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Review of Current First-Line Pharmacotherapy Strategies for Thyroid Eye Disease

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Abstract

Thyroid eye disease (TED) is a challenging autoimmune disorder that often requires therapeutic intervention. Glucocorticoids (GCs), particularly in intravenous (IV) regimens, remain the first-line treatment due to their strong anti-inflammatory and immunosuppressive effects. This paper focuses on the efficacy, protocols, and safety profiles of selenium supplementation and glucocorticoid therapy, emphasizing its central role in TED management.

Alternative therapies, such as teprotumumab, rituximab, and tocilizumab, are briefly discussed as potential options for patients with moderate-to-severe TED, who are unresponsive or intolerant to glucocorticoids. Adherence to recommended dosing protocols and careful monitoring of adverse effects are essential to optimize treatment outcomes.

Aim of the Study

The primary aim of this study is to evaluate the role of first-line treatments across the spectrum of clinical presentations of thyroid eye disease (TED), ranging from mild to sight-threatening forms. The study emphasizes their mechanisms of action, therapeutic efficacy, and safety profiles. Additionally, it briefly explores alternative pharmacological options for patients who do not respond to glucocorticoids or cannot tolerate their side effects.

Summary

Management of thyroid eye disease (TED) depends on its severity, with tailored approaches for mild, moderate-to-severe, and sight-threatening forms. In mild TED, first-line treatment typically involves conservative measures such as selenium supplementation, which has shown benefits in reducing oxidative stress and improving quality of life. For moderate-to-severe TED, intravenous glucocorticoids (IVGCs) demonstrate superior efficacy and tolerability compared to oral routes, effectively reducing inflammation and preventing disease progression. In sight-threatening TED, IVGCs are also the first-line therapy due to their rapid and potent anti-inflammatory effects, crucial for preventing vision loss.

This study explores the mechanisms of action and dosing protocols for glucocorticoids, emphasizing adherence to established guidelines to minimize risks such as hepatotoxicity, cardiovascular complications, and bone loss. For patients who are unresponsive to glucocorticoids, alternative therapies such as teprotumumab, rituximab, and tocilizumab provide emerging options, though their use remains supplementary to glucocorticoids in clinical practice. By focusing on glucocorticoids as the foundation of therapy, this study underscores their central role in the management of TED across different severities.

Keywords: Thyroid eye disease (TED), glucocorticoids (GCs), mild TED, moderate-to-severe TED, sight-threatening TED, intravenous glucocorticoids (IVGCs), first-line therapy, anti-inflammatory therapy

Introduction

There are several causes of hyperthyroidism, including postpartum thyroiditis, subacute thyroiditis, and the presence of thyroid nodules (toxic nodular goiter) [1], with the most common cause in Western countries being the Graves-Basedow disease [2] with an annual incidence of 20 to 50 cases per 100,000 persons [3]. Graves hyperthyroidism is an autoimmune, multisystem disorder, in which the anti-TSHR autoantigen occurs [4].

These autoantibodies, among other actions, activate thyroid follicular cells, resulting in hyperthyroidism and its associated clinical manifestations, underscoring the potential for extrathyroidal involvement in the disease.

Notably, TSH receptor expression is also observed on fibrocytes. fibroblasts, fibrocytes, adipocytes, osteoblasts, osteoclasts, and pituitary folliculostellate cells, which is associated with the impact of the disease on various organs, including the nervous, skeletal, respiratory, cardiovascular, gastrointestinal, and reproductive systems, skin, as well as the visual system [5], which is the most prevalent extrathyroidal manifestation associated with Graves' disease and will be discussed in detail.

Graves' ophthalmopathy/orbitopathy, also referred to as Thyroid Eye Disease (TED) is an autoimmune disorder characterised by constellation of ocular symptoms resulting from progressive, immune-mediated inflammation and remodeling of the orbit and periocular tissues, as well as enlargement of the extraocular muscles [6]. Moreover edema can be found in the endomysial interstitial space, along with cellular proliferation and expansion within the fibrofatty compartment. This results in a clinical presentation characterized by visual acuity deterioration, periorbital edema and swelling of the eyelid, ocular pain, photophobia, lid retraction, proptosis, diplopia, restriction of ocular motility, corneal breakdown, glaucoma and even optic nerve compression and damage. [5,7] These manifestations are associated with a substantial negative impact on the patient's quality of life.

