=1.98; P=0.05
Symptoms	3	1.53 (1.22, 1.91)	P=0.97; I^2=0	Z=3.75; P=0.0002
Protocols of interventions				
Weekly	3	1.48 (1.18, 1.87)	P=0.99; I^2=0	Z=3.38; P=0.0007
Monthly	1	1.59 (1.12, 2.25)	Not applicable	Z=2.61; P=0.009

OGC: Oral glucocorticoids; RR: Risk ratio.

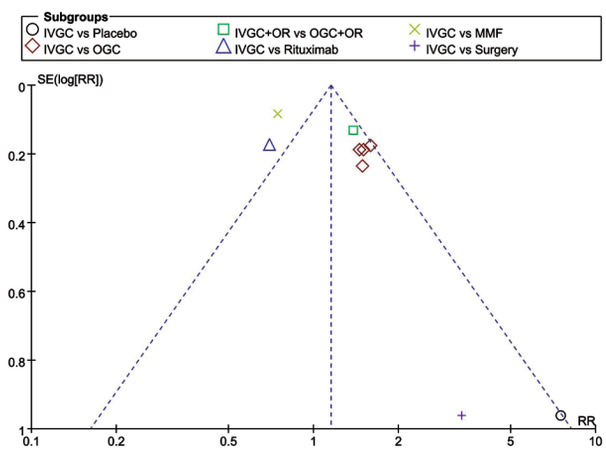

Figure 3 Funnel plot for the response of IVGC versus control
RR: Risk ratio; IVGC: Intravenous glucocorticoids; OGC: Oral glucocorticoids; IVGC+OR: Intravenous glucocorticoids plus orbital radiotherapy; OGC+OR: Oral glucocorticoids plus orbital radiotherapy; MMF: Mycophenolate mofetil.

One trial was included in the comparison of IVGC versus placebo. Participants receiving IVGC achieved significantly higher response compared to participants receiving placebo (RR 7.50, 95%CI 1.14 to 49.26, P=0.04). The evidence (one trial, 15 participants, low quality) was double-downgraded because the 95%CI was very wide because of only one included trial, subgroup analyses was not conducted.

Response was reported as outcomes in four trials comparing IVGC with OGC. No heterogeneity across the results of four included studies was identified (Chi^2=0.12, df=3, P=0.99; I^2=0). The finding was compatible with significantly increased chance of response for IVGC (RR 1.51, 95%CI 1.25 to 1.83, P<0.0001, four trials, 235 participants, moderate quality evidence). We did not perform sensitivity analysis as all trials had a high risk of bias. Table 3 shows the subgroup analyses, which also suggested that IVGC was associated with significantly higher response.

One trial comparing IVGC+OR with OGC+OR reported response as an outcome. The finding was compatible with appreciable benefit for the combination of IVGC and orbital radiotherapy (RR 1.38, 95%CI 1.07 to 1.79, P=0.01). The evidence (one trial, 82 participants, low quality) was double-downgraded because of serious imprecision (wide 95%CIs) and study limitations (high risk of bias).

Response was reported as an outcome in one trial comparing IVGC with rituximab. Participants receiving IVGC achieved significantly lower response compared to participants receiving rituximab (RR 0.70, 95%CI 0.50 to 0.98, P=0.04, one trial, 31 participants, moderate quality evidence).

One trial comparing IVGC with MMF reported composite outcome improvement as response. The finding was compatible with appreciable benefit for IVGC (RR 0.74, 95%CI 0.63 to 0.88, P=0.0005). The evidence (one trial, 158 participants, moderate quality) was downgraded depending on study limitations (high risk of bias).

One trial comparing IVGC with surgery reported visual improvement as response. Participants receiving IVGC were more likely to achieve visual improvement compared to participants receiving surgical decompression (RR 3.33, 95%CI 0.51 to 21.89, P=0.21). Although the finding was compatible with increased chance of response for IVGC (one trial, 15 participants, very low quality evidence), the effect of IVGC compared to surgery was uncertain because of serious imprecision (wide 95%CIs) and study limitations (high risk of bias).

