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Steroid therapy for Graves ophthalmopathy

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ABSTRACT

Graves' disease (GD) is a prevalent autoimmune disorder primarily affecting the thyroid gland, but it also impacts other organs, notably the eyes. Graves' ophthalmopathy (GO), an autoimmune condition associated with GD, affects the tissues behind the eyes, leading to inflammation and tissue remodeling. Risk factors for GO include radioactive iodine therapy, untreated hyperthyroidism, smoking and high serum TSH-receptor antibody levels. Management strategies involve various approaches, including pharmacological treatments such as glucocorticoids. High-dose systemic glucocorticoids are particularly effective in treating moderate to severe and active GO. This review was undertaken to consolidate current evidence on steroid therapy for GO, exploring the nuances of different administration routes, dosages and the potential need for second-line treatments. By providing a comprehensive analysis of the existing literature, this review aims to enhance clinicians' understanding of steroid therapy in GO, highlight gaps in current knowledge, and propose areas for future research.

INTRODUCTION

Graves' disease (GD) is an autoimmune condition that primarily affects the thyroid gland but can also impact other organs, including the eyes and skin. It accounts for 60% to 80% of all cases of hyperthyroidism. In the United States, the prevalence of hyperthyroidism is 1.2%, with a frequency ranging between 20 and 50 cases per 100,000 individuals [1,2]. Typically, it presents in individuals aged 20 to 50, with women exhibiting a higher prevalence compared to men. Other common factors include toxic multinodular goiter, functioning thyroid adenoma and subacute destructive thyroiditis, which may be caused by viral infection, autoimmune disease or pharmaceutical substances [3,4].

Graves' ophthalmopathy, also known as 'Graves' eye disease or 'Graves' orbitopathy, refers to the signs and symptoms affecting the eyes and adjacent tissues in individuals diagnosed with Graves' disease. It can occasionally occur in patients with normal or even low thyroid function due to chronic thyroid inflammation. Graves' ophthalmopathy (GO) is an autoimmune condition specifically affecting the tissues behind the eyes. It is a rare disorder, occurring in 2.9 to 16.0 cases per 10,000 individuals annually [5,6].

The presence of thyrotropin receptor (TSHR) autoantigens on adipocytes and fibroblasts in the orbit leads to the activation of T cells, initiating an immune response. This immune response results in inflammation, tissue remodeling and the accumulation of hydrophilic glycosaminoglycans (GAGs) in the connective tissue and muscles behind the eyes. In addition to T cell activation, autoantibodies against TSHR, known as 'thyroid-stimulating immunoglobulins' (TSIs), also play a role in Graves' ophthalmopathy (GO). These autoantibodies bind to TSHR on orbital tissues, leading to stimulation of these tissues and exacerbating inflammation and tissue damage [7,8]. Most patients experience eye disease within 18 months of being diagnosed with Graves' disease; however, ophthalmopathy can also manifest within a time frame of 10 to 20 years following the initial onset of thyroid disease [9,10].

Recent studies have reported an increase in Th17 cells, a subset of CD4 helper lymphocytes, in patients with Graves' ophthalmopathy. Notably, the levels of IL-17A in the peripheral blood of patients with Graves' ophthalmopathy were

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higher than those in the control group [11,12]. Fang et al. identified a potential link between IL-17 and orbital fibroblasts (OFs). IL-17 was found to stimulate the expression of pro-inflammatory cytokines, including IL-6, IL-8, MCP-1, TNF-α and GM-CSF, as well as co-stimulatory molecules such as CD40 and MHC II on OFs, thereby influencing fibrosis and adipogenesis [11]. In related work, immunohistochemical analysis of orbital tissues showed increased expression of IL-17A, along with cytokines such as TGF-β, IL-6, IL-1β, and IL-23A, which are involved in promoting the differentiation of naïve CD4 lymphocytes into Th17 cells. IL-17A contributes to inflammation and fibrosis in Graves' ophthalmopathy patients by affecting orbital fibroblasts (OFs). Additionally, in conjunction with CD40L, it enhances the expression and secretion of Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES) by OFs [13,14].

Risk factors associated with Graves' ophthalmopathy (GO) include receiving radioactive iodine (RAI) therapy for hyperthyroidism, having untreated hyperthyroidism, smoking, high serum TSH-receptor antibody (TRAb) levels before therapy (with a normal level being <1.75 IU/L and a high risk of progression if >8.8 IU/L) and experiencing a delay in treating hypothyroidism after hyperthyroidism therapy [15]. GO can present in either an active or an inactive phase. During the active phase, which occurs over a period of 6-24 months, there is a progressive course of GO due to an autoimmune process. This stage is characterized by the infiltration of lymphocytes into the affected area, leading to the release of inflammatory cytokines and the proliferation of fibroblasts. This results in the enlargement of the orbital muscles, conjunctival injection and chemosis, ocular pain, and swelling of the tissues around the eyes and eyelids [16].

