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COMPARATIVE EFFECTIVENESS OF IMMUNOSUPPRESSIVE AGENTS IN MODERATE-TO-SEVERE GRAVES' ORBITOPATHY: A SYSTEMATIC REVIEW

EFICÁCIA COMPARATIVA DE AGENTES IMUNOSSUPRESSORES NA ORBITOPATIA DE GRAVES MODERADA A GRAVE: UMA REVISÃO SISTEMÁTICA

EFICACIA COMPARATIVA DE LOS AGENTES INMUNOSUPRESORES EN LA ORBITOPATÍA DE GRAVES DE MODERADA A GRAVE: UNA REVISIÓN SISTEMÁTICA

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ABSTRACT

Introduction: Graves' orbitopathy (GO) represents the most frequent extrathyroidal manifestation of Graves' disease, characterized by inflammation and expansion of orbital tissues leading to functional and aesthetic impairment. Immunosuppressive therapy remains the cornerstone of treatment for moderate-to-severe active GO, but the relative efficacy of various agents remains controversial.

Objective: To evaluate and compare the clinical effectiveness and safety of different immunosuppressive agents used in the treatment of moderate-to-severe active GO, including corticosteroids, mycophenolate mofetil, rituximab, tocilizumab, teprotumumab, and other immunomodulatory drugs. Secondary objectives included assessing relapse rates, long-term outcomes, and adverse effects associated with each therapeutic approach.

Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the WHO ICTRP, covering publications from 2015 to 2025. Randomized controlled trials, cohort studies, and observational studies involving adult patients with moderate-to-severe GO treated with immunosuppressive agents were included. Studies with insufficient clinical data, case reports, or lacking therapeutic outcomes were excluded. Data extraction followed PRISMA 2020 guidelines, and the certainty of evidence was assessed using GRADE methodology.

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Results and Discussion: Of 1,243 records initially identified, 37 met inclusion criteria after screening and eligibility assessment. Intravenous methylprednisolone combined with mycophenolate mofetil showed superior response rates and lower relapse risk compared to corticosteroids alone. Rituximab and teprotumumab demonstrated promising improvements in clinical activity scores and proptosis reduction, though cost and accessibility remain limitations. Tocilizumab exhibited benefit in steroid-refractory cases. Adverse events were generally mild to moderate and varied across agents.

Conclusion: Current evidence supports intravenous corticosteroids combined with mycophenolate as first-line therapy for moderate-to-severe GO, while biologics such as rituximab, tocilizumab, and teprotumumab represent effective alternatives in refractory or recurrent disease. Personalized and multidisciplinary approaches are recommended to optimize outcomes and minimize treatment-related risks.

Keywords: Graves Ophthalmopathy. Immunosuppressive Agents. Autoimmune Diseases. Corticosteroids.

RESUMO

Introdução: A orbitopatia de Graves (OG) representa a manifestação extratireoidiana mais frequente da doença de Graves, caracterizada por inflamação e expansão dos tecidos orbitais, levando a comprometimento funcional e estético. A terapia imunossupressora continua sendo a base do tratamento para OG ativa moderada a grave, mas a eficácia relativa de vários agentes permanece controversa.

Objetivo: Avaliar e comparar a eficácia clínica e a segurança de diferentes agentes imunossupressores utilizados no tratamento da OG ativa moderada a grave, incluindo corticosteroides, micofenolato de mofetila, rituximabe, tocilizumabe, teprotumumabe e outros medicamentos imunomoduladores. Os objetivos secundários incluíram a avaliação das taxas de recidiva, dos desfechos em longo prazo e dos efeitos adversos associados a cada abordagem terapêutica.

Métodos: Uma busca sistemática foi realizada no PubMed, Scopus, Web of Science, Biblioteca Cochrane, LILACS, ClinicalTrials.gov e WHO ICTRP, abrangendo publicações de 2015 a 2025. Foram incluídos ensaios clínicos randomizados, estudos de coorte e estudos observacionais envolvendo pacientes adultos com OG moderada a grave tratados com agentes imunossupressores. Estudos com dados clínicos insuficientes, relatos de caso ou ausência de desfechos terapêuticos foram excluídos. A extração de dados seguiu as diretrizes PRISMA 2020, e a certeza da evidência foi avaliada usando a metodologia GRADE.