Epidemiology

Regarding the epidemiology of Thyroid Eye Disease (TED), the annual incidence of Graves' orbitopathy (GO) is approximately 16 cases per 100,000 females and 3 cases per 100,000 males [8]. Cases predominantly occur in patients with hyperthyroidism. It is estimated that approximately 90% of Thyroid Eye Disease (TED) cases occur in patients diagnosed with Graves' disease [9]. However, it is important to note that TED is not exclusive to hyperthyroid patients, with 1.6% to 8.6% of cases occurring in individuals who are hypothyroid or euthyroid [10]. TED is more common in younger females, although studies suggest that male patients and those of advanced age are at a higher risk of developing more severe forms of the disease [11]. An increased risk of developing Graves' orbitopathy is also linked to modifiable risk factors such as smoking, hyperthyroidism, hypothyroidism, radioiodine therapy, and the presence of TSH receptor antibodies [12]. A recent meta-analysis indicated that the overall pooled prevalence of TED was 40% (CI: 0.32 to 0.48), with regional variations: 38% (CI: 0.31 to 0.46) in Europe, 44% (CI: 0.32 to 0.56) in Asia, 27% (CI: 0.06 to 0.56) in North America, and 58% (CI: 0.55 to 0.61) in Oceania. Furthermore, subgroup analysis revealed that regions with a predominantly Caucasian population (37%; CI: 0.28 to 0.46) had a lower prevalence of TED compared to regions with a higher proportion of Asians (45%; CI: 0.33 to 0.58), although further investigation in this area is warranted [13].

Pathogenesis

Graves' Orbitopathy (GO), also referred to as Thyroid Eye Disease (TED), is a complex autoimmune disorder marked by inflammation, tissue remodeling, and fibrosis within the orbital structures. The pathophysiology of TED is driven by the activation of orbital fibroblasts (OF) and the infiltration of various immune cell populations, which together facilitate the progressive hypertrophy of extraocular muscles, retrobulbar adipose tissue, and connective tissue compartments.

This pathological tissue expansion is primarily attributed to the excessive deposition of extracellular matrix (ECM) components, particularly collagen and glycosaminoglycans (GAGs), which are synthesized in excess by activated fibroblasts. These processes are mediated by a dysregulated immune response targeting shared autoantigens present in both the thyroid gland and orbital tissues, such as thyroglobulin and thyroid-stimulating hormone (TSH) receptors. This aberrant immune activation drives the morphological and functional alterations characteristic of TED [4, 14]. Recent advancements in molecular and cellular research have provided further insights into the underlying mechanisms of this condition.

Autoimmune Mechanisms and Immune Cell Infiltration

The central role of autoimmune mechanisms in TED is well-established. These mechanisms involve a complex interplay between autoantibodies - primarily targeting the TSH receptor (TSHRAb), insulin-like growth factor 1 receptor (IGF-1RAb) - antibodies against a membrane receptor associated with tyrosine kinase, but also various immune cells. These interactions lead to both local inflammation and tissue remodeling in the orbit [15,16, 17]. The TSH receptor (TSHR) is expressed on orbital fibroblasts, with its expression notably increased during the active phase of GO [18, 19]. TSHR antibodies (TSHR-Ab) are typically classified into two types: TSHR-stimulating antibodies (TSAb), also known as TSHR-stimulating immunoglobulins (TSI), and TSHR-blocking antibodies (TBAb) [18, 19]. Studies have shown that TSHR expression on orbital fibroblasts is significantly elevated in TED patients, and this increase is most pronounced during the active phase of the disease [20]. Additionally, a strong correlation exists between the levels of TSHR-Ab and the severity of ophthalmopathy, particularly with respect to the differentiation of orbital fibroblasts into adipocytes, a process influenced by overexpression of TSHR and cytokines such as interleukin-1 (IL-1) or peroxisome proliferator-activated receptor gamma (PPARγ) agonists [21, 22].

