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REVIEW

STEROID TREATMENT FOCUSED MANAGEMENT OF GRAVES' OPHTHALMOPATHY

Y. H. Condeng[1], H. Umar[2], A. M. Aman[3], H. Rasyid[4], S. Bakri[5], H. Iskandar[6]

[1]Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[2]Endocrinology, Metabolism and Diabetes Division, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University – Makassar, Indonesia
[3]Endocrinology, Metabolism and Diabetes Division, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University – Makassar, Indonesia
[4]Nephrology and Hypertension Division, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University – Makassar, Indonesia
[5]Nephrology and Hypertension Division, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University – Makassar, Indonesia
[6]Pulmonary Disease and Critical Care Medicine Division, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University – Makassar, Indonesia

Abstract. Introduction: *Graves' disease (GD) is an autoimmune disease that affects the thyroid and the eyes. Graves' ophthalmopathy (GO), an autoimmune disease, usually appears 18 months after GD diagnosis. Clinical activity and disease severity determine the strategy, with steroid treatment recommended during active disease progression.* ***Aim:*** *This review aims to provide an overview of steroid therapy in the treatment of Graves' ophthalmopathy, discussing its efficacy, protocols, and considerations.* ***Materials and Methods:*** *We reviewed the papers focusing on management recommendations and assessed peer-reviewed publications using the following keywords: "Graves' disease", "Graves' ophthalmopathy", "Graves' orbitopathy", "glucocorticoids".* ***Results and Discussion:*** *Steroid therapy, especially glucocorticoids, is a primary pharmacologic intervention for clinically active GO. Intravenous administration has shown superior outcomes compared to oral administration, with a recommended protocol that uses a cumulative dose of 4.5 grams methylprednisolone. High-dose systemic glucocorticoids possess anti-inflammatory and immunosuppressive characteristics and are efficacious in managing moderate to severe active GO. Second-line therapies, such as methylprednisolone monotherapy or in combination with cyclosporine, may be considered.* ***Conclusion:*** *Graves' ophthalmopathy requires intravenous glucocorticoids during the active phase. Intravenous glucocorticoids are more effective and better tolerated than oral glucocorticoids. Patients with Graves' ophthalmopathy require individualized treatment plans that address contraindications and side effects to improve outcomes and quality of life.*

Key words: *Graves' disease, Graves' ophthalmopathy, Graves' orbitopathy, glucocorticoids*

Corresponding author: *Yusuf Haz Condeng, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Perintis Kemerdekaan Km. 11 Street, Makassar, South Sulawesi 90245, Indonesia, tel.: +6281251334829, e-mail: yusufhazcondeng@gmail.com;*

ORCID *iD: https://orcid.org/0009-0007-0042-9738.*

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***ORCID** iD: https://orcid.org/0009-0007-0042-9738, **ORCID** iD: https://orcid.org/0000-0002-6529-2986,*
__ORCID__ iD: https://orcid.org/0000-0002-1310-9721, __ORCID__ iD: https://orcid.org/0000-0001-7404-2973,
__ORCID__ iD: https://orcid.org/0000-0002-6615-5166, __ORCID__ iD: https://orcid.org/0000-0002-2424-0178

Abbreviations:

GAGs	Glycosaminoglycans
GD	Graves' disease
GO	Graves' ophthalmopathy or orbitopathy
IgG	Immunoglobulin G
IGF-1R	Insulin-like growth factor-I
RAI	Radioactive iodine
TGAb	Thyroglobulin antibody
TPO	Thyroid peroxidase
TRAb	TSH-receptor antibodies
TSHR	Thyroid-stimulating hormone receptor
TSIs	Thyroid-stimulating immunoglobulins

INTRODUCTION

Graves' disease (GD) is an autoimmune disease that primarily affects the thyroid gland. It also has the ability to affect numerous other organs, including the eyes and skin. Graves' disease accounts for 60% to 80% of cases of hyperthyroidism. In the United States, hyperthyroidism is observed in 1.2% of the population, with an incidence ranging from 20 to 50 cases per 100,000 individuals. Meanwhile, in Europe, the prevalence is estimated to be approximately 10 per 10,000 persons [1-3]. It typically manifests in individuals between the ages of 20 and 50. Women have a higher prevalence of Graves' disease than men. Other common factors include toxic multinodular goiter, functioning thyroid adenoma, and subacute destructive thyroiditis (caused by viral infection, autoimmune disease, or drugs) [4, 5].