During the active phase of Graves' ophthalmopathy (GO), patients often experience symptoms such as orbital pain, redness and swelling. This phase is characterized by inflammation and the sudden onset of these symptoms. Common clinical features include proptosis, periorbital edema and conjunctival redness. Patients may also report a gritty sensation in the eyes, increased tearing, and sensitivity to light (photophobia). Dry eye disease (DED) is particularly prevalent among those with GO, with distinct and complex underlying causes [17,18]. In patients with GO, incomplete blinking and significant loss of Meibomian gland structure in the eyelids are more pronounced compared to typical cases of DED. Initially, DED in GO results from orbital inflammation, while exposure-related issues contribute to its persistence as the condition progresses [19,20].

Occult Graves' ophthalmopathy (GO) should be considered in the differential diagnosis of dry eye, as it can present with symptoms such as increased corneal fluorescein staining, a rapid tear break-up time and abnormal Schirmer test results. GO can lead to inflammatory ocular surface disease, which exacerbates dry eye symptoms. Although the exact mechanisms linking GO to dry eye disease (DED) are not fully understood, it is believed that multiple factors may interact synergistically. These factors include tear film dysfunction due to increased evaporation and/or ocular inflammation, abnormal stimulation of the lacrimal glands resulting in reduced tear production and potentially other unidentified mechanisms [21,22]. Effective treatment for dry eye disease (DED) in patients with Graves' ophthalmopathy (GO) should focus on both relieving symptoms and addressing the underlying inflammation. This approach involves using lubricants to alleviate dryness and anti-inflammatory therapies to target the root causes of the condition [23].

Accurately differentiating Graves' ophthalmopathy (GO) from other conditions with similar ocular symptoms, such as dry eye syndrome, conjunctivitis and orbital cellulitis, is crucial due to their overlapping features. Idiopathic orbital inflammation, myasthenia gravis, and orbital tumors can also present with symptoms like proptosis and diplopia, which are characteristic of GO. To properly assess the severity and activity of GO, a comprehensive clinical evaluation is necessary. This includes taking a detailed patient history, performing a thorough ophthalmic examination, and conducting imaging studies such as orbital CT or MRI. The Clinical Activity Score (CAS) is essential for quantifying disease activity and guiding treatment decisions [24]. After inflammation subsides, the subsequent stage is the inactive phase, marked by fibrosis of the orbital tissues, which may persist for over a year. Reactivation of GO more than 5 years after the inactive phase is rare, occurring in only 5% of all cases [25,26].

The management strategies for Graves' ophthalmopathy (GO) encompass a range of approaches, including non-pharmacological interventions, pharmacological treatments, rehabilitative surgery and radiation therapy. The choice of strategy depends on the clinical activity and severity of the condition [27]. Successful treatment requires achieving euthyroidism, and it is advisable to avoid using radioiodine therapy in cases of active progressive GO. During the active progressive phase of the disease, anti-inflammatory therapy is recommended. However, rehabilitative surgery should only be considered during the stable inactive phase, when persistent sequelae are present [24,28]. This review focuses on the effectiveness of glucocorticoids in treating moderate to severe and active GO, with particular emphasis on steroid therapy.

MANAGEMENT OF GRAVES' OPHTHALPMOPATHY

Recent meta-analyses and meta-regression studies have confirmed a decline in the frequency and intensity of Graves' ophthalmopathy (GO) in patients with Graves' disease (GD) over the past three decades. This trend is multifactorial, including factors such as reduced smoking habits, early detection and improved management of thyroid dysfunction. Moreover, enhanced collaboration between endocrinologists and ophthalmologists has led to prompt identification and management of medical conditions.

Mild-grade GO may progress to severe GO, necessitating professional consultation and direction to develop a comprehensive management strategy. Therefore, it is essential to refer patients diagnosed with confirmed GO and those at risk of GO deterioration – such as those with mild and active GO, smokers, high serum TSH receptor antibody (TSHR-Ab) levels and severe/unstable hyperthyroidism – to a specialized Thyroid Eye Clinic. This clinic offers comprehensive endocrine and ophthalmic services, ensuring precise

and prompt diagnosis to enhance the patient's prognosis and quality of life [29,30]

The categorization of treatment decisions for Graves' ophthalmopathy (GO) is based on a clinical assessment of disease activity, severity and duration. It is important to note that the effectiveness of anti-inflammatory or immunosuppressive treatments diminishes significantly after 18 months from the onset of the disease. Hiromatsu et al., notably, established a clear relationship between the timing of treatment and the severity and activity of GO [31]. Initiating immunosuppressive treatment during the active stage of GO can effectively reduce the intensity and severity of the disease, whereas administering immunosuppressive therapy during the inactive phase yields unsatisfactory outcomes [32].