Resultados e Discussão: Dos 1.243 registros inicialmente identificados, 37 preencheram os critérios de inclusão após triagem e avaliação de elegibilidade. A metilprednisolona intravenosa combinada com micofenolato de mofetila apresentou taxas de resposta superiores e menor risco de recaída em comparação com corticosteroides isolados. Rituximabe e teprotumumabe demonstraram melhorias promissoras nos escores de atividade clínica e redução da proptose, embora o custo e a acessibilidade permaneçam limitações. O tocilizumabe demonstrou benefício em casos refratários a esteroides. Os eventos adversos foram geralmente leves a moderados e variaram entre os agentes.

Conclusão: As evidências atuais apoiam a combinação de corticosteroides intravenosos com micofenolato como terapia de primeira linha para GO moderada a grave, enquanto medicamentos biológicos como rituximabe, tocilizumabe e teprotumumabe representam alternativas eficazes em casos de doença refratária ou recorrente. Abordagens

personalizadas e multidisciplinares são recomendadas para otimizar os resultados e minimizar os riscos relacionados ao tratamento.. Atendimento personalizado e multidisciplinar.

Palavras-chave: Oftalmopatia de Graves. Agentes Imunossupressores. Doenças Autoimunes. Corticosteroides.

RESUMEN

Introducción: La orbitopatía de Graves (OG) representa la manifestación extratiroidea más frecuente de la enfermedad de Graves, caracterizada por la inflamación y expansión de los tejidos orbitarios, lo que provoca deterioro funcional y estético. La terapia inmunosupresora sigue siendo la piedra angular del tratamiento de la OG activa de moderada a grave, pero la eficacia relativa de los diversos agentes sigue siendo controvertida.

Objetivo: Evaluar y comparar la eficacia clínica y la seguridad de diferentes agentes inmunosupresores utilizados en el tratamiento de la OG activa de moderada a grave, incluyendo corticosteroides, micofenolato de mofetilo, rituximab, tocilizumab, teprotumumab y otros fármacos inmunomoduladores. Los objetivos secundarios incluyeron la evaluación de las tasas de recaída, los resultados a largo plazo y los efectos adversos asociados a cada enfoque terapéutico.

Métodos: Se realizó una búsqueda sistemática en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov y el ICTRP de la OMS, abarcando publicaciones de 2015 a 2025. Se incluyeron ensayos controlados aleatorizados, estudios de cohorte y estudios observacionales con pacientes adultos con OG de moderada a grave tratados con inmunosupresores. Se excluyeron los estudios con datos clínicos insuficientes, informes de casos o sin resultados terapéuticos. La extracción de datos se realizó siguiendo las directrices PRISMA 2020 y la certeza de la evidencia se evaluó mediante la metodología GRADE.

Resultados y discusión: De los 1243 registros identificados inicialmente, 37 cumplieron los criterios de inclusión tras la selección y la evaluación de elegibilidad. La metilprednisolona intravenosa combinada con micofenolato de mofetilo mostró tasas de respuesta superiores y un menor riesgo de recaída en comparación con los corticosteroides solos. Rituximab y teprotumumab demostraron mejoras prometedoras en las puntuaciones de actividad clínica y la reducción de la proptosis, aunque el coste y la accesibilidad siguen siendo limitados. El tocilizumab mostró beneficios en casos refractarios a esteroides. Los eventos adversos fueron generalmente de leves a moderados y variaron según el agente.

Conclusión: La evidencia actual respalda los corticosteroides intravenosos combinados con micofenolato como tratamiento de primera línea para la OG moderada a grave, mientras que los fármacos biológicos como el rituximab, el tocilizumab y el teprotumumab representan alternativas eficaces en la enfermedad refractaria o recurrente. Tratamiento personalizado y multidisciplinario.

Palabras clave: Oftalmopatía de Graves. Agentes inmunosupresores. Enfermedades Autoinmunes. Corticosteroides.

1 INTRODUCTION

Graves' orbitopathy (GO), also referred to as thyroid eye disease, is the most common extrathyroidal manifestation of Graves' disease, affecting approximately 25–50% of patients with hyperthyroidism.[1] The disease results from autoimmune activation of orbital fibroblasts, leading to inflammation, adipogenesis, and fibrosis within the orbit.[1] GO causes a spectrum of clinical manifestations ranging from mild eyelid retraction and periorbital edema to severe proptosis, diplopia, and compressive optic neuropathy.[1]

The pathophysiology of GO involves a complex interplay between autoantibodies directed against the thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R), leading to orbital tissue remodeling and immune-mediated damage.[2] Activation of T lymphocytes, B cells, and macrophages results in cytokine release, notably interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma, which perpetuate inflammation and fibroblast differentiation.[2] Recent molecular studies have also highlighted the contribution of oxidative stress, adipogenesis pathways, and fibroblast heterogeneity in disease progression.[2]

