

Comparison Between Weekly Regimens and Monthly Regimen Intravenous Methylprednisolone in Moderate To Severe and Active Graves' Ophthalmopathy: A Systematic Review

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ABSTRACT

Background: Graves' ophthalmopathy (GO) is the most common extrathyroidal manifestation of Graves' disease, with approximately 22% of cases being active and moderate-to-severe, warranting immunosuppressive therapy. Intravenous Methylprednisolone (IVMP) are recommended as first-line treatment, with the EUGOGO 2021 weekly 4.5 g protocol over 12 weeks as the established standard. Monthly regimens have been proposed as an alternative with a reduced infusion burden. However, comparative evidence on the efficacy and safety of these two regimens remains limited and has not been systematically synthesized.

Methods: A systematic review was conducted following PRISMA 2020 guidelines. PubMed, Scopus, Cochrane Library, EuropePMC, and Epistemonikos. Two reviewers independently screened records, extracted data, and assessed methodological quality using the Cochrane Risk of Bias 2 (RoB 2) and Newcastle-Ottawa Scale.

Results: Six studies (n=307) were included. Weekly IVMP showed consistently higher response rates (77-86%) compared with monthly regimens (67-72%), although differences were not statistically significant in direct comparisons. Both regimens demonstrated superior efficacy over oral glucocorticoid (77% vs 51%) and placebo (83% vs 11%). Safety profiles were comparable between weekly and monthly regimens, with weight gain as the most common adverse event and no major hepatotoxicity or mortality reported.

Conclusion: Weekly and monthly IVMP treatments showed similar effectiveness and safety for patients with active moderate-to-severe Graves' ophthalmopathy. This means the monthly regimen can be a practical option, especially where infusion facilities are harder to access.

Keyword: Graves ophthalmopathy, Intravenous Methylprednisolone, Weekly regimen, Monthly regimen, Systematic Review.

INTRODUCTION

Graves' ophthalmopathy (GO) is the most common extrathyroidal sign of Graves' disease. It affects about 30% of patients. Of these, 22% have moderate to severe symptoms, and only 1% face a risk to their sight^{1,2}. GO can cause proptosis, double vision, eyelid retraction, and reduced visual acuity, all of which can greatly affect a patient's quality of life.

The management of moderate-to-severe active GO relies on high-dose intravenous methylprednisolone (IVMPs) as first-line therapy, which are more effective and better tolerated than oral therapy, with response rates of 77–88%^{3,4}. The 2021 EUGOGO guidelines recommend a weekly protocol of methylprednisolone with a total cumulative dose of 4.5 g over 12 weeks as the standard of care⁵. However, this regimen requires 12 consecutive hospital infusion visits, which is a significant obstacle, particularly in countries with limited access to infusion facilities⁶. This has led to the development of monthly regimens as an alternative with a lower visit frequency, typically combined with tapering oral glucocorticoids⁷.

However, comparative evidence regarding the efficacy and safety of these two regimens is limited and has not been systematically summarized⁸. Therefore, this systematic review aims to compare the efficacy and safety of weekly and monthly IVMP regimens in patients with moderate-to-severe active GO.

METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and methodological rigour throughout the review process.

Search Strategy

A comprehensive literature search was carried out across five electronic databases, PubMed, Scopus, Cochrane Library, EuropePMC, and Epistemonikos. Search terms were structured using Boolean operators (AND/OR) and developed based on the PICOS framework (Population, Intervention, Comparator, Outcome, and Study Design).

Eligibility Criteria

The inclusion criteria for this review are listed below:

1. Patient with moderate-to-severe and active Graves' Ophthalmopathy (GO/TED/TAO) at any age and any sex
2. Patient is given treatment of Weekly IVMP (Methylprednisolone 0.5 g/week x 6 + 0.25 g/week x 6; cumulative dose 4.5 g) or monthly/modified monthly IVMP or oral glucocorticoids or placebo
3. Studies were eligible if they reported an overall response rate or adverse events as outcome measures.
4. RCT, prospective or retrospective cohort, and comparative studies were considered
5. The studies published in English or have an English translation

The exclusion criteria for this review are listed below:

1. Studies involving patients with inactive GO or GO classified as mild or without clear severity grading. Any orbital disorders not related to GO are excluded.
2. Studies lacking detailed descriptions of the IVMP protocols
3. Studies in which the comparator arm does not include weekly IVMP, monthly IVMP, oral glucocorticoids, or placebo.
4. Studies comprising review articles, editorials, book chapters, conference abstracts, and case reports, as well as case series with <30 patients.

Additionally, studies with overlapping patient populations or duplicated data were excluded to ensure the integrity and relevance of the findings.