TSIs, which are commonly found in TED patients, exacerbate thyroid dysfunction and further activate TSHR on orbital fibroblasts. This activation triggers downstream signaling pathways, such as cyclic AMP (cAMP)-dependent pathways, promoting the differentiation of fibroblasts into adipocytes and myofibroblasts. These processes contribute to the pathological tissue remodeling seen in TED. In rare cases, however, TSIs may be undetectable in patients with severe thyroid-associated ophthalmopathy [23]. Additionally, IGF-1R is overexpressed on orbital fibroblasts, where it forms a functional signaling complex with TSHR. Activation of IGF-1R leads to the secretion of GAGs and pro-inflammatory cytokines, driving tissue remodeling, edema, and fibrosis in the orbit. The close interaction between TSHR and IGF-1R allows for synergistic signaling, amplifying fibroblast activation and exacerbating the inflammatory response in TED [15, 16, 17, 24].

Role of Orbital Fibroblasts

Although the exact initiating trigger of Graves' Orbitopathy (GO) remains unclear, orbital fibroblasts (OF) play a pivotal role in the pathogenesis of thyroid eye disease (TED). Unlike other fibroblasts in the human body, OF are of neuroectodermal origin. Furthermore, they express TSH receptor (TSHR), insulin-like growth factor 1 receptor (IGF-1R), and the CD40 antigen, which interacts with CD154 (the ligand expressed on T cells).

This interaction induces the production of inflammatory cytokines, linking immune activity to local tissue remodeling. Additionally, leukoregulin contributes to the disease process by enhancing GAG production, including hyaluronic acid [25].

Infiltrating immune cells, such as B cells, T cells, and mast cells, interact with resident OF, which is critical for tissue remodeling in GO. The direct interaction between CD154 (present on T lymphocytes) and CD40 on OF stimulates the production of inflammatory mediators, including interleukins IL-1, IL-6, and IL-8, further linking immune activity to tissue remodeling [17]. Moreover, IL-17A has been implicated in the pro-inflammatory activity of OF, as it enhances the production of ECM proteins, promoting both inflammation and fibrosis in TED [17]. Mast cells also contribute to the production of hyaluronan and prostaglandin E2 (PGE2), further exacerbating the orbital changes seen in GO [26].

Fibroblast Subtypes and Their Role in TED

Orbital fibroblasts (OF) represent a heterogeneous cell population, which can be categorized based on the expression of specific surface markers, such as CD90 (Thy-1) and CD34 (myeloid cell marker). The differentiation and functional specialization of these subpopulations contribute significantly to the pathogenesis of Thyroid Eye Disease (TED). CD90+ fibroblasts, when stimulated by transforming growth factor-beta (TGF-β), undergo differentiation into myofibroblasts via the Smad signaling pathway. This differentiation is associated with the development of a pro-fibrotic phenotype, which plays a central role in the fibrotic changes characteristic of TED [27].

In contrast, CD90- fibroblasts are primarily directed towards adipogenesis under the influence of peroxisome proliferator-activated receptor gamma (PPARγ) agonists. This adipocyte differentiation contributes to the pathological accumulation of orbital fat, a hallmark of TED [28]. CD34+ fibrocytes, which are derived from bone marrow, are uniquely present within the TED orbit and are distinct from other fibroblastic populations. These fibrocytes express high levels of TSH receptor (TSHR) and insulin-like growth factor 1 receptor (IGF-1R), and play an important role in linking systemic autoimmunity with localized orbital inflammation. As antigen-presenting cells, CD34+ fibrocytes not only facilitate immune activation but also secrete a variety of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, IL-12, and IL-23, amplifying the immune response and perpetuating the inflammatory cascade [29]. Conversely, CD34- fibroblasts are key contributors to the synthesis of glycosaminoglycans (GAGs), such as hyaluronan, which lead to tissue edema and increased orbital pressure, both of which are clinical features of TED. The TGF-β-induced differentiation of fibroblasts into pro-fibrotic myofibroblasts and adipocytes is further enhanced by the activation of the Smad signaling pathway, intensifying the fibrotic and inflammatory processes within the orbit [30].

The dynamic interplay between these fibroblast subtypes contributes to the complex tissue remodeling observed in TED, underscoring their critical role in the pathogenesis of the disease.