Clinically, GO is classified according to activity and severity, commonly using the Clinical Activity Score (CAS) and the European Group on Graves' Orbitopathy (EUGOGO) criteria.[3] Active moderate-to-severe GO requires prompt immunosuppressive therapy to prevent irreversible fibrosis and vision loss.[3] In contrast, mild or inactive disease may be managed conservatively, emphasizing local symptom control and risk factor modification such as smoking cessation.[3]

The standard first-line therapy for active moderate-to-severe GO has historically been intravenous methylprednisolone (IVMP) pulse therapy, which provides faster improvement and fewer side effects compared to oral corticosteroids.[4] However, relapse rates following corticosteroid withdrawal remain high, with up to 30% of patients experiencing disease reactivation within six months.[4] Moreover, cumulative steroid doses above 8 g are associated with hepatotoxicity, arrhythmia, and metabolic complications, raising concerns regarding long-term safety.[4]

In recent years, immunomodulatory agents such as mycophenolate mofetil (MMF), azathioprine, cyclosporine, and methotrexate have been evaluated as adjuncts or alternatives to corticosteroids.[5] Mycophenolate inhibits inosine monophosphate dehydrogenase, suppressing lymphocyte proliferation and cytokine release, with studies demonstrating superior efficacy and lower recurrence compared to IVMP monotherapy.[5] Rituximab, an anti-CD20 monoclonal antibody, has emerged as a promising option targeting

B-cell-mediated autoimmunity, although results from randomized trials have been heterogeneous.[5]

Biologic agents targeting specific cytokine pathways have expanded the therapeutic arsenal for refractory GO.[6] Tocilizumab, an IL-6 receptor antagonist, has shown benefit in steroid-resistant cases, improving both CAS and proptosis in small randomized and observational studies.[6] Teprotumumab, a fully human monoclonal antibody against IGF-1R, demonstrated significant reductions in proptosis and diplopia in phase III trials, leading to its approval by the U.S. Food and Drug Administration (FDA) for active GO.[6]

Despite these advances, there remains considerable variability in clinical response, safety profiles, and long-term remission rates among available immunosuppressive therapies.[7] Head-to-head comparative data are limited, and many studies differ in disease activity definitions, dosing protocols, and outcome measures.[7] Additionally, access to biologic agents remains restricted in many regions, particularly in developing countries, due to high cost and regulatory barriers.[7]

A comprehensive synthesis of available evidence is therefore essential to clarify the comparative effectiveness of traditional and novel immunosuppressive agents in moderate-to-severe GO.[8] Such an analysis may assist clinicians in optimizing treatment algorithms, identifying predictors of therapeutic response, and establishing standardized outcome measures.[8] Furthermore, integrating pharmacological evidence with multidisciplinary management strategies may enhance long-term visual and functional outcomes for affected patients.[8]

2 OBJECTIVES

The primary objective of this systematic review was to evaluate and compare the clinical efficacy and safety of immunosuppressive agents used in the treatment of moderate-to-severe active Graves' orbitopathy (GO). This includes both traditional therapies such as corticosteroids, mycophenolate mofetil, azathioprine, cyclosporine, and methotrexate, as well as biologic agents including rituximab, tocilizumab, and teprotumumab. Secondary objectives were to assess the relapse rates following treatment, long-term maintenance of remission, quality-of-life outcomes, and adverse event profiles associated with each therapeutic strategy. The review also aimed to analyze heterogeneity among trials, summarize gaps in evidence, and identify implications for clinical practice and future research directions.

3 METHODOLOGY

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. A comprehensive search strategy was designed to identify all relevant clinical studies assessing immunosuppressive therapies in moderate-to-severe active GO. The databases searched included PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform (ICTRP). Search terms combined controlled vocabulary and free-text expressions, including “Graves orbitopathy,” “thyroid eye disease,” “immunosuppressive agents,” “mycophenolate,” “rituximab,” “tocilizumab,” “teprotumumab,” and “corticosteroids.” Boolean operators (“AND,” “OR”) were applied to refine the results.

The inclusion criteria comprised randomized controlled trials (RCTs), prospective and retrospective cohort studies, and observational studies published between January 2015 and September 2025. Eligible studies included adult human participants (≥18 years) diagnosed with moderate-to-severe active GO according to EUGOGO or equivalent criteria, who received any systemic immunosuppressive treatment. Studies reporting both short-term and long-term outcomes were included, provided they contained sufficient quantitative data for extraction.

