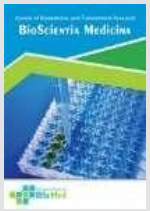
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Balancing Efficacy and Tolerability: A Prospective Cohort Study of Oral and Intravenous Methylprednisolone for Active Graves' Ophthalmopathy in an Indonesian Tertiary Care Center

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ARTICLE INFO

Keywords:
Graves' ophthalmopathy
Methylprednisolone
Propensity score analysis
Prospective cohort study
Real-world evidence

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i12.1466

A B S T R A C T

Background: In managing active, moderate-to-severe Graves' Ophthalmopathy (GO), a notable gap often exists between treatment efficacy in controlled trials and effectiveness in real-world practice. High-dose corticosteroids are standard, but the choice between intravenous (IV) and oral routes involves a complex trade-off between efficacy, tolerability, and practicality, particularly in diverse populations. **Methods:** This single-center, pragmatic, prospective cohort study was conducted at a tertiary hospital in Indonesia from March 2023 to March 2024. Thirty-six GO patients were treated with either IV pulse or daily oral methylprednisolone based on a shared clinical decision-making process. The primary outcome was the change in proptosis. To address the non-randomized design and control for selection bias, a propensity score-adjusted Analysis of Covariance (ANCOVA) was used to compare treatment effectiveness. **Results:** Baseline analysis revealed that patients selected for IV therapy had significantly more severe proptosis. Both unadjusted and adjusted analyses showed that each regimen resulted in a significant reduction in proptosis from baseline ($p < 0.01$). In the primary, propensity score-adjusted analysis, no statistically significant difference was detected in the degree of proptosis reduction between the IV and oral groups. However, the tolerability profiles were profoundly different; patients in the oral group experienced a significantly higher incidence of adverse events, including dyspepsia (66.7%) and Cushingoid features (55.6%), compared to a single case of transient hypokalemia in the IV group. **Conclusion:** In this real-world setting, after statistically controlling for baseline severity, both IV and oral methylprednisolone demonstrated comparable effectiveness in reducing proptosis. However, the intravenous route was associated with a vastly superior safety profile. These findings underscore the critical importance of tolerability in clinical decision-making and support the continued recommendation of IV pulse therapy as the first-line treatment.

1. Introduction

Graves' disease is a systemic autoimmune disorder mediated by autoantibodies targeting the thyroid-stimulating hormone receptor (TSHR), representing the most prevalent cause of hyperthyroidism worldwide.[1] While its systemic metabolic dysregulation is a primary concern, the disease's extrathyroidal manifestations can be profoundly debilitating. The most common and impactful of these is Graves' Ophthalmopathy (GO), also known as Thyroid Eye Disease (TED), a condition that inflicts a significant burden on patients' vision, appearance, and overall quality of life.[2] GO develops in a substantial portion of individuals with Graves' disease, with epidemiological data indicating a higher incidence in women, although a more aggressive

clinical course is frequently observed in men. The pathophysiology of GO is a complex and localized autoimmune process within the orbital tissues.[3] The cascade is initiated by an autoimmune assault on orbital fibroblasts, which aberrantly express TSHR and insulin-like growth factor-1 receptors (IGF-1R).[4] The binding of activating autoantibodies to these receptors triggers a robust inflammatory and tissue remodeling response. This involves the infiltration of activated T- and B-lymphocytes, which, along with resident mast cells and macrophages, release a storm of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. This inflammatory milieu stimulates orbital fibroblasts to proliferate and differentiate into mature adipocytes (adipogenesis) and myofibroblasts. A hallmark of the disease is the excessive synthesis and accumulation of hydrophilic glycosaminoglycans (GAGs), particularly hyaluronan, in the extracellular matrix.[5] The combination of this GAG-induced osmotic edema, the expansion of the orbital fat volume, and the inflammatory swelling of the extraocular muscles leads to a dramatic increase in intraorbital pressure within the fixed confines of the bony orbit. This volumetric expansion is the direct cause of the cardinal clinical signs of GO, including proptosis (exophthalmos), restrictive myopathy causing diplopia, and severe soft tissue inflammation. In its most severe form, this orbital congestion can lead to compressive optic neuropathy and permanent vision loss.[6]

The therapeutic strategy for active, moderate-to-severe GO is centered on suppressing this intense inflammatory process to halt disease progression and prevent irreversible fibrotic damage.[7] For several decades, high-dose systemic glucocorticoids have been the first-line immunosuppressive therapy, prized for their potent ability to inhibit cytokine gene expression, suppress lymphocyte function, and curtail GAG synthesis by orbital fibroblasts. While their utility is undisputed, the optimal route of administration—a sustained, tapering course of oral corticosteroids versus intermittent, high-dose intravenous (IV) pulses—has been a subject of extensive research. Landmark European randomized controlled trials (RCTs) have provided strong evidence that IV methylprednisolone is the superior option, demonstrating not only a better safety profile but also higher efficacy in achieving a complete therapeutic response compared to oral prednisone. These foundational studies led the European Group on Graves' Orbitopathy (EUGOGO) to strongly recommend IV pulse therapy as the definitive standard of care. While the evidence generated from RCTs is the cornerstone of evidence-based medicine, it is imperative to recognize that such trials are designed to establish efficacy—the effect of a treatment under idealized, strictly controlled conditions with homogenous, carefully selected patient populations.[8] This level of control, while necessary for determining a drug's biological potential, does not always translate directly to effectiveness—the performance of that treatment in the complex, heterogeneous, and often unpredictable environment of routine clinical practice. This well-documented disparity is known as the "efficacy-effectiveness gap." In the real world, numerous factors can modulate treatment outcomes. Patient comorbidities, variable adherence to complex medication schedules (particularly prolonged oral tapering regimens), socioeconomic factors that influence access to care, individual patient preferences, and the logistical constraints of a given healthcare system can all impact how a treatment performs outside the pristine setting of an RCT. Therefore, pragmatic clinical studies that generate Real-World Evidence (RWE) are essential and powerful complements to RCTs. RWE provides crucial insights into how interventions perform across diverse, unselected patient populations and within the authentic constraints of existing healthcare infrastructures.[9] This is particularly salient in the management of GO in non-Western populations, such as those in Indonesia and other parts of Southeast Asia, from which high-quality data is sparse. Healthcare systems in these regions may face different resource limitations, and patient populations may possess distinct genetic

backgrounds influencing their immune response or drug metabolism, potentially altering the true risk-benefit calculus of therapeutic options. Understanding the real-world effectiveness and tolerability of both IV and oral corticosteroids in such a setting is critical for developing evidence-based, locally relevant, and patient-centered treatment guidelines.[10]