Immune Cell Infiltration and Inflammatory Mediators

The pathological changes in orbital tissues during Thyroid Eye Disease (TED) are accompanied by extensive immune cell infiltration, which plays a crucial role in the inflammatory process. During the active phase of TED, T helper 1 (Th1) cells predominate, contributing to the acute inflammatory response. However, in the fibrotic phase, Th2 cells become more prominent, reflecting a shift towards a chronic, pro-fibrotic immune response. Additionally, Th17 cells, macrophages, and mast cells are actively involved in the orbital inflammatory milieu [31, 32]. These immune cells secrete a range of pro-inflammatory cytokines, including IL-1β, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), which not only exacerbate the inflammation but also directly activate orbital fibroblasts. IL-1β and TNF-α, in particular, trigger fibroblast activation, stimulating the production of GAGs and other inflammatory mediators, thereby sustaining the inflammatory cycle. Mast cells play a particularly important role by releasing prostaglandins and additional cytokines that further activate fibroblasts and promote the synthesis of hyaluronan, intensifying tissue remodeling and orbital changes [32, 33]. These immune cell interactions with orbital fibroblasts are central to the pathological process, as they facilitate the persistent inflammation and fibrosis that characterize TED. The secretion of multiple pro-inflammatory cytokines by infiltrating immune cells results in a sustained inflammatory environment, which perpetuates the immune-mediated damage to orbital tissues.

Oxidative stress and its role in TED pathogenesis

Oxidative stress is a key contributor to the pathogenesis of thyroid-associated orbitopathy (TAO), characterized by an imbalance between reactive oxygen species (ROS) production and the antioxidant defense mechanisms. This disruption leads to oxidative damage within orbital tissues and exacerbates inflammatory and fibrotic processes. Elevated ROS levels promote the activation of proinflammatory signaling pathways, including NF-κB, enhancing immune cell recruitment and cytokine production. These processes amplify the inflammatory cascade and contribute to the progression of the disease. Furthermore, oxidative stress stimulates the differentiation of orbital fibroblasts into adipocytes and myofibroblasts, facilitating tissue remodeling, glycosaminoglycan deposition, and fibrosis, hallmarks of TAO. The oxidative damage also drives the pathological expansion of retrobulbar fat and the thickening of extraocular muscles, further contributing to the clinical manifestations of TED [34, 35].

Treatment strategies

The management of thyroid eye disease (TED) is guided by the disease's activity and severity, as well as the patient’s prior treatment history and overall clinical profile. Disease activity is commonly assessed using the Clinical Activity Score (CAS) - a validated scoring system for determining the phase of a disease, which evaluates clinical manifestations and indicators of inflammation.

The CAS is a 7-item scale that assigns 1 point for each of the following symptoms:

spontaneous retrobulbar pain, pain on attempted up or lateral gaze, redness of the eyelids, redness of the conjunctiva, swelling of the eyelids, conjunctival edema (chemosis) and inflammation of the lacrimal caruncle and/or plica semilunaris [36].

TED treatment strategies are generally categorized into two phases: active (CAS ≥3/7 usually implies active TED) and inactive (CAS <3). In the active phase, the primary goal is to control inflammation and prevent disease progression, while in the inactive phase, the focus shifts toward addressing residual structural changes, such as proptosis and diplopia. Another critical factor in TED management is the severity of orbitopathy. According to the 'Consensus Statement by the American Thyroid Association and the European Thyroid Association' and the 2021 EUGOGO guidelines, severity is classified into three categories:
Mild TED - patients whose features of TED have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually exhibit one or more of the following: minor lid retraction (<2 mm), mild soft tissue involvement, proptosis <3 mm above normal for race and sex, transient or no diplopia, and corneal exposure responsive to lubricants.
Moderate-to-severe TED - in patients without sight-threatening disease whose eye disease has sufficient impact on daily life to justify the risks of medical or surgical intervention. Patients with moderate-to-severe TED usually have any one [7] / two [37] or more of the following: lid retraction ≥2 mm, moderate or severe soft tissue involvement, proptosis ≥3 mm above normal for race and sex, inconstant or constant diplopia (Gorman score 2–3).
Sight-threatening TED - in patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown and/or global subluxation [7, 37].
Treatment decisions are also influenced by the patient's response to previous therapies and the presence of comorbidities, underscoring the need for a personalized approach to managing this complex disease.