Two reviewers independently extracted data from each included study using a standardized extraction form. Extracted variables encompassed study identification (author, year, country), study design, study period, total sample size, population characteristics, intervention details (Methylprednisolone regimen, cumulative dose, treatment duration), comparator details, primary outcomes (overall response rate, CAS, proptosis, diplopia, soft tissue improvement, and adverse events), follow-up duration, and main conclusions. Discrepancies between reviewers were resolved through discussion and consensus.

Quality of Studies Assessment

Five RCT studies were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, and one cohort study was assessed using the Newcastle-Ottawa Scale (NOS). One study achieved low risk of bias (Li et al., 2024), three studies remains concerned (He et al., 2017; Geest et al., 2008; Kahaly et al., 2005), and one study achieved high risk of bias (Roy et al., 2015). One cohort study (Stoynova et al., 2023; 6/9) was rated moderate risk

Synthesis of Evidence

Quality assessment results were documented alongside extracted data to ensure thorough documentation of study methods. Because of the limited number of studies, differences in cumulative doses and response criteria, and variability in study designs, a narrative synthesis was conducted instead of a quantitative meta-analysis. Findings were summarised and compared across studies with respect to overall response rate, clinical activity score, proptosis, diplopia, soft-tissue improvement, and adverse event.

RESULT

The included studies can be seen in Figure 1. Our initial search strategy found a total of 386 studies from electronic databases with 2 self-included study. After removing 153 duplicates, 233 were evaluated based on their titles and abstracts, leaving 10 studies that were screened through full text. Of these, 223 were excluded because they did not meet the inclusion criteria. After a careful screening process, we identified 6 studies considered eligible for this final analysis.

Efficacy Outcome

Overall Response Rate

Among the studies that examined direct comparison between monthly and weekly regimens, all three studies found no statistically significant difference in overall response rates between weekly and monthly IVMP regimens. He et al. reported a total response rate of 71.9%, with similar results for the monthly and weekly groups (76.5% vs 66.7%; $p > 0.05$). Li et al. also found comparable effective rates at week 12 (WR 86.21% vs MR 72.41%; $p = 0.195$) and week 24 (WR 86.21% vs MR 82.61%; $p = 0.441$). Stoyanova et al. saw no significant difference in therapeutic response between the modified monthly and weekly regimens at months 1 ($p = 0.08$) and 3 ($p = 0.14$).

Another comparison of IVMP with other comparators yielded consistent results. Kahaly et al. (2005) demonstrated that weekly IVMP resulted in rapid, significant, and sustained improvement. Based on the predefined criteria, 27 of 35 patients (77%) in the IVMP group achieved treatment response at 3 months, compared with 18 of 35 patients (51%) in the oral GC group ($p < 0.01$). Monthly regimens also showed their superiority over oral GC. Roy et al. (2015) find consistent superiority of monthly IVMP over oral GC at the 6-month (80.65% vs 38.71%, $p < 0.001$) and 1-year (87.10% vs 54.84%, $p = 0.005$) follow-ups. Furthermore, Geest et al. (2008), as the only placebo-controlled study, find that 83% (5/6) of patients with monthly IVMP undergoing treatment had success compared to the placebo group (11%; $n = 1/9$) with significant ($p = 0.005$).

Other (CAS, Diplopia, Exopthalmos, and Soft tissue improvement)

In both two similar protocols, Geest et al. (2008) and He et al. (2017) showed a significant improvement in the CAS score in the IVMP group. Geest et al. (2008) showed a significant improvement in CAS score in the IVMP (6 g) group compared to the placebo group ($p = 0.005$). He et al. (2017) also found that CAS decreased significantly in both groups (47% vs 40%); however 20% of patients deteriorated in the weekly group. Stoyanova et al. (2023) also reported significant lower CAS at 1st month in the WR group (4.5 vs 4.9), but without significant difference between the two therapeutic groups in terms of CAS relative reduction.

A decrease in diplopia is reported in most studies, with a wide range of statistical significance. Kahaly et al. (2005) showed a significant reduction of diplopia in weekly IVMP (23 to 10; $p < 0.001$). Roy et al. (2015) reported improvement in diplopia in both groups at the 1-year follow-up compared with baseline, with statistical significance achieved only in the monthly IVMP group ($p = 0.009$). Furthermore, Geest et al. (2008) reported improvement in diplopia in 50% (2/4) of IVMP patients, compared with 0% in placebo patients, although this difference did not reach statistical significance. Consistently, three direct comparison studies (He et al; Stoyanova et al; Li et al) showed diplopia improvement in both regimens without significant differences, although Li et al. (2024) demonstrated a higher responsiveness in the monthly group (66.67% vs 35.29% at week 12, $p = 0.063$).