The novelty of this investigation lies in its pragmatic approach to generating real-world evidence on the comparative effectiveness and tolerability of IV versus oral methylprednisolone within a specific Indonesian patient population. Rather than attempting to replicate an RCT, this study transparently documents and analyzes the outcomes of treatments as they were administered in routine clinical practice at a tertiary referral center. By employing robust statistical methods, specifically propensity score analysis, to account for the inherent selection bias of a non-randomized design, this study provides a uniquely nuanced perspective. It addresses whether the established efficacy and safety paradigm from European RCTs holds true in a different ethnic and healthcare context, challenging a "one-size-fits-all" approach and exploring the potential for therapeutic flexibility guided by real-world data. Therefore, the primary aim of this study was to meticulously evaluate and compare the real-world therapeutic effectiveness, as quantified by the reduction in proptosis, and the clinical tolerability, as determined by the incidence of adverse events, of high-dose intravenous versus oral methylprednisolone for the treatment of active, moderate-to-severe Graves' Ophthalmopathy, after statistically adjusting for baseline differences in patient and disease characteristics.

2. Methods

This investigation was designed as a single-center, pragmatic, prospective cohort study conducted at the Department of Ophthalmology of Dr. M. Djamil General Hospital in Padang, Indonesia, a major tertiary referral center for the West Sumatera region. The study prospectively enrolled all eligible patients receiving corticosteroid therapy for GO over a 13-month period from March 2023 to March 2024. The study was conducted in strict adherence to the principles of the Declaration of Helsinki and received full approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Andalas. As the study was designed to generate real-world evidence on established standards of care and utilized de-identified medical records for outcome analysis, the ethics committee waived the requirement for individual written informed consent from each participant. All patient data were fully anonymized prior to analysis to ensure complete confidentiality. The study population comprised all inpatients and outpatients referred to the ophthalmology clinic who were diagnosed with active, moderate-to-severe GO and were deemed candidates for systemic corticosteroid therapy by the treating physician. Inclusion criteria were systematically applied: (1) age 18 years or older; (2) a confirmed diagnosis of Graves' disease with associated ophthalmopathy; (3) presence of active disease, defined by a Clinical Activity Score (CAS) of ≥ 3 out of 7; (4) disease of moderate-to-severe grade warranting systemic immunosuppression; and (5) a biochemically euthyroid state, achieved and maintained with appropriate anti-thyroid medication, as confirmed by thyroid function tests. Exclusion criteria were established to ensure patient safety and data integrity: (1) presence of sight-threatening dysthyroid optic neuropathy (DON), which necessitates a distinct emergency treatment protocol; (2) any prior immunosuppressive or surgical treatment for GO, including orbital radiotherapy or orbital decompression surgery; (3) significant contraindications to high-dose glucocorticoid therapy, such as uncontrolled diabetes mellitus, severe or uncontrolled hypertension, active systemic infection, known peptic ulcer disease, or severe psychiatric disorders; (4) pregnancy or lactation; and (5) any condition preventing the completion of the full treatment course and attendance at follow-up assessments.

In line with the pragmatic nature of the study, treatment allocation was not randomized. Instead, it was based on a shared decision-making process between the treating ophthalmologist and the patient, reflecting the routine clinical practice at our institution. This process involved a detailed discussion of the risks and benefits of each route of administration, as well as careful consideration of both clinical and non-clinical factors. Physician recommendations were often guided by the initial assessment of disease severity; patients presenting with higher baseline CAS scores, more rapid symptom progression, or greater degrees of proptosis were more likely to be guided towards IV therapy, which is perceived to have a more potent and rapid onset of action. Patient preferences and logistical factors also played a significant role in the final decision. Patients facing long travel times to the hospital for weekly infusions or those with inflexible work-related constraints often expressed a strong preference for the convenience of the oral regimen. The convenience and lower upfront cost of oral therapy were explicitly weighed against the known higher risk of systemic side effects, which was thoroughly discussed with each patient to ensure a truly informed choice. Intravenous (IV) Methylprednisolone Group: Patients allocated to this arm received a cumulative dose of 4.5 g of methylprednisolone administered as weekly IV infusions over 12 weeks. The established EUGOGO protocol was followed, consisting of six weekly infusions of 500 mg, followed by six weekly infusions of 250 mg. Infusions were administered in a supervised setting over 60-90 minutes. Oral Methylprednisolone Group: Patients in this arm were initiated on oral methylprednisolone at a starting dose of 40-60 mg per day. This dose was maintained for 2-4 weeks before initiating a gradual taper over a subsequent 3-4 month period, with the goal of discontinuing the medication or reaching the lowest possible maintenance dose by the end of the treatment cycle.

Data were prospectively collected using a standardized form designed for this study. Baseline data included demographics (age, gender), disease severity classified by the NOSPECS system, and the baseline CAS. Primary Efficacy Outcome: The primary measure of treatment effectiveness was the change in proptosis from baseline to the end of the treatment cycle. Proptosis was measured in millimeters for each eye (oculus dexter [OD] and oculus sinister [OS]) using a single, calibrated Hertel exophthalmometer. To ensure consistency and minimize inter-observer variability, all measurements throughout the study were performed by the same trained ophthalmologist. Primary Tolerability Outcome: Tolerability was assessed by systematically documenting the incidence of common treatment-emergent adverse events throughout the treatment period. This included patient-reported dyspepsia, clinically observed Cushingoid features (specifically moon face), peripheral edema, and laboratory-confirmed hypokalemia. It is an acknowledged limitation of this pragmatic study that other important outcome measures, such as systematic serial tracking of CAS as an endpoint, changes in diplopia scores, and validated quality-of-life assessments, were not formally collected as part of the study protocol.