First-line pharmacotherapy for mild TED

Recommended by the EUGOGO treatment, except from watchful monitoring, for mild and active TED of recent onset is a 6-month selenium supplementation, because basing on the study [38], 200 µg of sodium selenite (91.2 µg selenium) (according to country availability, sodium selenite can be replaced by selenomethionine) improves eye manifestations and quality of life, moreover usually prevents GO progression to more severe forms. According to the study, the benefit of selenium was maintained 6 months after treatment withdrawal. The oral selenium supplementation can be beneficial for the patients living in selenium-deficient areas, although in selenium-replete areas the benefit of this treatment has to be confirmed [7, 38].
Moreover the meta-analysis of 1684 records on the efficacy and safety of selenium supplementation versus placebo showed that at six months, selenium supplementation was significantly more effective in reducing the CAS (mean difference [MD] = −1.27, 95% confidence interval [CI]: −1.68 to −0.85, $p < .0001$), enhancing total GO-QOL (relative risk [RR] = 2.54, 95% CI: 1.69–3.81, $p < .00001$), and improving both visual (MD = 10.84, 95% CI: 4.94–16.73, $p = .003$) and psychological functioning scores (MD = 12.76, 95% CI: 8.51–17.00, $p < .00001$).
These benefits were sustained at 12 months. Additionally, selenium significantly reduced the palpebral aperture at six months (MD = −1.49, 95% CI: −2.90 to −0.08, $p = .04$). However, no significant changes were noted in proptosis, soft tissue involvement, ocular motility, or adverse effects [39].

Also a controlled, randomized, single-center trial conducted at an ophthalmology referral center in Mexico City showed that the oral selenium supplementation reduces clinical activity and prevents disease progression in patients with mild thyroid-associated orbitopathy (TAO). The study included 30 patients (30 eyes) with mild TAO according to the Clinical Activity Score (CAS) classification. Patients were randomized into two groups: group A received placebo tablets (100 μg of starch twice daily for 6 months), while group B received selenium supplementation (100 μg twice daily for 6 months). Pretreatment values showed no statistically significant differences between the two groups ($P > 0.05$). However, intergroup analysis revealed statistically significant improvements in the palpebral fissure and CAS score in the selenium group after six months of treatment compared to baseline ($P < 0.05$). No significant changes were observed in the placebo group during the study period ($P > 0.05$), and no adverse events were reported [40]. Summarizing the current studies, although the selenium treatment for OT is promising, an in-depth analysis of relevant long-term clinical measures of therapeutic success (such as remission rate after antithyroid drug treatment), besides surrogate markers (for example, hormone or autoantibody concentrations), is generally missing [41].

First-line pharmacotherapy for moderate-to-severe TED

Glucocorticoids

Glucocorticoids (GCs) are pivotal in managing moderate-to-severe thyroid eye disease (TED) due to their potent anti-inflammatory and immunosuppressive properties. Their mechanisms of action encompass both genomic and non-genomic pathways.

Mechanisms of glucocorticoid action in TED

In genomic mechanisms, GCs diffuse easily through the cellular membrane, penetrate target cells and bind to cytoplasmic glucocorticoid receptors, forming a complex that translocates to the nucleus thanks to importins. This complex modulates gene expression by:

- **Transactivation:** Upon binding of the GR homodimer to its positive response element, coactivators SRC-1 and CBP interact with the receptor-ligand complex, initiating DNA transcription. This process upregulates the expression of anti-inflammatory genes, leading to the production of anti-inflammatory proteins such as annexin-1 (lipocortin-1), cytokines (IL-10, IL-12, IL-1 receptor antagonist), IκB, and MAPK phosphatase-1 (MAPKP-1)
- **Transrepression:** Glucocorticoids exert their anti-inflammatory effects by interacting with inflammatory proteins such as NF-κB and AP-1. The glucocorticoid receptor binds to NF-κB or AP-1, blocking their ability to activate pro-inflammatory genes, thus inhibiting DNA transcription. GR, in its dimeric form, associates with the NF-κB-DNA complex, preventing DNA unwinding and transcription initiation, thereby blocking inflammatory gene activation. The anti-inflammatory effect of GCs is modulated by the levels of coactivators like SRC-1 and CBP.