Improvement in proptosis and soft tissue involvement was reported in most studies. Kahaly et al (2005) demonstrated that 21 of 35 patients (60%) in the weekly IVMP group had a proptosis decrease of ≥ 2 mm compared with 14 of 35 patients (40%) in the oral GC group ($p < 0.02$), accompanied by significant reductions in chemosis ($p = 0.002$) and conjunctivitis ($p = 0.003$). Similarly, Roy et al. (2015) reported significantly lower proptosis in the monthly IVMP group compared with oral GC at 6-month follow-up ($p = 0.02$), although not significant at 1 year ($p = 0.083$). In direct comparison studies between weekly and monthly regimens, He et al. (2017), Stoyanova et al. (2023), and Li et al. (2024) showed comparable proptosis improvement without significant between-group differences (He: 35.3% vs 33.3%; Stoyanova: 28.1% vs 26.7%, $p = 0.90$; Li: 37.93% vs 43.48%). Notably, Stoyanova et al. (2023) demonstrated significantly higher improvement in subjective symptoms in the modified monthly group (81.3%) compared with the weekly group (46.7%) at 3-month follow-up ($p < 0.01$), indicating potential effects on subjective patient complaints. Additionally, Geest et al. (2008) reported soft tissue swelling improvement in 50% (3/6) of IVMP patients versus 11% (1/9) of placebo patients (RR=4.5; 95% CI 0.6-33.7; $p = 0.095$).

Adverse event

IVMP regimens were generally well tolerated across all included studies. Kahaly et al. (2005) reported a higher incidence of major adverse events (depression, severe hypertension) in the oral GC group compared with weekly IVMP, with a significant decrease in bone mineral density observed only in the oral group ($p < 0.05$). In direct comparison, He et al. (2017) (one patient discontinued due to gastric ache; no severe hepatotoxicity) and Li et al. (2024) (31% vs 27.59%, $p = 0.773$) found no significant differences between regimens, with weight gain as the most common adverse event and no cases of diabetes, hepatic dysfunction, or infections. Stoyanova et al. (2023) reported

mild/transient AEs comparable between regimens, with one case of gluteal abscess attributable to intramuscular injection in the modified monthly group. Furthermore, Van Geest et al. (2008) and Roy et al. (2015) reported no major AEs, with only mild, reversible elevations in liver enzymes in a minority of patients. No deaths or severe hepatotoxicity were reported across all studies.

Relapse

Recurrence data were reported in a limited number of studies. Only one study reported recurrence data in a direct comparison⁹, with a lower rate in the monthly regimen (29.4%) than in the weekly regimen (53.3%). Kahaly et al. (2005) reported a relatively low additional treatment rate in the weekly IVMP group, consistent with van Geest et al. (2008), who showed that patients receiving monthly IVMP did not require additional therapy after the trial.

DISCUSSION

This systematic review of 6 comparative studies evaluated the weekly and monthly IVMP regimens in patients with moderate-to-severe active Graves' orbitopathy (GO). The findings of this review consistently indicate that both regimens yielded comparable therapeutic responses, with no statistically significant differences in overall response rates. Furthermore, either weekly or monthly protocol showed better results than oral GC. These results suggest that the monthly regimen, including its modified versions, may serve as a viable alternative to the weekly protocol, which has been the standard for moderate-to-severe active GO.

The direct comparison studies between weekly and monthly regimens (He et al., 2017; Stoyanova et al., 2023; Li et al., 2024) consistently showed a higher response rate with the weekly regimen (77–86%) than with the monthly regimen (67–72%). Although this difference did not reach statistical significance, this consistent trend suggests the relative superiority of the weekly regimen, supporting its position as first-line treatment per EUGOGO guidelines.

The superiority of weekly regimens can be explained by pharmacological theories. Weekly regimens maintain stable drug concentrations, while monthly administration produces transient peak concentrations, resulting in less sustained inflammatory suppression. Moreover, the weekly regimen mechanism of action activates the genomic pathway, namely trans-repression of NF- κ B and suppression of pro-inflammatory cytokines (IL-1, IL-6, TNF- α), providing sustained anti-inflammatory effects compared to monthly regimens, which predominantly engage the non-genomic pathway, which acts rapidly but transiently, leading to rebound inflammation during the extended inter-dose intervals¹⁵. Studies by Zang et al., 2011 also showed that a 7-day treatment interval is needed to allow adequate methylprednisolone clearance and maintain sustained anti-inflammatory suppression, while consecutive-day administration increases the risk of serum accumulation¹⁶. However, in the three direct-comparison studies, the safety profiles of the weekly and monthly regimens were relatively comparable, with minimal major adverse events in both groups, because the doses used in the studies did not exceed the recommended dose limits (>8 g), as shown in Beleslin et al., 2020 which use 10.2 cumulative dose, 74% of the subjects developed major side effects¹⁷.