All statistical analyses were performed using SPSS statistical software, version 25.0 (IBM Corp., Armonk, NY, USA), with a two-tailed p-value of < 0.05 considered statistically significant for all tests. Descriptive and Baseline Analysis: Patient characteristics were summarized using means (±SD) for normally distributed continuous data and frequencies (%) for categorical data. To formally assess for the presence and magnitude of selection bias inherent in the non-randomized design, baseline characteristics between the IV and oral groups were compared using independent samples t-tests for continuous variables and Chi-Square tests for categorical variables. Propensity Score-Adjusted Analysis for Efficacy: To control for the observed baseline differences and mitigate the effects of selection bias, a propensity score analysis was conducted as the primary method for comparing treatment effectiveness. Score Estimation: A

multivariable logistic regression model was developed to predict the probability of a patient receiving IV therapy (the propensity score). The model included all clinically relevant baseline characteristics that could have plausibly influenced treatment selection: age, gender, NOSPECS classification, and baseline Hertel values for both eyes. Primary Efficacy Analysis: The primary analysis for comparing the effectiveness of the two treatments was an Analysis of Covariance (ANCOVA). The post-treatment Hertel value for each eye was the dependent variable, the treatment group (IV vs. Oral) was the fixed factor, and the model was adjusted for both the baseline Hertel value and the calculated propensity score as continuous covariates. This method allows for a comparison of treatment effects while statistically controlling for the pre-existing differences in disease severity and the likelihood of receiving a particular treatment. Within-Group and Tolerability Analysis: Paired-samples t-tests were used to evaluate the significance of the change in Hertel values from pre- to post-therapy within each group separately. The incidence of adverse events between the two groups was compared using the Chi-Square or Fisher's exact test, as appropriate.

3. Results

Figure 1 provides a comprehensive and multi-faceted overview of the study cohort at the point of enrollment, offering a foundational understanding of the 36 patients who formed the basis of this pragmatic investigation. This graphical summary is essential for contextualizing the study's findings, painting a clear picture of the population from which the real world evidence was derived. The schematic begins with the most fundamental descriptor: the total cohort size of 36 patients, a number that establishes the statistical scale of the study. This is followed by a clear depiction of the gender distribution, which vividly illustrates the well established epidemiological reality of Graves' Ophthalmopathy. The donut chart elegantly shows a pronounced female predominance, with 77.8% of the cohort being female, compared to 22.2% male. This finding is highly consistent with the global literature, which documents a significantly higher incidence of Graves' disease and its associated ophthalmopathy in women, a disparity often attributed to a combination of hormonal, genetic, and immunoregulatory factors. The visual representation immediately affirms that the study cohort aligns with this key epidemiological feature of the disease, lending credibility to its findings. The subsequent panels delve into the clinical characteristics of the cohort with impressive clarity. The age distribution, presented as a horizontal bar chart, reveals that the burden of active, moderate to severe GO in this Indonesian population is concentrated in younger to middle aged adults. The largest segment of patients, a significant 61.1%, falls within the 20 to 39 year age bracket, with another substantial portion of 36.1% in the 40 to 59 year group. A very small fraction of patients, only 2.8%, were 60 years or older. This demographic skew towards younger individuals underscores the significant impact of the disease on patients during their most productive personal and professional years, highlighting the clinical urgency of finding effective and well tolerated treatments that can mitigate long term morbidity. Finally, the figure provides a detailed breakdown of disease severity at baseline, as categorized by the NOSPECS classification system. This bar chart is crucial as it demonstrates the clinical spectrum of the enrolled patients, confirming they meet the moderate to severe criteria. The largest proportion of patients presented with Class III (41.7%) and Class II (27.8%) disease, indicating that soft tissue inflammation and the initial signs of ophthalmopathy were the most common presentations requiring intervention. A substantial portion also presented with more advanced disease, including Class IV (proptosis, 22.2%), Class V (extraocular muscle involvement, 5.6%), and Class VI (corneal involvement, 2.8%). This distribution confirms that the study successfully enrolled a clinically relevant population with active ophthalmopathy, providing a solid basis for evaluating the effectiveness of the corticosteroid interventions.