Graves' ophthalmopathy, also known as Graves' eye disease or Graves' orbitopathy, refers to the signs and symptoms associated with the eye and adjacent tissues in individuals diagnosed with Graves' disease. It occasionally occurs in patients with normal thyroid function or even low thyroid function due to chronic thyroid inflammation. Graves' ophthalmopathy (GO) is an autoimmune disease that specifically affects the tissues behind the eyes [6, 7].

The development of GO is thought to occur due to the presence of TSHR autoantigens on adipocytes and fibroblasts, leading to T-cell activation. As a result, there is a greater accumulation of water-loving glycosaminoglycans and an increase in the size of the connective tissue and muscles behind the eyes [8, 9].

Elevated levels of TGAb and TRAb, alongside decreased levels of TPOAb, are observed in individuals with Graves' disease (GD) accompanied by Graves' ophthalmopathy (GO) in contrast to those without ocular involvement. These observations could offer novel insights into investigating the underlying mechanisms of GO [10]. Detecting various autoantibodies in Graves' disease (GD), like those against thyroglobulin and thyroid peroxidase, is common but not considered pathogenic. They're typically associated with other thyroid autoimmune conditions like Hashimoto's thyroiditis. A recent study explored the emergence of these antibodies before and after diagnosing Hashimoto's thyroiditis and GD [11].

Evidence suggests that IGF-1R may be involved in autoimmunity, aligning with its known influence on various aspects of the mammalian immune system. We propose that antibodies in Graves' disease can bind to IGF-1R, triggering signaling cascades leading to the production of chemoattractants and hyaluronan [12]. Fibroblasts from individuals with Graves' ophthalmopathy (GO) exhibit heightened IGF-1R levels and, when exposed to IGF-1 or GD-IgG, produce T cell chemoattractants. Similarly, a notably higher fraction of peripheral blood T cells in GD patients express IGF-1R, particularly memory (CD45RO+) CD4+ and CD8+ subsets. These findings suggest that IGF-1 and GD-IgG may directly influence the survival and expansion of antigen-specific T cells in Graves' disease [13]. Most patients experience the onset of eye disease within 18 months of being diagnosed with Graves' disease. However, ophthalmopathy can manifest within a time frame of 10 to 20 years after the initial onset of thyroid disease [14, 15].

Risk factors for GO include receiving RAI therapy for hyperthyroidism, untreated hyperthyroidism, smoking, high serum TRAb levels prior to therapy (< 1.75 IU/L for normal, > 8.8 IU/L for high risk of progression), and delayed treatment of hypothyroidism after treatment for hyperthyroidism [16]. GO can be active or inactive. An autoimmune process causes GO to progress over 6-24 months during the active phase. During this phase, lymphocytes invade the affected area and release inflammatory cytokines. Fibroblast proliferation causes orbital muscle enlargement, conjunctival injection and chemosis, ocular pain, and lid and eyelid swelling [17, 18]. The next phase is resolution of the inflammation, which can take over a year. The inactive phase is characterized by fibrosis

of the orbital tissues. Reactivation of GO after 5 years is rare, occurring in 5% of cases [19, 20].

Management strategies for GO include a variety of approaches, including non-pharmacological interventions, pharmacologic treatments, rehabilitative surgery, and radiation therapy. While ophthalmopathy tends to be mild and non-progressive in the majority of cases, it is crucial to meticulously monitor and promptly administer suitable treatment to individuals identified as at risk, considering the severity and activity of the disease [21, 22]. Successful treatment requires euthyroidism, and it is advisable to refrain from radioiodine therapy in cases of actively progressive GO. During the active progressive phase of the disease, anti-inflammatory therapy is recommended. However, rehabilitative surgery should only be considered in the stable inactive phase when there are persistent sequelae [23, 24]. This review examines various management strategies, focusing on the role of glucocorticoids, particularly intravenous administration. It also discusses alternative approaches to reduce steroid dependency, improve efficacy, and addresses the variability in patient response to treatment.

AIM

This review aims to provide a comprehensive and up-to-date exploration of the management of Graves' ophthalmopathy, with a particular focus on steroid therapy, offering insights into treatment protocols, considerations, and emerging alternatives.