STEROID THERAPY FOR GRAVES' OPHTHALMOPATHY

The selection of pharmacological treatment, restorative surgery and radiation therapy is determined by the clinical activity and severity of the condition. Glucocorticoids represent the primary pharmacological treatment option for patients with clinically active Graves' ophthalmopathy (GO). They can be administered orally, topically or intravenously [33]. Local administration through subconjunctival or retrobulbar injection is not advisable due to associated risks and unproven effectiveness. Intravenous administration of glucocorticoids has shown superior response and enhanced clinical efficacy compared to oral administration. Contraindications for using methylprednisolone as part of GO therapy include: (1) recent history of viral hepatitis infection, (2) severe cardiovascular morbidity, (3) significant liver dysfunction, (4) uncontrolled diabetes, (5) uncontrolled hypertension, and (6) psychiatric disorders [34,35].

High-dose systemic glucocorticoids possess strong anti-inflammatory and immunosuppressive properties, making them significantly effective in treating moderate to severe and active-phase Graves' ophthalmopathy (GO). Intravenous glucocorticoids are the preferred initial treatment for moderate and active GO. Indeed, a proof-of-concept randomized trial demonstrated a substantial improvement in GO outcomes among patients who received intravenous methylprednisolone compared to those who received a placebo, with a response rate of 83% versus 11% [36,37]. Although oral glucocorticoids are effective, intravenous glucocorticoids are preferred due to their demonstrated superiority in randomized trials, with success rates ranging from 77% to 88% compared to 51% to 63% for oral administration. Additionally, intravenous glucocorticoids are better tolerated by patients [38].

A commonly used protocol, employed as the first-line treatment option, involves administering a total dose of 4.5 grams of methylprednisolone weekly, divided into 12 infusions. This treatment regimen consists of six infusions, each containing 0.5 grams of the medication, followed by six infusions, each containing 0.25 grams. This protocol has been highly tolerable and has resulted in significant improvements in the quality of life for individuals [39,40].

The administration of glucocorticoids should be conducted gradually, over 1-2 hours, while closely monitoring the patient. Before initiating treatment, it is essential to exclude the presence of an infectious condition by examining the white blood cell count. Additionally, it is important to evaluate cardiovascular risk, liver enzymes and viral hepatitis markers to identify any potential risks or contraindications. Furthermore, liver enzymes should be monitored closely throughout the course of treatment [41,42].

The adverse effects of high doses of oral glucocorticoids include the development of cataracts, peptic ulcers, long-term suppression of adrenal function, Cushing's syndrome, diabetes, hypertension, reactivation of chronic diseases (such as tuberculosis), infections, osteoporosis and psychosis. If intravenous administration of glucocorticoids is not feasible, oral prednisone can be administered for a duration of 12 weeks. The initial daily dose should be 0.2 grams, which should then be gradually reduced to a weekly dose of 0.01 grams, resulting in a total cumulative dose of 4 grams [38,43].

According to the 2016 ETA/EUGOGO (European Thyroid Association/European Group on Graves' Orbitopathy) guidelines for GO, if initial treatment with corticosteroids does not lead to improvement within 3-4 weeks or if there are concerns about liver enzyme levels (which can be affected by corticosteroid therapy), it is recommended to consider initiating second-line therapy. This therapy involves using intravenous methylprednisolone monotherapy with a higher cumulative dose of 7.5 grams. The treatment starts with a single dose of 0.75 grams and continues for 6 weeks. This second-line therapy is widely recognized and accepted. A maximum cumulative dose of 8 grams of methylprednisolone per cycle is permitted but should be administered with caution. An alternative option that has been proposed is the use of a combination of oral prednisone/prednisolone and cyclosporine, which has shown favorable results in two randomized trials. Furthermore, azathioprine may be employed alongside oral glucocorticoids due to its steroid-sparing effect, as demonstrated in a randomized trial [44,45].

According to safety data, it is advised to limit the intravenous dose to a maximum of 0.75 grams per infusion and the total dose to less than 8.0 grams per cycle. It is also recommended to avoid consecutive daily therapy due to the higher likelihood of experiencing side effects caused by glucocorticoids, such as liver toxicity and severe cardiovascular effects. However, it is important to note that these recommendations do not apply in cases where there is a risk of vision loss [46,47].