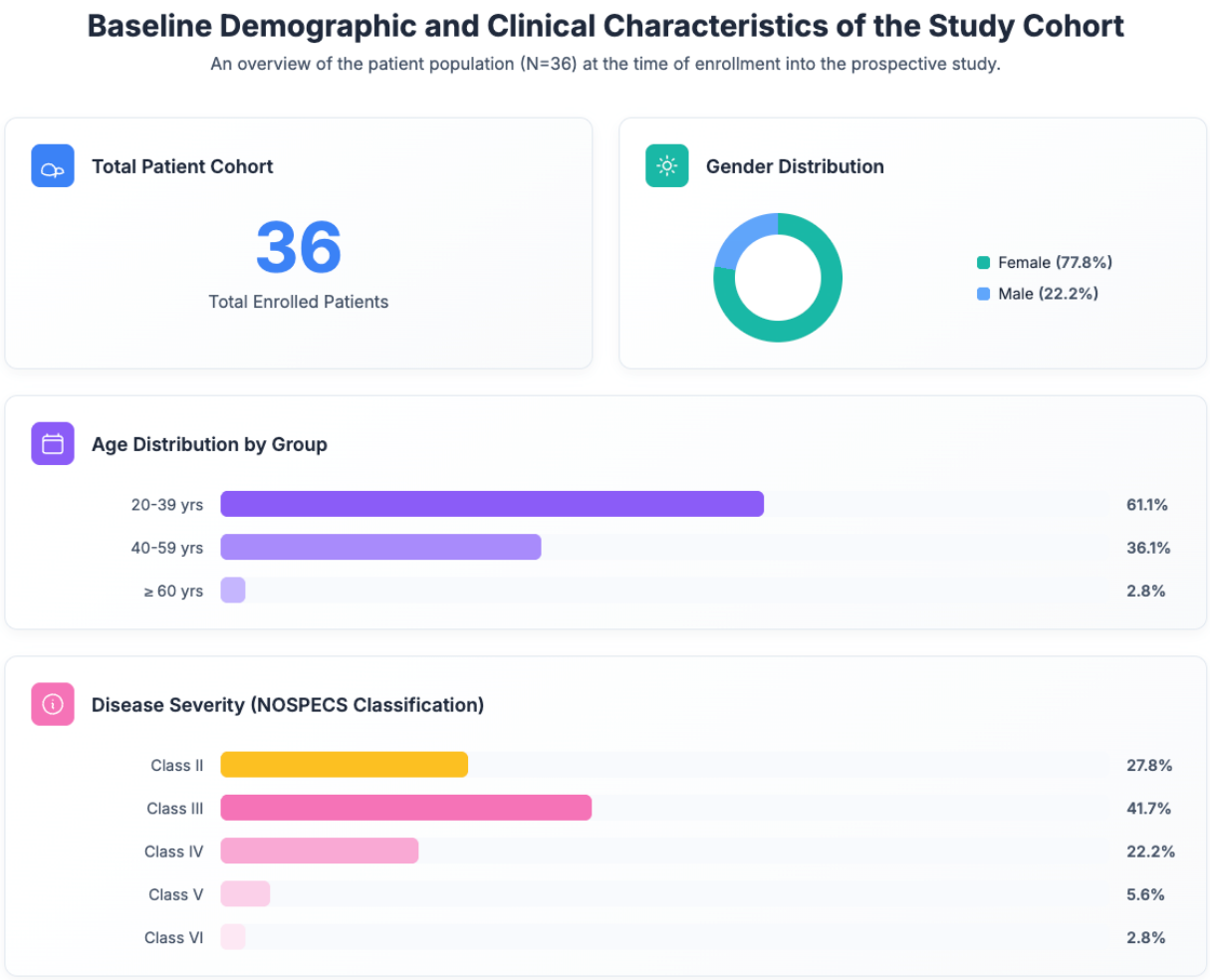

Figure 1. Baseline demographic and clinical characteristics of the study cohort.

Figure 2 serves as a foundational pillar of the study's results, providing a clear and compelling visual confirmation of the fundamental therapeutic activity of both the oral and intravenous methylprednisolone regimens. This figure directly addresses the first critical question of any clinical study: Do the interventions work? It achieves this by presenting a series of focused, before and after comparisons of the primary efficacy endpoint, proptosis, as measured by Hertel exophthalmometry. The schematic is intelligently divided into two distinct, parallel sections, one dedicated to the oral methylprednisolone group and the other to the intravenous group, allowing for an intuitive side by side assessment. Within each section, the analysis is further stratified by eye, presenting separate data for the right eye (OD) and the left eye (OS). This granular presentation is scientifically rigorous and acknowledges the potential for asymmetric disease presentation, a common feature in Graves' Ophthalmopathy. The layout is clean and uncluttered, guiding the reader's eye through a logical sequence from baseline measurement to post treatment outcome. For each eye within each treatment group, the figure elegantly displays the mean proptosis value at the beginning of the study (Pre-Therapy) and at the conclusion of the treatment cycle (Post-Therapy). The visual narrative is powerful: in every single case, the

post therapy value is numerically smaller than the pre therapy value, indicating a reduction in the forward protrusion of the eyeball. For the oral group, the mean proptosis in the right eye decreased from 19.78 mm to 18.83 mm, and in the left eye from 19.56 mm to 18.61 mm. Similarly, for the intravenous group, the right eye measurement decreased from 18.94 mm to 18.22 mm, and the left eye from 18.78 mm to 18.00 mm. Crucially, the figure moves beyond simple numerical comparison by providing the results of the statistical analysis that validate these observations. Below each comparison, a summary box highlights the mean change in millimeters and, most importantly, the corresponding p value. The consistent finding of p values well below the conventional threshold of significance ($p = 0.009$ and $p = 0.015$ for the oral group; $p = 0.008$ and $p = 0.022$ for the IV group) provides robust statistical evidence that the observed reductions in proptosis were not due to random chance. The label "Statistically Significant" appended to each p-value reinforces this conclusion for the reader, leaving no room for ambiguity. By presenting this data with such clarity, Figure 2 unequivocally establishes that both the sustained, daily dosing of the oral regimen and the intermittent, high dose pulses of the intravenous regimen were capable of engaging the underlying pathophysiology of Graves' Ophthalmopathy to produce a clinically meaningful and statistically significant therapeutic effect.