Efficacy: clinical activity score improvement One trial was included in the comparison of IVGC versus placebo. The finding was compatible with significantly increased chance of the improvement of CAS for IVGC (RR 2.65, 95%CI 1.11 to 6.33, P=0.03). The evidence (one trial, 15 participants, low quality) was double-downgraded depending on very serious imprecision.

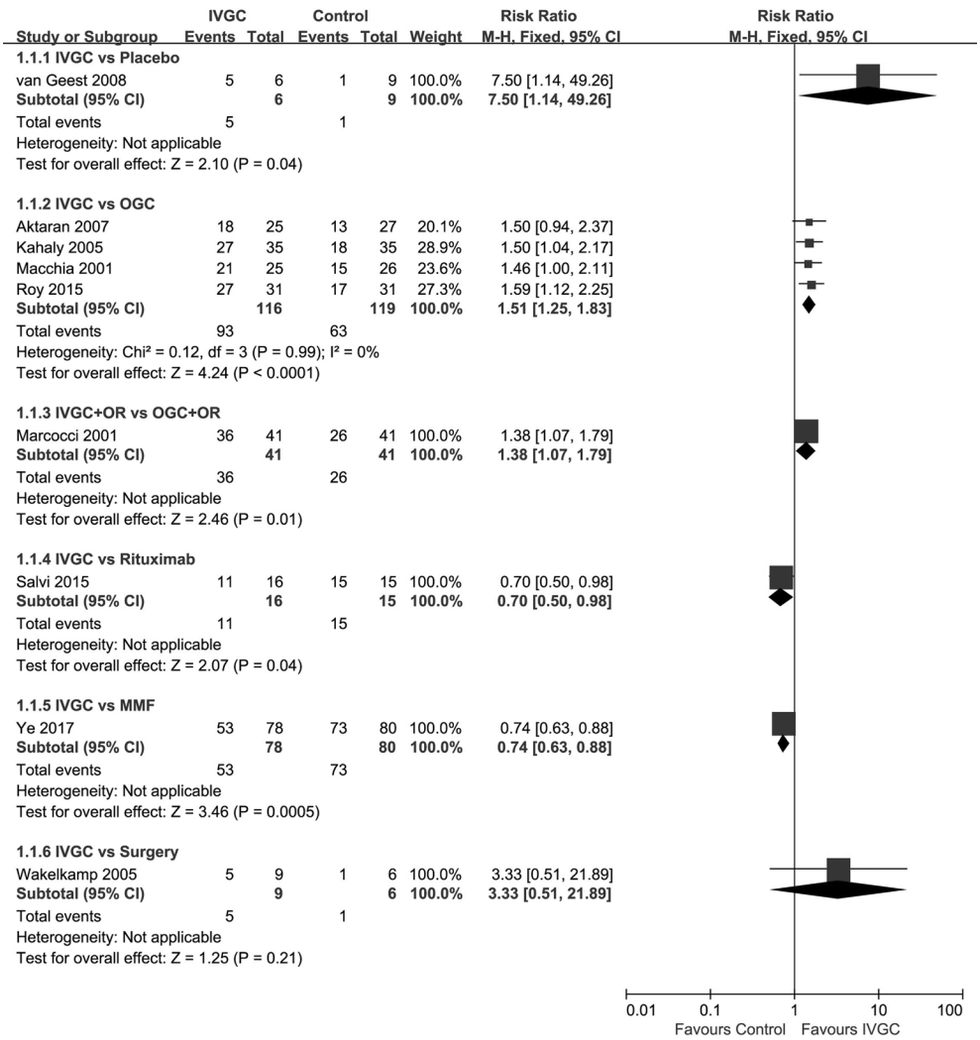

Figure 4 Forest plot of response compared IVGC with control IVGC: Intravenous glucocorticoids; OGC: Oral glucocorticoids; IVGC+OR: Intravenous glucocorticoids plus orbital radiotherapy; OGC+OR: Oral glucocorticoids plus orbital radiotherapy; MMF: Mycophenolate mofetil.

The improvement of CAS was reported as an outcome in one trial comparing IVGC with OGC. Participants receiving IVGC achieved significantly more improvement of CAS compared to participants receiving OGC (RR 1.50, 95%CI 1.04 to 2.17, *P*=0.03). Because of serious imprecision (wide 95%CIs) and study limitations (high risk of bias), the evidence (one trial, 70 participants, low quality) was double-downgraded.