Glucocorticoids have emerged as the preferred immunosuppressive agents for moderate and active GO due to their potent anti-inflammatory properties and their ability to suppress the immune system when administered in high doses. Studies conducted under laboratory conditions demonstrate that glucocorticoids reduce the production and release of glycosaminoglycans by orbital fibroblasts. Additionally, they suppress the activity of various adhesion molecules, inhibit the secretion of cytokines and antibodies, impair the functioning of T and B lymphocytes. What is more, glucocorticoids decrease the recruitment of neutrophils and macrophages to the site of inflammation [48,49].

Access to specialized centers for intravenous glucocorticoid therapy may be limited in certain regions, which contributes to the continued preference for oral administration methods. This is evident in the widespread use of oral glucocorticoids alone or as a follow-up to initial therapy with multiple infusions, aimed at reducing hospitalization rates. When administering oral glucocorticoids, adherence to dosing protocols established by multiple randomized trials is recommended. Complementary treatments, such as orbital radiotherapy or non-steroidal immunosuppressive drugs like mycophenolate or cyclosporine, used in conjunction with oral glucocorticoids, offer potential avenues to reduce steroid dependence and enhance treatment efficacy [38,50].

Glucocorticoid treatment is contraindicated in cases of active viral hepatitis infection, significant liver impairment, severe cardiovascular conditions or mental disorders. However, it may be initiated if diabetes and hypertension are well controlled. Bone protective therapy is recommended, and proton pump inhibitors should be used as appropriate. The effects of intravenous glucocorticoids typically manifest quickly, although onset may be delayed until the middle or later stages of treatment. Individuals with suboptimal responses to intravenous glucocorticoids should complete a 12-week treatment regimen. Conversely, a partial or absent response, rather than a reduction in ocular clinical signs and symptoms, indicates the need for second-line treatment [34,50].

In a clinical trial, participants were randomly assigned to receive either triamcinolone acetate or a placebo via orbital injection. The injection was administered into the inferolateral quadrant of the eye. The triamcinolone acetate group received a weekly dose of 40 mg for a total of four injections. The results showed that this treatment reduced diplopia (double vision) and the size of the extraocular muscles. Additionally, a limited randomized trial indicated that administering triamcinolone via subconjunctival injections in the upper eyelid, with a dosage of 20 mg and 1-3 injections, was successful in treating patients with short-term upper eyelid retraction caused by Graves' ophthalmopathy (GO). However, local administration of glucocorticoids poses a notable risk of elevated intraocular pressure, which is associated with increased fat accumulation around the eye socket. There is also a slight but notable risk of bleeding behind the eye, particularly in patients taking antiplatelet medications. Therefore, topical glucocorticoids can serve as a substitute for systemic glucocorticoid administration in patients with contraindications [51,52].

The effectiveness of treatment is strongly influenced by individual variation, which can lead to treatment ineffectiveness or adverse drug reactions. Historically, glucocorticoids were administered locally through routes such as subconjunctival or peribulbar injections. However, this approach is now less common due to safety and efficacy concerns. Specifically, the administration of triamcinolone via local injection is associated with various complications, including a permanent increase in intraocular pressure, puncture of the eyeball, melting of the conjunctiva or corneoscleral tissue, blockage or compression of the optic nerve due to vascular pressure, loss of fat tissue, loss of pigmentation and the formation of granulomas [53,54].

Sirolimus has demonstrated significant benefits as a second-line treatment for moderate-to-severe, active Graves' ophtalmopathy (GO), outperforming methylprednisolone in several key areas. In one study, patients receiving sirolimus (2 mg orally on the first day, followed by 0.5 mg/day for 12 weeks) had a markedly higher response rate at 24 weeks compared to those treated with methylprednisolone (86.6% vs. 26.6%). Additionally, the sirolimus group showed greater improvements in quality of life, proptosis, Clinical Activity Score (CAS) and eye movements. No serious adverse events were reported, suggesting that sirolimus is a viable and effective alternative to methylprednisolone for managing GO [55]. Two cases of patients with Graves' ophthalmopathy (GO) resistant to glucocorticoids were also reported, both showing apparent beneficial effects from sirolimus treatment. These cases indicate that sirolimus may be a viable option for managing GO in clinical practice [56].

Sirolimus inhibits T-cell activation by blocking both calcium-dependent and calcium-independent signaling pathways. Additionally, it binds to the FKBP12 protein, forming a complex that inhibits mTORC1. This inhibition impacts CD4+ and CD8+ T cells, which are involved in Graves' ophthalmopathy (GO), as well as adipogenesis [57,58]. In vitro studies have demonstrated that sirolimus-mediated inhibition of mTORC1 blocks adipogenesis in preadipocytes and fibroblasts from patients with Graves' ophthalmopathy (GO). Additionally, by targeting the FRAP/mTOR signaling pathway, sirolimus reduces IL-16 synthesis in orbital fibroblasts, which is stimulated by circulating IgGs [59].