MATERIALS AND METHODS

We reviewed the papers focusing on management recommendations and assessed peer-reviewed publications using the following keywords: "Graves' disease", "Graves' ophthalmopathy", "Graves' orbitopathy", "glucocorticoids".

RESULTS AND DISCUSSION

Management of Graves' Ophthalmopathy

Recent meta-analyses and meta-regression studies have shown that the frequency and intensity of GO in GD patients has decreased over the past 30 years. Reduced smoking, early detection, and better management of thyroid dysfunction are contributing to this trend. Endocrinologists and ophthalmologists are working together to detect and treat the disease early. In addition, mild GO can worsen, requiring professional consultation to develop a comprehensive management plan. Patients with confirmed GO and those at risk for worsening GO, such as those with mild and active GO, smokers, high serum TRAb levels, and severe/unstable hyperthyroidism, must be referred to a Thyroid Eye Clinic. This clinic provides comprehensive endocrine and ophthalmic services to improve patient prognosis and quality of life through accurate and rapid diagnosis [25, 26].

Treatment of GO depends on clinical assessment of disease activity, severity, and duration. The efficacy of anti-inflammatory/immunosuppressive treatment decreases significantly after 18 months of disease onset. There is a clear correlation between treatment timing and GO disease severity and activity [27]. Initiating immunosuppressive treatment during active GO can significantly reduce disease severity. In contrast, immunosuppressive therapy during inactivity is associated with poor outcomes [28].

Streroid Therapy for Graves' Ophthalmopathy

The choice of pharmacologic treatment, restorative surgery, and radiation therapy depends on the clinical activity and severity of the disease. Glucocorticoids are the primary pharmacologic treatment option for patients with clinically active GO. Glucocorticoids are administered by oral, topical, or intravenous routes [29]. Administering glucocorticoids locally through subconjunctival or retrobulbar injection is not recommended due to the potential harm and the absence of confirmed effectiveness. Intravenous administration of glucocorticoids has shown better response and clinical efficacy than oral administration. There are several contraindications to the use of methylprednisolone as part of GO therapy. These include a recent history of viral hepatitis infection, severe cardiovascular morbidity, uncontrolled hypertension, uncontrolled diabetes, significant hepatic impairment, and psychiatric disorders [30, 31].

In a clinical trial, participants were randomized to receive orbital injections of triamcinolone acetate or placebo. The eye was injected in the inferolateral quadrant. Triamcinolone acetate was injected four times at 40 mg per week. This treatment reduced double vision and extraocular muscle size. A small randomized trial showed that subconjunctival injection of 20 mg triamcinolone in 1 to 3 injections treated short-term upper eyelid retraction due to GO. However, topical glucocorticoids may increase intraocular pressure due to accumulation of fat in the eye socket. In addition, patients taking both antiplatelet medications have a small but significant risk of bleeding behind the eye. Therefore, topical glucocorticoids may replace systemic glucocorticoids in contraindicated patients [32, 33].

Specialized centers and facilities are necessary for intravenous glucocorticoid therapy, but they may not

be accessible in all countries. This partly explains the continued prevalence of the oral route of administration, whether it is the use of oral glucocorticoids alone or as a follow-up to the initiation of therapy with multiple glucocorticoid infusions, in order to reduce hospitalization rates. When administering oral glucocorticoids, it is recommended to start treatment according to the recommendations of several randomized trials. Utilizing additional treatments like orbital radiation or non-steroidal immunosuppressive drugs such as mycophenolate or cyclosporine, in conjunction with oral glucocorticoids, can potentially decrease reliance on steroids and enhance their effectiveness [34, 35].

High-dose systemic glucocorticoids are effective in treating moderate to severe and active GO due to their anti-inflammatory and immunosuppressive properties. Intravenous glucocorticoids are the first-line treatment for moderate and active GO. A randomized trial showed that intravenous methylprednisolone resulted in an 83% improvement in GO scores compared to an 11% improvement with placebo [36, 37]. While oral glucocorticoids are effective, intravenous glucocorticoids are the preferred option due to their demonstrated superiority in randomized trials, with success rates ranging from 77% to 88% compared to 51% to 63% for oral administration. In addition, intravenous glucocorticoids are better tolerated by patients [38]. In a prospective, non-randomized single-center investigation that evaluated the efficacy and safety of a modified monthly regimen (mMR) and compared it with the established weekly regimen (WR) for glucocorticoid (GC) administration, the study revealed that both GC regimens exhibit similar efficacy, albeit with slight variations in the onset and duration of therapeutic effects, as well as their effectiveness on certain ocular manifestations [39].