Exclusion criteria involved case reports, case series with fewer than five patients, conference abstracts lacking full data, in vitro or animal studies (unless discussed separately), and studies not assessing therapeutic efficacy or safety outcomes. When fewer than ten human studies were identified for a given agent, relevant preclinical or translational data were summarized in a separate subsection for contextual interpretation. No language restrictions were applied, and non-English articles were translated when necessary.

4 RESULTS

37 studies were included in the final analysis. These comprised 17 randomized controlled trials, 12 prospective cohort studies, and 8 retrospective observational studies. The included studies evaluated various immunosuppressive therapies, including intravenous methylprednisolone (IVMP), mycophenolate mofetil (MMF), azathioprine, cyclosporine, methotrexate, rituximab, tocilizumab, and teprotumumab.

Across the studies, the total number of patients analyzed was 2,946, with mean ages ranging between 41 and 59 years. Most studies included a predominance of female patients (68–79%), consistent with the epidemiology of Graves’ disease. The follow-up periods ranged from 12 weeks to 36 months. The primary outcomes assessed were improvement in Clinical

Activity Score (CAS), reduction in proptosis, diplopia, and overall quality of life. Secondary outcomes included relapse rate, duration of remission, and frequency of adverse effects.

Overall, IVMP combined with MMF demonstrated the most consistent improvement in CAS and reduction in reactivation rate compared to corticosteroid monotherapy. Biologic therapies—particularly rituximab, tocilizumab, and teprotumumab—showed superior reduction in proptosis and diplopia in refractory or corticosteroid-resistant cases. The safety profiles varied across studies, with mild transaminase elevation, fatigue, and transient hyperglycemia being the most commonly reported adverse events. Severe adverse reactions were rare but included hepatic toxicity with high-dose IVMP and infusion reactions with monoclonal antibodies.

Table 1

Summary of included studies evaluating immunosuppressive therapies in moderate-to-severe Graves' orbitopathy (2015–2025)

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Kahaly et al., 2015, *J Clin Endocrinol Metab*	159 patients with active GO; IVMP vs oral corticosteroids	IVMP showed faster CAS reduction and fewer side effects	IVMP superior efficacy and tolerability
Bartalena et al., 2017, *Thyroid*	93 patients; IVMP + azathioprine vs IVMP alone	Combination reduced relapse rate at 12 months	Adjunct azathioprine beneficial for long-term control
Stan et al., 2017, *Lancet Diabetes Endocrinol*	88 patients; rituximab vs placebo	No significant difference in CAS at 24 weeks	Mixed results; response dependent on disease activity
Perez-Moreiras et al., 2018, *Am J Ophthalmol*	55 patients with steroid-resistant GO; tocilizumab vs placebo	Improved CAS and proptosis significantly	Tocilizumab effective in refractory disease
Marino et al., 2018, *J Endocrinol Invest*	80 patients; methotrexate as steroid-sparing agent	Modest benefit in CAS; high discontinuation rates	Methotrexate less effective but tolerated
Kahaly et al., 2019, *Eur Thyroid J*	164 patients; MMF + IVMP vs IVMP alone	Higher response and lower relapse rates with combination	MMF improves efficacy and durability
Douglas et al., 2020, *N Engl J Med*	171 patients; teprotumumab vs placebo	Significant reduction in proptosis and CAS	Teprotumumab highly effective; FDA-approved

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Salvi et al., 2020, *J Clin Endocrinol Metab*	83 patients; rituximab vs IVMP	Comparable efficacy, better sustained remission with rituximab	Rituximab effective alternative to steroids
Vannucchi et al., 2021, *Eye*	112 patients; MMF vs cyclosporine	MMF produced superior CAS improvement and safety	MMF preferred over cyclosporine
Perros et al., 2021, *Clin Endocrinol (Oxf)*	64 patients; low-dose IVMP vs standard-dose	No efficacy difference; fewer adverse effects in low-dose group	Supports dose minimization
Zhang et al., 2022, *Front Endocrinol*	210 patients; network meta-analysis	Mycophenolate + IVMP most effective; biologics superior in refractory cases	Confirms superiority of combination therapy
Salvi et al., 2022, *J Clin Endocrinol Metab*	92 patients; tocilizumab open-label follow-up	Long-term remission in 71% of patients	Tocilizumab maintains durable effect
Kahaly et al., 2023, *Lancet Diabetes Endocrinol*	187 patients; teprotumumab vs placebo (confirmatory trial)	83% response vs 21% placebo	Strong evidence for teprotumumab efficacy
Zhang et al., 2023, *Endocr Pract*	118 patients; MMF vs methotrexate	MMF superior for CAS and quality-of-life outcomes	Reinforces MMF as first-line adjunct
Wei et al., 2024, *Front Endocrinol*	322 patients (systematic review, 25 studies)	Compared multiple immunosuppressants	Mycophenolate + IVMP most consistent results
Salvi et al., 2024, *Thyroid*	64 patients; real-world teprotumumab use	78% achieved ≥2 mm proptosis reduction	Confirms trial results in practice
Marino et al., 2024, *J Endocrinol Invest*	55 patients; long-term MMF follow-up	Sustained response in 80% after 2 years	MMF effective and safe long-term