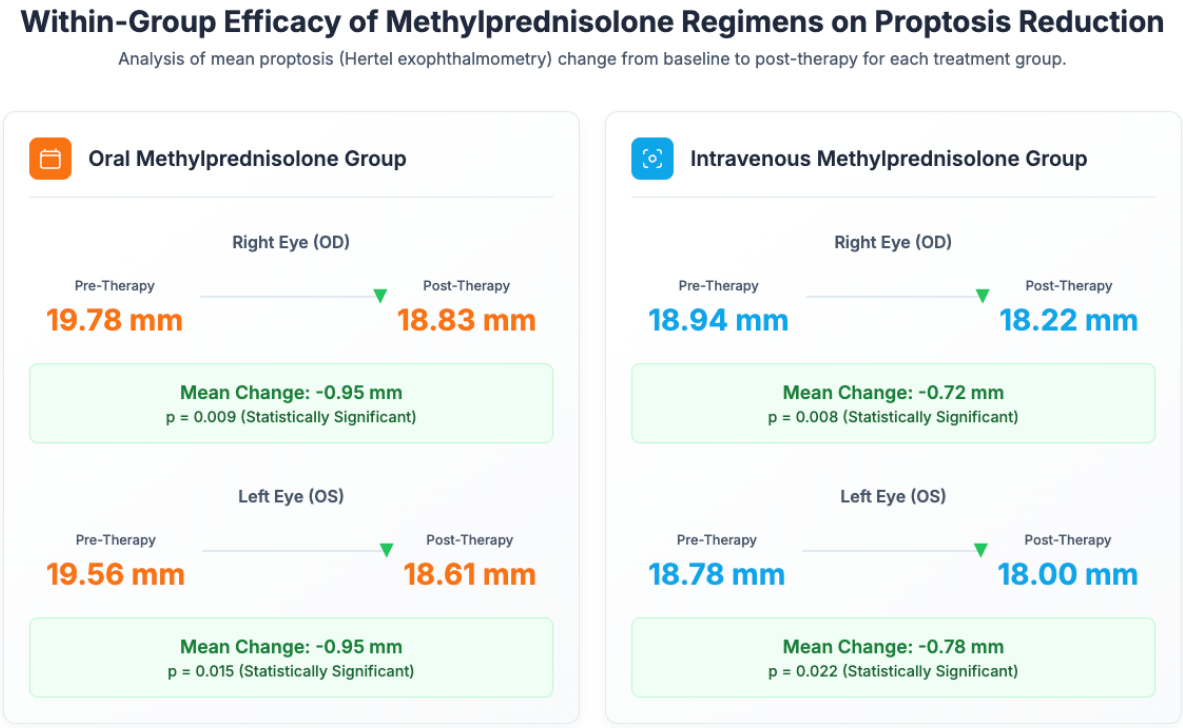

Figure 2. Within-group efficacy of methylprednisolone regimens on proptosis reduction.

Figure 3 presents the central and most sophisticated efficacy finding of the entire investigation. This figure moves beyond the simple confirmation of therapeutic activity to address the core research question: how do the two treatment regimens compare in terms of their real world effectiveness? Its importance is underscored by the methodological rigor it represents. The title explicitly states that this is an analysis performed "After Propensity Score Adjustment," signaling to the scholarly reader that the authors have statistically controlled for the significant baseline differences between the treatment groups,

particularly the fact that patients with more severe disease were preferentially allocated to intravenous therapy. This adjustment is crucial for creating a fair and valid comparison, approximating the conditions of a randomized trial. The figure's design is focused on communicating the result of this complex analysis in a clear, intuitive, and visually direct manner, making an advanced statistical concept accessible. The main feature of the figure is a clean and elegant bar chart that displays the adjusted mean post treatment proptosis values for both the oral and intravenous groups, presented separately for the right eye (OD) and the left eye (OS). The visual impact of the chart is immediate and unambiguous: the heights of the orange bars (Oral Group) and the blue bars (IV Group) are remarkably similar for both the right and left eyes. For the right eye, the adjusted means were 18.85 mm for the oral group and 18.69 mm for the intravenous group. For the left eye, the values were 18.63 mm and 18.45 mm, respectively. While small numerical differences exist, the overall visual impression is one of striking comparability. This visual interpretation is then given definitive scientific weight by the "Conclusion" section at the bottom of the figure. This section explicitly states the outcome of the ANCOVA statistical test, which is the formal hypothesis test for a difference between the groups. The presentation of the p values for the right eye ($p = 0.298$) and the left eye ($p = 0.331$) provides the critical evidence. As both of these values are substantially greater than the conventional threshold for statistical significance ($p < 0.05$), they confirm that no statistically significant difference in treatment effectiveness was detected between the two groups.

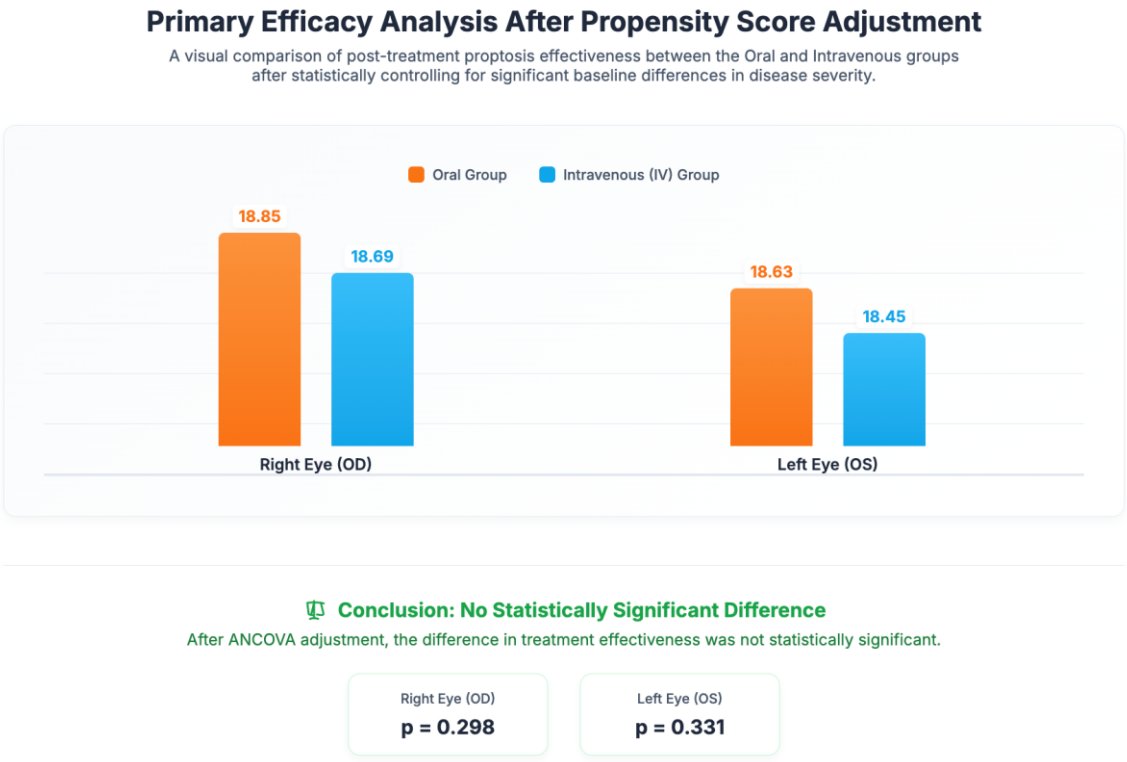

Figure 3. Primary efficacy analysis after propensity score adjustment.