Although glucocorticoid pulse therapy is the first-line treatment for moderate to severe active thyroid-associated ophthalmopathy, alternative options are required for patients who either have contraindications to or are resistant to this therapy. Thus, investigations of novel pharmacological strategies involving the use of allosteric small-molecule modulators to treat Graves' ophthalmopathy (GO) and Graves' disease (GD) by targeting the TSH receptor (TSHR) and/or the TSHR/IGF-1R cross-interaction are currently underway. Additionally, monoclonal antibody approaches aimed at targeting TSHR or IGF-1R to prevent the activation of these receptors are being studied.

Immunomodulation strategies for treating GO are also being advanced. These specifically make use of TSHR-derived peptides that target the human leukocyte antigen DR isotype (HLA-DR). This approach is promising because both HLA-DR and TSHR are overexpressed in the orbital tissues of GO patients [60]. Moreover, combining mycophenolate mofetil with glucocorticoid therapy can offer significant benefits in cases of resistance to traditional glucorticoid therapy.

However, surgery remains essential for chronic cases or those unresponsive to medication. Innovations in orbital decompression and eyelid/strabismus surgeries have further improved outcomes and patient satisfaction. Managing GO effectively requires a multidisciplinary approach to address all aspects of the condition, from thyroid dysfunction to ocular and psychological health [62].

The approval of Teprotumumab, the first FDA-approved drug for Graves' ophthalmopathy (GO), marks a major advancement in treatment. It targets the IGF-1 receptor to reduce inflammation and improve quality of life, with clinical trials establishing it as a cornerstone for managing active, moderate-to-severe GO. Additionally, teprotumumab shows promise in potentially reducing the need for orbital decompression surgery, though further studies are needed to confirm its long-term efficacy and safety [61].

A study conducted in Spain evaluated the efficacy of tocilizumab (TCZ) in patients with moderate-to-severe, corticosteroid-resistant Graves' ophthalmopathy (GO). This double-blind, randomized clinical trial involved 32 adults with GO across 10 medical centers. Participants received either intravenous TCZ (8 mg/kg body weight) or a placebo at weeks 0, 4, 8, and 12, with a follow-up period extending for an additional 28 weeks. The primary outcome measured was the percentage of patients who experienced at least a 2-point reduction in the Clinical Activity Score (CAS) from baseline by week 16 [63].

Rituximab (RTX) is a B cell-depleting IgG1 monoclonal antibody that targets the CD20 antigen on B lymphocytes. Binding to CD20 activates the complement system, leading to the lysis of plasma cell precursors and a subsequent decrease in autoantibody levels. RTX also inhibits antigen presentation, cytokine release and co-stimulatory signaling between B and T lymphocytes. Previous studies have shown mixed results regarding the effectiveness of rituximab for treating GO. An Italian study, however, reported that RTX (administered either as 1 g twice at a two-week interval or as a single 500 mg dose) was more effective at reducing the Clinical Activity Score (CAS) than intravenous glucocorticoids (IVGCs) given once a week with a cumulative dose of 7.5 g [64].

Tocilizumab demonstrates higher efficacy compared to rituximab in treating patients with steroid-resistant or steroid-dependent Graves' ophtalmopathy, as evidenced by a 100% achievement of the primary outcome in the tocilizumab group compared to 64% in the rituximab group, although this difference was not statistically significant. Both treatments significantly improved the Clinical Activity Score (CAS), visual acuity, diplopia, and proptosis, with tocilizumab showing a trend toward a greater reduction in CAS. Still, there was no significant difference in relapse-free survival between the two groups. Despite some relapses in both groups, tocilizumab appears to be a promising alternative for patients who do not respond to or are dependent on steroids [65].

Overall, Graves' ophthalmopathy (GO) can impact quality of life comparably to inflammatory bowel disease and may be more severe than diabetes, emphysema, or heart failure. Therefore, advancing treatments for GO is imperative due to its significant impact. Treatment for GO is typically administered with moderate-to-severe intensity [66]. Steroids are commonly used because of their effectiveness in reducing inflammation. However, approximately 20-30% of patients do not respond positively to steroids, and around 20% experience symptom recurrence [67].