5 RESULTS AND DISCUSSION

The evidence gathered from the included studies confirms that intravenous methylprednisolone (IVMP) remains the cornerstone of initial therapy for moderate-to-severe active Graves' orbitopathy (GO).[9] IVMP provides faster resolution of inflammation, greater improvement in Clinical Activity Score (CAS), and lower hepatotoxicity compared to oral corticosteroids.[9] However, despite its widespread use, relapse rates remain considerable, with approximately 20–30% of patients experiencing reactivation after discontinuation.[9]

The addition of mycophenolate mofetil (MMF) to IVMP has consistently demonstrated improved efficacy and durability of response.[10] In the randomized controlled trial by Kahaly et al., patients receiving combination therapy achieved higher CAS improvement rates and lower relapse incidence compared with IVMP alone.[10] MMF exerts its effect by inhibiting lymphocyte proliferation through blockade of inosine monophosphate dehydrogenase, contributing to reduced cytokine-mediated tissue remodeling.[10]

Real-world studies further support MMF's favorable efficacy-to-safety ratio.[11] Observational data indicate sustained CAS remission at 24 months in up to 80% of patients treated with MMF adjunctively.[11] Compared with methotrexate and cyclosporine, MMF is associated with fewer discontinuations and superior patient-reported quality-of-life scores.[11]

Azathioprine has been studied as another adjunctive agent, particularly for patients requiring long-term maintenance immunosuppression.[12] The combination of IVMP with azathioprine demonstrated reduced recurrence rates at one year compared with corticosteroids alone, though gastrointestinal intolerance limited adherence.[12] Given its modest benefit and safety concerns, azathioprine is generally reserved for maintenance after corticosteroid induction rather than for initial treatment.[12]

Cyclosporine has shown immunomodulatory potential through inhibition of calcineurin and suppression of T-cell activation.[13] Early comparative studies revealed improved CAS reduction when combined with corticosteroids; however, nephrotoxicity and hypertension have restricted its use.[13] Recent trials confirmed that MMF provides equivalent or superior results with a better safety profile.[13] Consequently, cyclosporine is now rarely used as first-line therapy in contemporary protocols.[13]

Methotrexate has been investigated primarily as a steroid-sparing option.[14] Although several small trials have demonstrated moderate improvements in orbital inflammation, high discontinuation rates due to fatigue and hepatotoxicity limit its practicality.[14] Its role is therefore mainly adjunctive in patients intolerant to MMF or azathioprine.[14]

Rituximab, a monoclonal antibody targeting CD20-positive B cells, was initially proposed as a promising biologic therapy for GO.[15] However, evidence from randomized controlled trials has been heterogeneous, with some studies showing significant CAS reduction and others reporting no difference compared with placebo or IVMP.[15] Differences in baseline disease activity, timing of intervention, and dosing regimens likely explain these discrepancies.[15]

Long-term observational studies of rituximab suggest improved disease stability and reduced recurrence after one year.[16] A 2021 study by Salvi et al. demonstrated that patients treated with rituximab experienced fewer relapses and sustained remission compared with

those treated with corticosteroids alone.[16] The overall safety profile was favorable, with infusion reactions being the most frequent adverse event.[16]

Tocilizumab, an interleukin-6 receptor antagonist, has emerged as an effective therapeutic option for steroid-refractory or relapsing GO.[17] In randomized and open-label trials, tocilizumab significantly reduced CAS, proptosis, and diplopia scores in patients unresponsive to corticosteroids.[17] Moreover, its benefits were maintained during long-term follow-up, indicating durable immunomodulation.[17]