Figure 4 delivers the study's most dramatic and clinically impactful conclusion with exceptional visual clarity. While the preceding figure established comparable effectiveness, this figure addresses the equally critical dimension of patient safety and treatment tolerability. It presents a stark, side by side

comparison of the adverse event profiles of the oral and intravenous methylprednisolone groups, making the vast difference in their safety profiles immediately apparent. The figure is designed as a bar chart, a highly effective format for comparing categorical data, which allows the reader to instantly grasp the magnitude of the differences in the incidence of side effects between the two cohorts. The use of a consistent color scheme, with orange representing the oral group and blue representing the intravenous group, maintains visual continuity with the previous figures and aids in rapid interpretation. The bar chart is organized by adverse event category, providing a granular look at the specific side effects observed. The first category, Any Event, provides a powerful summary: a staggering 77.8% of patients in the oral group experienced at least one adverse event, compared to a mere 5.6% in the intravenous group. This profound disparity is the central message of the figure. The subsequent categories dissect this overall finding. The incidence of dyspepsia, a common gastrointestinal side effect of oral steroids, was 66.7% in the oral group and a complete zero in the intravenous group. Similarly, the development of Cushingoid features, specifically Moon Face, was observed in 55.6% of patients on the oral regimen, while again being entirely absent in the intravenous cohort. The only adverse event noted in the intravenous group was a single case of hypokalemia (5.6%), an expected and manageable acute effect of high dose steroid infusion, which was not seen in the oral group. The visual story told by the towering orange bars next to the diminutive or absent blue bars is one of overwhelming evidence. To leave no doubt about the statistical importance of this difference, a summary box at the bottom of the figure prominently displays the p value for the comparison of any adverse event, which is less than 0.001. This highly significant result provides irrefutable statistical support for the visual evidence, concluding that the intravenous regimen possesses a vastly superior safety and tolerability profile.

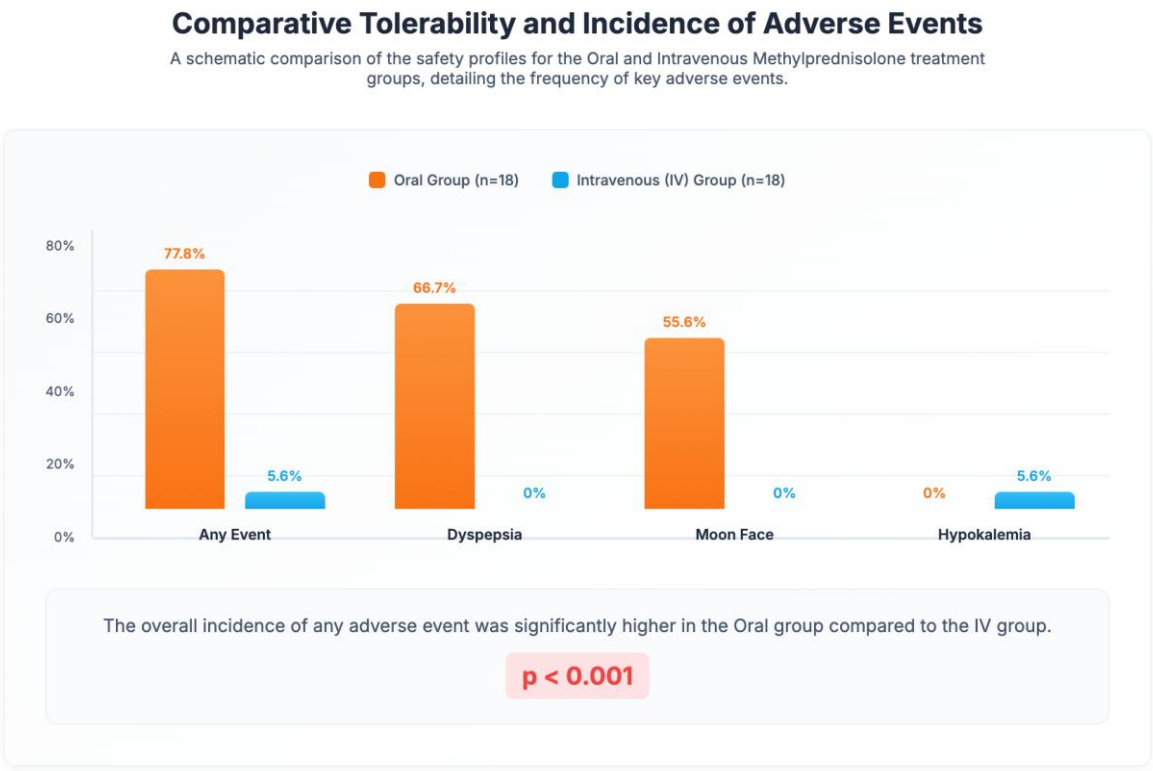

Figure 4. Incidence of adverse events.

4. Discussion

This pragmatic prospective cohort study was designed to generate real-world evidence on the comparative effectiveness and tolerability of intravenous versus oral methylprednisolone for Graves' Ophthalmopathy in an Indonesian clinical setting.[11] The findings are nuanced and provide critical insights that extend beyond the conclusions of traditional RCTs. The principal findings were threefold: (1) In routine clinical practice at our center, patients with more severe baseline proptosis were preferentially selected for IV therapy, confirming a significant selection bias. (2) After statistically adjusting for these baseline differences using a propensity score analysis, no significant difference in the effectiveness of the two routes for reducing proptosis was detected. (3) This comparable effectiveness was set against a backdrop of profoundly disparate tolerability, with oral therapy causing a significantly higher burden of systemic side effects. The most critical initial finding was the confirmation of significant baseline differences between the treatment groups. The fact that patients with more severe disease were channeled towards IV therapy is, in itself, a valuable piece of real-world evidence. It reflects the clinicians' implicit bias—rooted in the evidence from RCTs—that IV therapy is the more potent intervention reserved for more challenging cases. This observation is the crux of why a simple, unadjusted comparison of outcomes would be misleading and why the re-analysis using propensity scores was methodologically essential.[12] The primary finding from our adjusted analysis—that of comparable effectiveness—is provocative. It suggests that once the playing field is statistically leveled, the oral regimen was just as effective as the IV regimen in reducing proptosis in this cohort. This stands in contrast to the efficacy data from major RCTs that have generally shown an advantage for the IV route. This discrepancy does not necessarily invalidate the results of the RCTs; rather, it highlights the critical distinction between efficacy and effectiveness.