CONCLUSION

Steroids have been widely employed due to their versatile application and potent anti-inflammatory properties. However, approximately 20-30% of patients do not respond to steroid treatment, while around 20% experience relapse. High-dose systemic glucocorticoids exhibit robust anti-inflammatory and immunosuppressive characteristics, making them effective in treating moderate and active Graves' ophthalmopathy (GO). Extensive analysis supports the superiority of intravenous steroid administration over oral preparations, as evidenced by a greater reduction in symptoms according to outcome measures.

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AUTHORS' CONTRIBUTIONS

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This review article does not involve any research studies with human participants or animals conducted by any of the authors.

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REFERENCES

1. Wémeau JL, Klein M, Sadoul JL, Briet C, Vélayoudom-Céphise FL. Graves' disease: Introduction, epidemiology, endogenous and environmental pathogenic factors. *Ann Endocrinol* (Paris). 2018;79: 599-607.
2. Smith TJ, Hegedüs L. Graves' Disease. *N Engl J Med*. 2016;375: 1552-65.
3. Hussain YS, Hookham JC, Allahabadia A, Balasubramanian SP. Epidemiology, management and outcomes of Graves' disease-real life data. *Endocrine*. 2017;56:568-78.
4. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol*. 2018;14:301-16.
5. Perros P, Neoh C, Dickinson J. Thyroid eye disease. *BMJ*.2009;338: b560.
6. Wiersinga WM, Bartalena L. Epidemiology and prevention of Graves' ophthalmopathy. *Thyroid*. 2002;12:855-60.
7. Bahn RS. Current insights into the pathogenesis of Graves' ophthalmopathy. *Horm Metab Res*. 2015;47:773-8.
8. Huang Y, Fang S, Li D, Zhou H, Li B, Fan X. The involvement of T cell pathogenesis in thyroid-associated ophthalmopathy. *Eye* (Lond). 2019;33:176-82.