The supporting comparative studies, which compare weekly IVMP with oral glucocorticoid, favor the intravenous regimen as the preferred option. The landmark trial by Kahaly et al. (2005) demonstrated the superiority of weekly IVMP (77%) over oral prednisone (51%, $p < 0.05$), which formed the basis of the 2008 EUGOGO recommendations and remains a reference in the 2021 guidelines. This finding is also consistent with Roy et al. (2015), who reported that monthly IVMP (87%) was superior to oral prednisone (55%). Indirect comparison showed that both IVMP regimens are superior to oral GC. However, oral GC remains a relevant alternative in settings with limited access to intravenous therapy.

Van Geest et al. (2008) is the only placebo-controlled RCT in the literature to show the superiority of monthly IVMP (83%) over placebo (11%) in patients with moderate-to-severe active GO. This finding indicates that IVMP is far more effective than the non-intervention group. The absence of an RCT comparing a weekly regimen with a placebo regimen should not be considered a weakness of the evidence but rather an ethical consideration, given the established efficacy of IVMP, which makes placebo administration no longer acceptable in patients with active GO.

Overall, weekly regimens showed an acceptable safety profile across the included studies. Most core studies reported no major adverse events in the weekly group and showing a superior safety profile compared with oral GC and combined IV + oral GC^{14,17}. Another supporting study also reported the overall morbidity rate 6.5% and the mortality rate 0.6% of IVMP therapy¹⁶, followed by Riedl et al. (2015), who stated that IVMP regimens are well tolerated, with the majority of adverse events being mild to moderate¹⁸. Concerns regarding glucocorticoid-induced osteoporosis with weekly regimens were also addressed by Harsløf et al. (2023), demonstrating decreased bone turnover and

increased BMD¹⁹. Nevertheless, serious complications such as acute hepatotoxicity, cardiovascular events, and thromboembolism still remain concerns²⁰, comprehensive pre-treatment screening, including liver function test, viral hepatitis serology, and cardiovascular evaluation, before initiating therapy is recommended²¹.

Beyond considerations of efficacy and safety, the practical aspects of treatment delivery need careful attention when selecting an IVMP regimen for GO. The standard EUGOGO weekly regimen requires patients to attend 12 infusion visits over 12 consecutive weeks, which can be difficult for patients who live far from tertiary care centers or have limited mobility. This is particularly relevant given that both the 2021 EUGOGO guidelines and the 2022 ATA/ETA consensus statement emphasise that IVMP therapy should only be delivered at specialised centres equipped to handle potential serious adverse events, and that access to such facilities varies widely across institutions and countries^{5,6}.

In this context, monthly regimens requiring only 3–4 visit cycles at four-week intervals offer a considerably reduced treatment burden while maintaining comparable efficacy, as supported by all three studies included in this review. The practical relevance of monthly regimens is further illustrated by Stoyanova et al. (2023), in which the mMR protocol was developed as a local adaptation to the limitations of the Bulgarian healthcare system in consistently implementing the weekly regimen. Similar considerations apply across various developing countries, where a limited number of tertiary referral centers and geographical barriers can represent real obstacles to adherence to weekly infusion schedules. In such setting, IVMP remains a more accessible and cost-effective option compared to newer biologic agents²², and having a monthly regimen as a viable alternative makes IVMP therapy more accessible across different healthcare settings. This is consistent with the findings of Aishwarya et al. (2025) in their systematic review, which documented that monthly regimens are frequently combined with oral glucocorticoid tapering in practice as part of protocol adaptations across various care centers⁷.

This systematic review has some important limitations. Although we employed standard methodology to conduct direct and indirect comparisons with relevant clinical characteristics, the studies still have a risk of bias. Substantial heterogeneity and risk of bias were present at both the study and outcome levels among the included trials, reflecting differences in IVMP regimens and follow-up durations. All included studies were single-center with small sample sizes, which limits the statistical power of the findings.

These findings suggest that monthly and modified monthly regimens are valid alternatives to the standard weekly protocol, with comparable efficacy and safety. Treatment should be tailored to each patient's clinical profile, disease severity, and access to infusion facilities. The weekly regimen may be preferred for patients requiring rapid anti-inflammatory effect, while the monthly regimen is equally effective for those with limited access. All patients should be treated at tertiary centers that can monitor and manage serious side effects^{5,6}.

CONCLUSION

This systematic review found that weekly and monthly intravenous methylprednisolone treatments work equally well and are similarly safe for patients with moderate to severe active Graves' ophthalmopathy. Monthly treatments could be a good alternative to weekly ones, especially where infusion facilities are limited. More studies comparing equal doses, with longer follow-up and at multiple centers, are needed to make stronger recommendations.

Declaration of generative AI in scientific writing

The author(s) declare that no generative AI or AI-assisted technologies were used in the writing process of this manuscript. All content, including text, analysis, and interpretation, was produced solely by the author(s).

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