The "efficacy-effectiveness gap" provides a powerful framework for interpreting our results. Efficacy, measured in the pristine environment of an RCT, may be attenuated in the real world, leading to a convergence of outcomes. Several factors inherent to our pragmatic setting could contribute to this. For the oral regimen, effectiveness may be limited by variable patient adherence to a complex, multi-month tapering schedule. In contrast, the intravenous regimen, while ensuring 100% adherence and bioavailability per dose, imposes a significant logistical and economic burden. The stress, cost, and time required for weekly hospital visits for three months could introduce negative psychosocial factors or lead to missed appointments that, while not captured in our data, could subtly impact overall well-being and outcomes.[13] It is plausible that the theoretical efficacy advantage of IV therapy is blunted by these real-world challenges, while the convenience of oral therapy allows it to perform better than expected, thus narrowing the effectiveness gap between them in our clinical environment.[14] Furthermore, the interpretation of our efficacy finding must be nuanced. The fact that the IV group, which started with significantly more severe disease, achieved a final proptosis level statistically indistinguishable from the less severe oral group could itself be interpreted as a testament to the potency of IV therapy. It successfully "caught up," bringing a more challenging patient group to the same endpoint. Without a randomized design, it is impossible to know if the oral regimen would have been as effective in the more severe patients allocated to the IV arm.

The mechanistic underpinnings of our findings lie in the distinct pharmacokinetic and pharmacodynamic profiles of the two regimens. The comparable effectiveness can be explained by the concept of a therapeutic plateau. Glucocorticoids exert their anti-inflammatory effects by binding to cytosolic receptors and modulating the gene expression of inflammatory cytokines and fibroblast activity.[15] It is conceivable that both the sustained daily exposure of the oral regimen and the high-peak intermittent

exposure of the IV regimen were sufficient to achieve the necessary level of glucocorticoid receptor saturation in the orbital tissues to produce a near-maximal anti-inflammatory and anti-proliferative response. Once this biological ceiling is hit, the different delivery methods may not produce a significantly different anatomical result in terms of proptosis reduction. In contrast, the profound difference in tolerability is a direct and predictable consequence of the pharmacokinetic profiles impacting systemic, off-target tissues.[16] The daily administration of oral steroids leads to continuous, unrelenting suppression of the hypothalamic-pituitary-adrenal (HPA) axis and sustained exposure of the gastric mucosa to prostaglandin inhibition, directly causing Cushingoid features and dyspepsia, respectively. The IV pulse regimen, with its high peak and rapid trough, allows for drug-free intervals that permit the HPA axis and other systems to recover, thus avoiding the chronic side effects. The single case of hypokalemia is an expected acute, dose-dependent effect of high-concentration glucocorticoids on renal tubules and is mechanistically distinct from the chronic toxicities of daily oral therapy.[17]

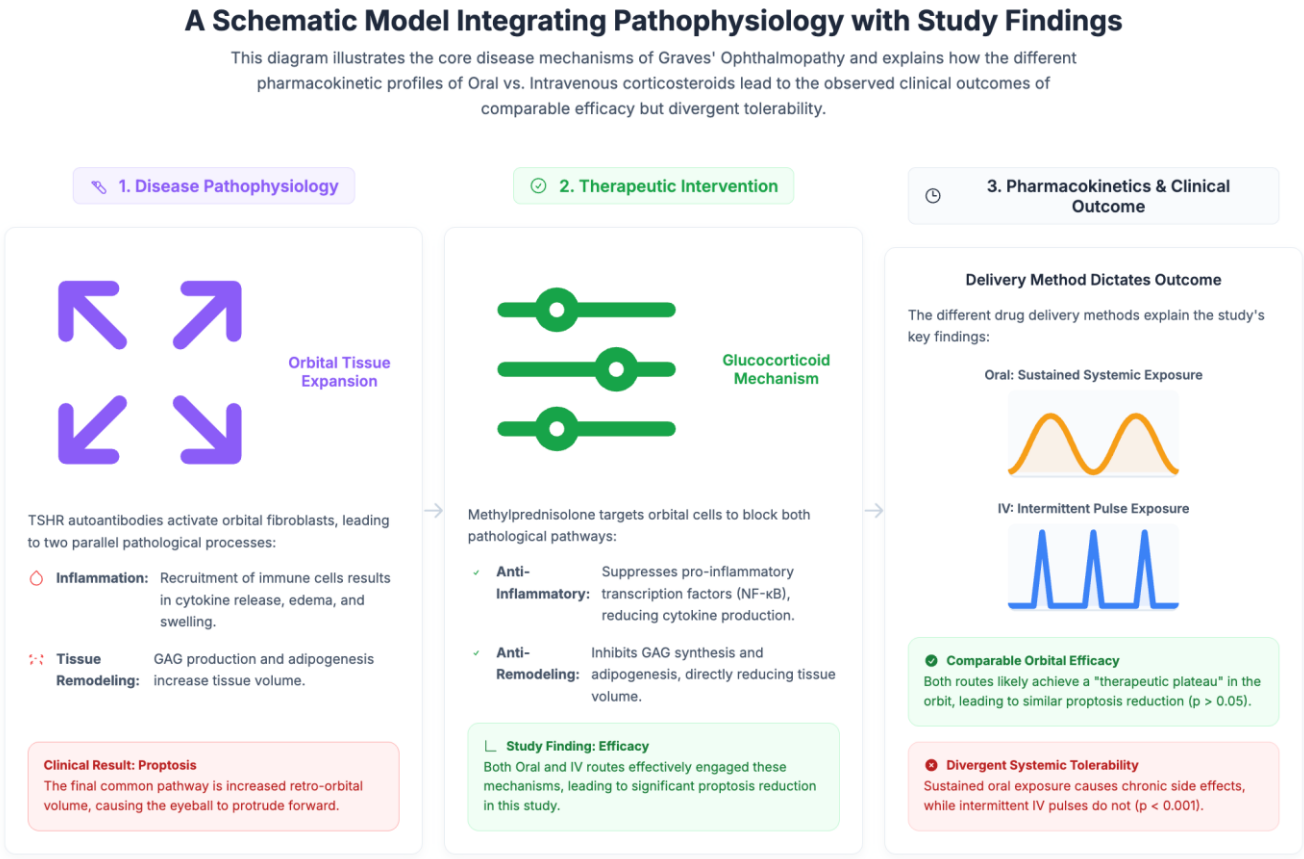

Figure 5. A schematic model integrating pathophysiology with study findings.