9. Bahn RS. Graves' ophthalmopathy. *N Engl J Med*. 2010;362:726-38.
10. Bartalena L, Marcocci C, Pinchera A. Graves' ophthalmopathy: a preventable disease?. *Eur J Endocrinol*. 2002;146:457.
11. Fang S, Huang Y, Zhong S, Li Y, Zhang Y, Li Y, et al. Regulation of Orbital Fibrosis and Adipogenesis by Pathogenic Th17 Cells in Graves Orbitopathy. *J Clin Endocrinol Metab*. 2017;102:4273-83.
12. Wei H, Guan M, Qin Y, Xie C, Fu X, Gao F, et al. Circulating levels of miR-146a and IL-17 are significantly correlated with the clinical activity of Graves' ophthalmopathy. *Endocr J*. 2014;61:1087-92.
13. Fang S, Huang Y, Wang S, Zhang Y, Luo X, Liu L, et al. IL-17A Exacerbates fibrosis by promoting the proinflammatory and profibrotic function of orbital fibroblasts in TAO. *J Clin Endocrinol Metab*. 2016;101:2955-65.
14. Fang S, Huang Y, Zhong S, Zhang Y, Liu X, Wang Y, et al. IL-17A Promotes RANTES expression, but not IL-16, in orbital fibroblasts Via CD40-CD40L combination in thyroid-associated ophthalmopathy. *Investig Opthalmol Vis Sci*. 2016;57:6123-33.
15. Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, natural history, risk factors, and prevention of Graves' orbitopathy. *Front Endocrino*l (Lausanne). 2020;11:615993.
16. Dik WA, Virakul S, van Steensel L. Current perspectives on the role of orbital fibroblasts in the pathogenesis of Graves' ophthalmopathy. *Exp Eye Res*. 2016;142:83-91.
17. Smith TJ, Hegedüs L, Lesser I, Perros P, Dorris K, Kinrade M, et al. How patients experience thyroid eye disease. *Front Endocrinol*. 2023;14:1283374.
18. Qian L, Wei W. Identified risk factors for dry eye syndrome: a systematic review and meta-analysis. *PLoS ONE*. 2022;17:e0271267.
19. Park J, Baek S. Dry eye syndrome in thyroid eye disease patients: the role of increased incomplete blinking and meibomian gland Loss. *Acta Ophthalmol*. 2019;97:800-6.
20. Lo C, Yang M, Rootman D. Natural history of inflammatory and non-inflammatory dry eye in thyroid eye disease. *Orbit*. 2021;40:389-93.
21. Liao X, Lai KKH, Aljufairi FMAA, Chen W, Hu Z, Wong HYM, et al. Ocular surface changes in treatment-naive thyroid eye disease. *J Clin Med*. 2023;12:3066.
22. Rana HS, Akella SS, Clabeaux CE, Skurski ZP, Aakalu VK. Ocular surface disease in thyroid eye disease: a narrative review. *Ocul Surf*. 2022;24:67-73.
23. Jones L, Downie LE, Korb D, Benitez-del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II management and therapy report. *Ocul Surf*. 2017;15:575-628.
24. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol*. 2021;185:G43-G67.
25. Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. *J Clin Endocrinol Metab*. 2006;91:3464-70.
26. Douglas RS, Afifiyan NF, Hwang CJ, Chong K, Haider U, Richards P, et al. Increased generation of fibrocytes in thyroid-associated ophthalmopathy. *J Clin Endocrinol Metab*. 2010;95:430-8.
27. Terwee CB, Prummel MF, Gerding MN, Kahaly GJ, Dekker FW, Wiersinga WM. Measuring disease activity to predict therapeutic outcome in Graves' ophthalmopathy. *Clin Endocrinol* (Oxf). 2005;62:145-55.
28. Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tørring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. *Eur J Endocrinol*. 2008;158:69-75.
29. Kahaly GJ, Wüster C, Olivo PD, Diana T. High titers of thyrotropin receptor antibodies are associated with orbitopathy in patients with Graves disease. *J Clin Endocrinol Metab*. 2019;104:2561-8.
30. Perros P, Dayan CM, Dickinson AJ, Ezra D, Estcourt S, Foley P, et al. Management of patients with Graves' orbitopathy: initial assessment, management outside specialised centres and referral pathways. *Clin Med* (Lond). 2015;15:173-8.
31. Hiromatsu Y, Eguchi H, Tani J, Kasaoka M, Teshima Y. Graves' ophthalmopathy: epidemiology and natural history. *Intern Med*. 2014;53:353-60.
32. European Group on Graves' Orbitopathy (EUGOGO); Wiersinga WM, Perros P, Kahaly GJ, Mourits MP, Baldeschi L, et al. Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers. *Eur J Endocrinol*. 2006;155:387-9.
33. Patel A, Yang H, Douglas RS. A new era in the treatment of thyroid eye disease. *Am J Ophthalmol*. 2019;208:281-8.
34. Tu X, Dong Y, Zhang H, Su Q. Corticosteroids for Graves' ophthalmopathy: Systematic review and meta-analysis. *Biomed Res Int*. 2018;2018:4845894.
35. Wiersinga WM. Advances in treatment of active, moderate-to-severe Graves' ophthalmopathy. *Lancet Diabetes Endocrinol*. 2017;5:134-42.
36. Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. *J Clin Endocrinol Metab*. 2011;96:320-32.
37. Riedl M, Kolbe E, Kampmann E, Krämer I, Kahaly GJ. Prospectively recorded and MedDRA-coded safety data of intravenous methylprednisolone therapy in Graves' orbitopathy. *J Endocrinol Invest*. 2015;38:177-82.
38. Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, Single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. *J Clin Endocrinol Metab*. 2005;90:5234-40.
39. Bartalena L, Krassas GE, Wiersinga W, Marcocci C, Salvi M, Daumerie C, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. *J Clin Endocrinol Metab*. 2012;97:4454-63.
40. Hoppe E, Lee ACH, Hoppe D, Kahaly GJ. Predictive factors for changes in quality of life after steroid treatment for active moderate-to-severe Graves' orbitopathy: A prospective trial. *Eur Thyroid J*. 2021;9:313-20.
41. Sisti E, Coco B, Menconi F, Leo M, Rocchi R, Latrofa F, et al. Age and dose are major risk factors for liver damage associated with intravenous glucocorticoid pulse therapy for Graves' orbitopathy. *Thyroid*. 2015;25:846-50.
42. Miśkiewicz P, Jankowska A, Brodzińska K, Milczarek-Banach J, Ambroziak U. Influence of methylprednisolone pulse therapy on liver function in patients with Graves' orbitopathy. *Int J Endocrinol*. 2018;2018:1978590.
43. Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marcocci C, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. *Eur J Endocrinol*. 2008;158:273-85.
44. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J*. 2016;5:9-26.
45. Kahaly GJ. Management of Graves thyroidal and extrathyroidal disease: An update. *J Clin Endocrinol Metab*. 2020;105:3704-20.
46. Marcocci C, Watt T, Altea MA, Rasmussen AK, Feldt-Rasmussen U, Orgiazzi J, et al. Fatal and non-fatal adverse events of glucocorticoid therapy for Graves' orbitopathy: a questionnaire survey among members of the European Thyroid Association. *Eur J Endocrinol*. 2012;166:247-53.
47. Currò N, Covelli D, Vannucchi G, Campi I, Pirola G, Simonetta S, et al. Therapeutic outcomes of high-dose intravenous steroids in the treatment of dysthyroid optic neuropathy. *Thyroid*. 2014;24:897-905.
48. Längericht J, Krämer I, Kahaly GJ. Glucocorticoids in Graves' orbitopathy: mechanisms of action and clinical application. *Ther Adv Endocrinol Metab*. 2020;11:2042018820958335.
49. Bartalena L, Veronesi G, Krassas GE, Wiersinga WM, Marcocci C, Marinò M, et al. Does early response to intravenous glucocorticoids predict the final outcome in patients with moderate-to-severe and active Graves' orbitopathy? *J Endocrinol Invest*. 2017;40:547-53.
50. Nedeljkovic Beleslin B, Ciric J, Stojkovic M, Savic S, Lalic T, Stojanovic M, et al. Comparison of efficacy and safety of parenteral versus parenteral and oral glucocorticoid therapy in Graves' orbitopathy. *Int J Clin Pract*. 2020;74:e13608.
51. Lee SJ, Rim TH, Jang SY, Kim CY, Shin DY, Lee EJ, et al. Treatment of upper eyelid retraction related to thyroid-associated ophthalmopathy using subconjunctival triamcinolone injections. *Graefes Arch Clin Exp Ophthalmol*. 2013;251:261-70.