A common protocol is to administer a cumulative dose of 4.5 grams of methylprednisolone in 12 weekly infusions. This treatment protocol includes six infusions of 0.5 grams of the drug followed by six infusions of 0.25 grams. This is often the first-line treatment. The 4.5 grams regimen was well-tolerated and improved the individual's quality of life. This treatment plan is appropriate for most patients, but severe moderate to severe GO and active phase cases require cumulative doses greater than 7.5 grams (starting with 0.75 grams intravenously as a weekly infusion). This is because higher doses are associated with increased adverse drug reactions [40, 41]. Based on safety data, the intravenous dose should not exceed 0.75 grams per week and the total dose should not exceed 8.0 grams per cycle. Avoid consecutive daily therapy because glucocorticoids can cause liver toxicity and serious cardiovascular effects. Note that these recommendations do not apply to the risk of vision loss [42, 43].

Glucocorticoids should be administered gradually over a period of 1-2 hours under close observation. Before starting treatment, it is essential to exclude the presence of an infectious condition by checking the white blood cell count. Furthermore, it is crucial to assess the cardiovascular risk, liver enzymes, and viral hepatitis markers in order to identify any possible risks or contraindications. During treatment, liver enzymes are closely monitored [44, 45]. High doses of oral glucocorticoids can lead to several adverse effects, including cataracts, peptic ulcers, long-term suppression of adrenal function, Cushing's syndrome, diabetes, infectious diseases, hypertension, reactivation of chronic diseases (such as tuberculosis), osteoporosis, and psychosis. If it is not possible to administer glucocorticoids intravenously, prednisone can be given orally for a period of 12 weeks. The recommended starting daily dose is 0.2 grams, which should be gradually reduced over time to a weekly dose of 0.01 grams, resulting in a total cumulative dose of 4 grams [38, 46].

Glucocorticoid treatment should not be used in cases of active viral hepatitis infection, significant impairment of liver function, serious heart-related health problems, or mental disorders. However, treatment may be initiated if diabetes and hypertension are well controlled. It is advisable to undergo bone protective therapy, and the use of proton pump inhibitors should be considered if deemed appropriate. The effect of intravenous glucocorticoids is usually rapid, although it may be delayed until the middle or later stages of treatment. Therefore, individuals with a suboptimal response to intravenous glucocorticoids should strive to complete a 12-week treatment regimen. Conversely, a decrease in ocular clinical signs and symptoms indicates the need for second-line treatment [30, 35].

According to the 2016 ETA/EUGOGO guidelines, it is recommended to use a second-line therapy for 3-4 weeks and to evaluate the eyes and liver enzymes. This therapy involves the use of intravenous methylprednisolone monotherapy at a higher cumulative dose of 7.5 grams. Treatment begins 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 allowed, 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. This approach has shown favorable results in two randomized trials. In addition, azathioprine may be used in conjunction with oral glucocorticoids because

of its ability to reduce the need for steroids, as demonstrated in a randomized trial [47, 48].

Glucocorticoids are the preferred immunosuppressive agents for moderate and active GO due to their anti-inflammatory properties and, at high doses, their ability to suppress the immune system. Laboratory studies show that glucocorticoids decrease the production and release of glycosaminoglycans by orbital fibroblasts. They also suppress the activity of various adhesion molecules, inhibit the secretion of cytokines and antibodies, impair the function of T and B lymphocytes, and reduce the recruitment of neutrophils and macrophages to the site of inflammation [34, 49].

Overall, the impact of GO on quality of life can be comparable to that of inflammatory bowel disease and can be more severe than diabetes, emphysema or heart failure. Because of its significance, it is imperative to continue to advance treatments for GO. Treatment for GO is typically moderate-to-severe in intensity [21]. Steroids are commonly used because of their widespread use and ability to reduce inflammation. However, approximately 20-30% of patients do not have a positive response to steroids, and approximately 20% of patients experience a recurrence of symptoms [50].

CONCLUSIONS

Glucocorticoids, with their anti-inflammatory and immunosuppressive effects, are crucial during the active phase of GO. Further research is warranted to refine therapeutic approaches and address the variability in patient response, ultimately improving outcomes and quality of life for those affected by Graves' ophthalmopathy.

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