One trial comparing IVGC+OR with OGC+OR reported the improvement of CAS. Participants receiving IVGC+OR achieved significantly more improvement of CAS compared to participants receiving OGC+OR (RR 2.36, 95%CI 1.35 to 4.12, *P*=0.002). The evidence (one trial, 82 participants, low quality) was double-downgraded depending on serious imprecision (wide 95%CIs) and study limitations (high risk of bias).

One trial compared IVGC with rituximab. Participants receiving IVGC were less likely to achieve the improvement of CAS compared to participants receiving rituximab (RR 0.76, 95%CI 0.56 to 1.02, *P*=0.07). Because of serious imprecision, the evidence was downgraded (one trial, 31 participants, moderate quality).

The improvement of CAS was reported as an outcome in one trial comparing IVGC with MMF. Participants receiving IVGC were significantly less likely to achieve the improvement of CAS compared to participants receiving MMF (RR 0.76, 95%CI 0.65 to 0.89, *P*=0.0007). Because of high risk of bias, the evidence was downgraded (one trial, 158 participants, moderate quality).

Efficacy: clinical activity score change Four trials comparing IVGC with OGC reported the change of CAS. Significant heterogeneity across four included studies was identified (Chi^2=14.09, *df*=3, *P*=0.003; I^2=79%), and the random effects model was used. The decrease of CAS was significantly higher in the IVGC group compared to the OGC group (SMD -1.07, 95%CI -1.73 to -0.40, *P*=0.002). Depending on serious imprecision (wide 95%CIs) and study limitations (high risk of bias), the evidence was double-downgraded (four trials, 198 participants, low quality).

One trial reported the change of CAS between IVGC+OR and OGC+OR. The decrease of CAS was significantly higher in the IVGC+OR group compared to the OGC+OR group (SMD

-1.09, 95%CI -1.56 to -0.63, *P*<0.00001). Because of serious imprecision (wide 95%CIs) and study limitations (high risk of bias), the evidence was double-downgraded (one trial, 82 participants, low quality).

The change of CAS was reported in one trial comparing IVGC with rituximab. The finding was compatible with significantly lower decrease of CAS for IVGC (SMD 0.95, 95%CI 0.20 to 1.69, *P*=0.01). The evidence was downgraded (one trial, 31 participants, moderate quality) because of imprecision.

One trial reported the change of CAS between IVGC and MMF. The finding was compatible with significantly lower decrease of CAS for IVGC (SMD 0.67, 95%CI 0.35 to 1.00, *P*<0.00001). The evidence was downgraded (one trial, 158 participants, moderate quality), because of study limitations.

Adverse Events Participants receiving IVGC were more likely to achieve Cushingoid symptoms (OR 19.00, 95%CI 0.77 to 469.21, *P*=0.07), and hypertension (OR 8.00, 95%CI 0.58 to 110.27, *P*=0.12) compared to participants receiving placebo.

Participants receiving IVGC were significantly less likely to achieve adverse events compared to participants receiving OGC (OR 0.24, 95%CI 0.08 to 0.67, *P*=0.006). The findings were compatible with significantly decreased chance of Cushingoid symptoms (OR 0.12, 95%CI 0.02 to 0.66, *P*=0.01) and hypertension (OR 0.24, 95%CI 0.08 to 0.69, *P*=0.008) for IVGC. Participants receiving IVGC were less likely to weight gain (OR 0.40, 95%CI 0.07 to 2.20, *P*=0.29) and gastrointestinal events (OR 0.60, 95%CI 0.24 to 1.50, *P*=0.28) compared to participants receiving OGC. The finding was compatible with little difference in hyperglycaemia between IVGC and OGC (OR 1.02, 95%CI 0.46 to 2.27, *P*=0.96). Participants receiving IVGC were less likely to achieve adverse events compared to participants receiving rituximab (OR 0.26, 95%CI 0.04 to 1.55, *P*=0.14). Participants receiving IVGC were more likely to achieve adverse events compared to participants receiving MMF (OR 0.26, 95%CI 0.04 to 1.55, *P*=0.14).