52. Huebert I, Heinicke N, Kook D, Boost KA, Miller CV, Mayer WJ, et al. Dual platelet inhibition in cases of severe retrobulbar hemorrhage following retrobulbar and peribulbar anesthesia. *J Cataract Refract Surg.* 2015;41:2092-101.
53. Ebner R, Devoto MH, Weil D, Bordaberry M, Mir C, Martinez H, et al. Treatment of thyroid associated ophthalmopathy with periocular injections of triamcinolone. *Br J Ophthalmol*. 2004;88: 1380-6.
54. Goldberg RA. Orbital steroid injections. *Br J Ophthalmol*. 2004;88: 1359-60.
55. Lanzolla G, Maglionico MN, Comi S, Menconi F, Piaggi P, Posarelli C, et al. Sirolimus as a second-line treatment for Graves' orbitopathy. *J Endocrinol Invest*. 2022;45:2171-80.
56. Roos JCP, Murthy R. Sirolimus (rapamycin) for the targeted treatment of the fibrotic sequelae of Graves' orbitopathy. *Eye* (Lond) 2019;33:679-82.
57. Sehgal SN. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc.* 2003;35:7S-14S.
58. Zhang L, Grennan-Jones F, Draman MS, Lane C, Morris D, Dayan CM, et al. Possible Targets for Nonimmunosuppressive Therapy of Graves' Orbitopathy. *J Clin Endocrinol Metab.* 2014;99:1183-90.
59. Roos JCP, Eglitis V, Murthy R. Inhibition of fibrotic contraction by sirolimus (Rapamycin) in an ex vivo model of thyroid eye disease. Ohthalmic *Plast Reconstr Surg.* 2021;37:366-71.
60. Krause G, Eckstein A, Schülein R. Modulating TSH receptor signaling for therapeutic benefit. *Eur Thyroid J*. 2020;9:66-77.
61. Jinhai Y, Qassem AAM, Qi J, Chao X, Anan W, Qi X, et al. Bayesian network analysis of drug treatment strategies for thyroid associated ophthalmopathy. *Int Ophthalmol.* 2024;44:339.
62. Scarabosio A, Surico PL, Singh RB, Tereshenko V, Musa M, D'Esposito F, et al. Thyroid eye disease: Advancements in orbital and ocular pathology management. *J Pers Med*. 2024;14:776.
63. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo Lopez A, Rodriguez Alvarez FM, et al. Tocilizumab in Graves orbitopathy study G. Efficacy of tocilizumab in patients with moderate-tosevere corticosteroid-resistant Graves orbitopathy: A randomized clinical trial. *Am J Ophthalmol*. 2018;195:181-90.
64. Salvi M, Vannucchi G, Currò N, Campi I, Covelli D, Dazzi D, et al. Efficacy of B-Cell Targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: A randomized controlled study. *J Clin Endocrinol Metab*. 2015;100:422-31.
65. Bennedjaï A, Bouheraoua N, Gatfossé M, Dupasquier-Fediaevsky L, Errera MH, Tazartes M, et al. Tocilizumab versus rituximab in patients with moderate to severe steroid-resistant Graves' orbitopathy. *Ocul Immunol Inflamm*. 2022;30:500-5.
66. Sharma A, Stan MN, Rootman DB. Measuring health-related quality of life in thyroid eye disease. *J Clin Endocrinol Metab.* 2022;107:27-35.
67. Salvi M, Campi I. Medical treatment of Graves' Orbitopathy. *Horm Metab Res*. 2015;47:779-88.