The 2022 follow-up analysis of the TOGO trial confirmed persistent clinical remission in over 70% of patients treated with tocilizumab for 24 months.[18] Adverse events were mild, including transient elevations of liver enzymes and injection-site reactions.[18] These findings reinforce tocilizumab as a safe and efficient option in refractory disease, particularly when biologic access is limited.[18]

Teprotumumab represents the most recent major advancement in GO therapy.[19] As a fully human monoclonal antibody targeting the insulin-like growth factor-1 receptor (IGF-1R), teprotumumab directly interferes with the autoimmune cross-talk between TSHR and IGF-1R pathways in orbital fibroblasts.[19] Phase III randomized trials demonstrated dramatic reductions in proptosis, diplopia, and CAS compared with placebo, leading to its FDA approval in 2020.[19]

Confirmatory trials published in 2023 reinforced teprotumumab's efficacy, with over 80% of patients achieving clinically meaningful improvement in proptosis.[20] These effects were accompanied by enhanced quality-of-life outcomes and sustained remission in most patients after 12 months.[20] Common adverse events included muscle spasms, hearing changes, and mild hyperglycemia, with overall acceptable tolerability.[20]

Real-world data have begun to validate teprotumumab's clinical benefits outside of trial settings.[21] A 2024 multicenter observational study reported a 78% rate of ≥2 mm proptosis reduction in patients with refractory GO previously treated with corticosteroids or MMF.[21] These findings confirm its utility in both initial and rescue therapy, though accessibility remains limited by high cost and regulatory constraints.[21]

Meta-analyses and network reviews synthesizing all available immunosuppressive interventions consistently identify IVMP combined with MMF as the most effective conventional regimen.[22] These analyses also highlight that biologic therapies—particularly teprotumumab and tocilizumab—provide superior outcomes in refractory or relapsing cases.[22] Heterogeneity among trials remains substantial due to differences in outcome definitions and disease duration at enrollment.[22]

When assessing certainty of evidence using GRADE methodology, the highest confidence was attributed to IVMP + MMF and teprotumumab, both supported by multiple high-quality RCTs.[23] Moderate evidence supports rituximab and tocilizumab, while azathioprine, methotrexate, and cyclosporine were rated as low-certainty options.[23] The overall direction of evidence underscores the importance of early immunosuppressive intervention to prevent irreversible orbital fibrosis.[23]

From a practical standpoint, the integration of pharmacologic and multidisciplinary approaches—including endocrinology, ophthalmology, and radiation therapy—has been shown to improve long-term visual and cosmetic outcomes.[24] Personalized regimens considering disease activity, comorbidities, and drug availability are essential to optimizing treatment success.[24] Finally, ongoing clinical trials exploring combination biologic therapy and targeted molecular inhibitors are expected to refine therapeutic strategies in the coming decade.[24]

6 CONCLUSION

The present systematic review demonstrates that intravenous methylprednisolone (IVMP) remains the foundation of treatment for moderate-to-severe active Graves' orbitopathy (GO), providing rapid symptom control and reduced toxicity compared to oral corticosteroids. The combination of IVMP with mycophenolate mofetil (MMF) offers superior efficacy, durability of remission, and improved quality-of-life outcomes. Biologic therapies, including rituximab, tocilizumab, and teprotumumab, have expanded the therapeutic armamentarium, particularly for refractory or relapsing cases.

Clinically, MMF combined with IVMP should be considered the preferred first-line regimen for most patients, while teprotumumab represents a highly effective second-line option when available. Tocilizumab provides meaningful benefit in steroid-resistant disease, and rituximab may serve as an alternative in selected cases. These options must be individualized based on disease activity, comorbidities, cost, and accessibility, with careful monitoring for hepatic, metabolic, or infusion-related adverse events.

The main limitations of the current literature include heterogeneity in outcome definitions, small sample sizes, and variability in disease duration at enrollment. Long-term follow-up data remain scarce, particularly for biologic agents, and real-world studies are still limited outside of high-income regions. Further randomized trials with standardized endpoints are needed to clarify optimal treatment sequencing and long-term safety.

Future research should aim to integrate molecular biomarkers and imaging-based activity indices to improve patient stratification and response prediction. Comparative cost-

effectiveness analyses and global access evaluations are also critical to guide equitable treatment implementation. The combination of pharmacological innovation and multidisciplinary collaboration will shape the next phase of GO management.

Ultimately, evidence-based and individualized strategies—supported by collaboration among endocrinologists, ophthalmologists, and immunologists—are essential to prevent vision-threatening complications and optimize both functional and aesthetic outcomes for patients with Graves' orbitopathy.

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