DISCUSSION

Intravenous Glucocorticoids Versus Placebo The IVGC versus placebo trial provided low quality evidence which supported the use of IVGC for the treatment of active and moderate-to-severe GO.

The finding was compatible with significantly increased chance of composite outcome improvement for IVGC, suggesting that for patients using placebo with a response rate of 11%, the response rate using IVGC would be between 12.5% and 100%. Additionally, participants receiving IVGC achieved significantly more improvement of CAS compared to participants receiving placebo. Participants receiving IVGC were more likely to achieve Cushingoid symptoms and hypertension compared to participants receiving placebo.

Although good methodological quality of the IVGC versus placebo trial was found, a small sample size was the main limitation. The evidence of the effect of IVGC on both response and CAS improvement was low quality.

Intravenous Versus Oral Glucocorticoids The IVGC versus OGC trials provided moderate quality evidence which was sufficient to support appreciable benefit of IVGC for the treatment of active and moderate-to-severe GO.

Participants receiving IVGC achieved significantly higher response compared to participants receiving OGC, assuming approximately 53% overall response of participants receiving OGC, the anticipated overall response of participants receiving IVGC would be between 66.3% and 97.0%. The findings were compatible with significantly increased chance of the improvement and decrease of CAS for IVGC. Additionally, participants receiving IVGC were less likely to achieve adverse events compared to participants receiving OGC.

All five included trials had limitations in methodology. Therefore, we downgraded the evidence of the effect of IVGC on overall response to moderate quality. In addition, the evidence of the effect of IVGC on CAS improvement and change was double-downgraded to be of low quality.

Intravenous Versus Oral Glucocorticoids Combined With Orbital Radiotherapy The IVGC+OR versus OGC+OR trial provided low quality evidence which supported appreciable benefit of the combination of IVGC and orbital radiotherapy.

The finding was compatible with significantly increased chance of response for IVGC+OR, suggesting that for patients receiving OGC+OR with approximately 63% response rate, the response rate receiving IVGC+OR would be between 67.4% and 100%. Participants receiving IVGC+OR achieved significantly more improvement and higher decrease of CAS compared to participants receiving OGC+OR.

The included trial had a high risk of bias in performance bias. The evidence of the effect of between IVGC+OR and OGC+OR was double-downgraded to be of low quality.

Intravenous Glucocorticoids Versus Rituximab The IVGC versus rituximab trial provided moderate quality evidence which supported the use of rituximab for moderate to severe and active GO. Participants using IVGC were significantly less likely to achieve disease inactivation compared to participants using rituximab, assuming approximately 100% inactivation rate of rituximab, the anticipated inactivation rate of IVGC would only be between 50.0% and 98.0%. Participants receiving IVGC achieved significantly less improvement and lower decrease of CAS compared to participants receiving rituximab. However, participants receiving IVGC were less likely to achieve adverse events compared to participants receiving rituximab.

The included trial had low risk of bias in the majority of domains, however, small sample size was still one main limitation. The evidence of the effect of between IVGC and rituximab was downgraded to be of moderate quality.

Intravenous Glucocorticoids Versus Mycophenolate Mofetil The IVGC versus MMF trial provided moderate quality evidence which supported the use of MMF for moderate-to-severe and active GO.

Participants using IVGC were significantly less response compared to participants using MMF, assuming approximately 91% response rate of MMF, the anticipated response rate of IVGC would only be between 57.3% and 80.1%. Participants receiving IVGC achieved significantly less improvement and lower decrease of CAS compared to participants receiving MMF. Otherwise, participants receiving IVGC were more likely to achieve adverse events compared to participants receiving MMF. The included trial had a high risk of bias in performance bias, and the evidence of the effect of between IVGC and MMF was downgraded to be of moderate quality.

Intravenous Glucocorticoids Versus Surgery The IVGC versus surgery trial provided the evidence of very low quality which was insufficient to support the use of either IVGC or orbital decompression as the first-line treatment of DON. Assuming that approximately 17% of participants receiving surgical decompression achieve visual improvement, the anticipated rate of visual improvement using IVGC would be between 8.7% and 100%. Participants receiving IVGC were more likely to achieve visual improvement compared to participants receiving surgical decompression, but no significant difference was found.