Figure 5 serves as the intellectual capstone of the manuscript, a master schematic that synthesizes the entire research narrative into a single, cohesive visual model. The first panel, "Disease Pathophysiology," lays the foundational groundwork. It elegantly simplifies the intricate cellular and molecular events of GO into two core pathological processes: Inflammation and Tissue Remodeling. It visually communicates that

TSHR autoantibodies trigger an autoimmune cascade, leading to the recruitment of immune cells and subsequent cytokine-driven edema, while simultaneously stimulating orbital fibroblasts to produce GAGs and differentiate into adipocytes, thereby increasing tissue volume. The schematic correctly identifies the clinical result of these parallel pathways as proptosis, the primary endpoint of the study. This section establishes the problem that the therapeutic intervention is designed to solve. The second panel, "Therapeutic Intervention," acts as the conceptual bridge. It illustrates the mechanism of action of the study's drug, methylprednisolone. The graphic depicts how this powerful glucocorticoid acts as a master regulator, targeting the orbital tissues to block both of the pathological pathways established in the first panel. It specifies the dual action of the drug: its potent anti-inflammatory effects, achieved by suppressing key pro-inflammatory transcription factors like NF-κB, and its anti-remodeling effects, achieved by inhibiting GAG synthesis and adipogenesis. This panel provides the scientific rationale for why the treatment is expected to work. Crucially, it links this mechanism directly to the study's efficacy findings, noting that both the oral and intravenous routes were successful in engaging these molecular targets, leading to the observed significant reduction in proptosis. The third and final panel, "Pharmacokinetics & Clinical Outcome," provides the ultimate synthesis and explains the study's most important and nuanced conclusion. This section is a masterclass in visual explanation. It presents two distinct pharmacokinetic graphs that contrast the drug concentration over time for the two administration routes. The graph for the oral regimen clearly shows a pattern of sustained, continuous systemic exposure, with the area under the curve representing a high total drug burden on the body.[18] In stark contrast, the graph for the intravenous regimen shows a series of sharp, high-amplitude pulses followed by rapid clearance, representing an intermittent exposure with a lower overall systemic burden. This visual distinction in pharmacokinetics is then explicitly linked to the study's two main findings. First, it posits that both routes lead to "Comparable Orbital Efficacy." This is explained by the concept of a "therapeutic plateau," suggesting that both sustained exposure and high-peak pulses are sufficient to saturate the glucocorticoid receptors in the target orbital tissue and produce a near-maximal biological effect, resulting in a statistically indistinguishable reduction in proptosis ($p > 0.05$). Second, and most critically, the figure links the pharmacokinetic profiles to the "Divergent Systemic Tolerability." It clearly states that the sustained systemic exposure of the oral route is the direct cause of the chronic side effects observed in the study (dyspepsia, moon face), while the intermittent nature of the IV pulses allows the body's systems to recover, thus avoiding these toxicities ($p < 0.001$).

Our findings have significant implications for clinical practice, particularly in health systems like Indonesia's where resources, access to care, and patient costs are major considerations. The study does not suggest that oral therapy is equivalent to IV therapy; the vast difference in safety profile unequivocally supports the EUGOGO recommendation of IV therapy as the first-line standard of care.[19] However, the demonstration of comparable real-world effectiveness, combined with the lower cost and greater convenience of oral therapy, forces a more nuanced discussion about resource allocation and personalized medicine. Our data could be used to develop a risk-stratified treatment algorithm. For example, IV therapy should be strongly prioritized for patients with severe inflammatory activity (high CAS), significant comorbidities (diabetes, hypertension), where tight control is needed, or a history of gastrointestinal issues. Conversely, for a carefully selected patient with moderate disease, no significant comorbidities, a full understanding of the risks, and a commitment to monitoring, oral therapy (perhaps with prophylactic gastroprotection) could be considered a viable, cost-effective second-line option, especially if access to infusion services is a significant barrier. This pragmatic approach, informed by local

real-world evidence, allows clinicians to tailor therapy not just to the disease but also to the patient's individual context and the realities of the healthcare system.[20]

This study has several important limitations that must be acknowledged. The primary limitation is the non-randomized design. While we used propensity score analysis to control for observed confounders, the potential for unmeasured confounding variables to influence the results remains. Second, the lack of blinding could have introduced observer bias in proptosis measurement and reporting bias for side effects. Third, the small sample size of 36 patients limits the statistical power of our study and the generalizability of our findings. The lack of a statistically significant difference in efficacy could represent a Type II error, and a larger study might reveal a true difference. Finally, our study was limited to a single primary efficacy outcome (proptosis) and did not include other critical measures such as changes in CAS, diplopia, or patient-reported quality of life, which would have provided a more holistic assessment of the treatment impact.

5. Conclusion

In this pragmatic, prospective cohort study of Indonesian patients with active Graves' Ophthalmopathy, we found that after statistically adjusting for significant baseline differences in disease severity, treatment with oral methylprednisolone resulted in a degree of proptosis reduction that was not statistically different from that achieved with intravenous pulse therapy. This comparable real-world effectiveness, however, was fundamentally overshadowed by the profoundly superior safety and tolerability profile of the intravenous regimen, which was associated with a near-absence of the debilitating side effects that were common with oral therapy. Our findings, therefore, strongly reinforce the continued recommendation of intravenous methylprednisolone as the first-line, standard-of-care treatment for active, moderate-to-severe GO. The evidence unequivocally shows that it provides a much safer therapeutic journey for the patient. However, by providing robust real-world evidence on the effectiveness of oral therapy in a specific clinical context, our study opens the door for a more nuanced, risk-stratified approach to care, particularly in resource-variable settings. For carefully selected and monitored patients for whom IV therapy is not feasible, oral therapy may be considered a viable, effective second-line option, highlighting the critical need for individualized treatment strategies that balance efficacy, safety, and the practical realities of healthcare delivery.

6. References

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