The included trial had a high risk of bias in performance bias and detection bias. A small sample size was also the limitation. Therefore, the applicability of the available trial data to clinical practice is still relatively limited.

Depending on very serious imprecision and study limitations, the evidence of the effect of between IVGC and surgery on visual improvement was downgraded to be of very low quality.

Potential Biases in the Review Process No obvious bias could be identified from the review process. However, there are several limitations should be discussed. First, the limitation is the potential of publication bias. It was attempted to avoid the potential of publication bias by searching in multiple databases. Unfortunately, it is possible that some papers might be missed, especially those published in languages other than English. A second limitation is different durations of the examination of the data across included studies. Third, the criteria of "response" also differed among studies. Fourth, the cumulative doses and protocols were different among the included studies, which significantly influenced the efficacy and safety of IVGC[28-29].

Agreements and Disagreements with Other Studies or Reviews A previous systematic review included 33 randomized clinical trials of all treatment modalities for GO[8]. Four trials compared OGC with IVGC, and the findings suggested that in patients with moderate-to-severe GO, participants receiving IVGC achieved significantly higher chance in the decrease of CAS compared to participants receiving OGC (SMD -0.64, 95%CI -1.11 to -0.17, random effects model), also less likely to achieve adverse events. However, the systematic review did not assess methodological quality of the included studies.

A recently systematic review of methylprednisolone pulse therapy for GO included eight randomized clinical trials[10]. The study quality was assessed by the Jadad scoring system (range from 1 to 5). A higher response rate using IVGC was found than using placebo (RR 7.50, 95%CI 1.14 to 49.26) and OGC (RR 1.48, 95%CI 1.18 to 1.86), and IVGC+OR was markedly more effective than OGC+OR (RR 1.40, 95%CI 1.11 to 1.77). One trial (15 patients) compared IVGC with surgery, with an RR of 3.33 (95%CI 0.51 to 21.89). Except for PubMed, EMBASE, and CENTRAL, the systematic review also searched Chinese Biomedicine Database, and one trial (75 participants) published in Chinese was included. However, the "response" in the included trial was defined as an improvement in diplopa, which was found in 60 participants at baseline.

The present systematic review included nine randomized clinical trials of IVGC therapy for GO. The Meta-analysis was performed using the standard methodological guidance of Cochrane Handbook for Systematic Reviews of Interventions. There is currently moderate quality evidence which is sufficient to support IVGC for moderate-to-severe and active GO. In addition, low quality evidence supports the effect of the combination of orbital radiotherapy with IVGC.

Currently in the present systematic review, there is moderate quality evidence of to support the appreciable benefit of rituximab, compared to IVGC. A prospective, randomized, double-masked, placebo-controlled trial published recently[30], and the finding was compatible with no significant difference in disease inactivation between rituximab and placebo (RR 1.50, 95%CI 0.60 to 3.74, P=0.38). However, depending on very serious imprecision and high risk of bias (stopping early for benefit), the evidence of rituximab versus placebo was downgraded to be of very low quality.

In conclusion, currently evidence is sufficient to support IVGC for the treatment of moderate-to-severe and active GO, compared to placebo (low quality) and OGC (moderate quality). There is evidence of moderate quality to support the use of rituximab or MMF, which might be a second-line treatment instead of IVGC. In addition, there is low quality evidence to support orbital radiotherapy as the combined

therapy of IVGC. However, the evidence is very low quality which is insufficient to support the use of either IVGC or orbital decompression as a first-line treatment of DON.

Of note is that the findings of the rituximab versus IVGC trial, which were compatible with appreciable benefit of rituximab on disease inactivation, conflicted with those of the rituximab versus placebo trial, which were compatible with no significant difference between rituximab and placebo on disease inactivation. Therefore, in order to draw more comprehensive conclusions, much more RCTs should focus on the benefit and harms of rituximab for the treatment of GO, compared to IVGC, measuring as the efficacy outcomes such as overall response defined as an improvement in composite outcome, the improvement and change in CAS , and adverse outcomes. In addition, it is needed to evaluate the balance of benefit and harms of between IVGC and orbital decompression for the treatment of DON.

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