Excessive coactivator concentrations can diminish GC's anti-inflammatory efficacy. GR exists in two isoforms: GRα, which binds corticosteroids, and GRβ, which does not bind steroids but can inhibit the expression of genes such as osteocalcin and CRF-1. GRβ can recruit histone deacetylase (HDAC-2), leading to histone deacetylation and DNA compaction. This prevents transcription factors from accessing the DNA, thus inhibiting gene transcription [42, 43].

These actions collectively contribute to the reduction of inflammatory responses. The anti-inflammatory effects of GCs are primarily attributed to the transrepression mechanism. However, this genomic effect also plays a role in some of the side effects associated with GCs - improper interactions and concentrations of proteins can also lead to the suppression of gene expression essential for normal physiological functions, such as osteocalcin or keratin [42, 43]. Non-genomic mechanisms of glucocorticoids provide rapid anti-inflammatory effects within minutes of intravenous administration [44, 45], whereas after oral administration effects occur after 1-2 hours [46]. GCs inhibit cytokines, adhesion molecules, and prostaglandin synthesis by suppressing COX-2, cPLA2α, and MAPKs. They also destabilize mRNA of pro-inflammatory mediators, halting inflammatory protein production [42, 46].

Immunosuppressive effects in TED

In the context of TED, glucocorticoids exert their immunosuppressive effects by reducing the infiltration of inflammatory cells into orbital tissues. This is achieved through:

- Decreasing the expression of adhesion molecules on endothelial cells and fibroblasts, thereby inhibiting lymphocyte migration.
- Markedly reducing the number and activity of dendritic cells (DC), the most potent antigen-presenting cells, by inducing apoptosis, limiting their differentiation, and promoting their homing to lymphoid tissues.
- Altering T-cell dynamics by blocking the proliferation of immature T-cells, reducing differentiation into various T-cell phenotypes, and lowering expression of adhesion molecules like LFA-1 and CD2. These actions impair T-cell migration and reduce interactions with other immune cells, such as B-cells, natural killer cells, and antigen-presenting cells.

Therapeutic implications

These combined effects alleviate inflammation, decrease tissue edema, and prevent further tissue remodeling and fibrosis within the orbit, thereby mitigating the clinical manifestations of TED. Understanding these mechanisms highlights the therapeutic efficacy of glucocorticoids in treating moderate-to-severe TED [42].

Comparative approaches to glucocorticoid administration in TED management

Glucocorticoids have been utilized in the management of TED for over 70 years. While oral and intravenous administrations are the most common methods, local application is also a potential option [47]. Intravenous glucocorticoids are considered by ETA the first-line treatment for moderate-to-severe, active thyroid eye disease.

The standard protocol typically involves a cumulative dose of 4.5 g of methylprednisolone administered over 12 weeks, consisting of six weekly infusions of 0.5 g followed by six infusions of 0.25 g [37, 48]. Although oral glucocorticoids are effective, randomized controlled trials (RCTs) have demonstrated that the IV route is both more effective (with response rates of 77–88% compared to 51–63%) and better tolerated, a finding supported by the European Thyroid Association [37, 48].

Moreover, reviewing the studies compiled in the article [49], oral and intravenous glucocorticoids in the treatment of moderate-to-severe Graves' orbitopathy (GO) exhibit significant differences in efficacy and safety profiles.

Oral GCs (OGCs) are easier to administer but are less effective compared to intravenous therapy. Studies show that oral prednisone demonstrates efficacy in approximately 53% of patients with moderate-to-severe GO, but it is more frequently associated with adverse effects, such as Cushing's syndrome symptoms, hypertension, and metabolic disturbances. In contrast, intravenous GCs, such as methylprednisolone in pulse regimens, show higher therapeutic efficacy (up to 77%), particularly in reducing inflammatory symptoms like chemosis and restricted eye mobility. Intravenous therapy also acts faster and is associated with fewer adverse events, although higher doses can lead to severe complications, such as liver damage or cardiovascular incidents [46].

When comparing the methods of glucocorticoid administration, it is essential to also consider local treatments, such as subconjunctival or retrobulbar injections. These methods have shown limited effectiveness compared to systemic treatment, particularly when combined with orbital radiotherapy. While some studies have reported benefits, including reduced diplopia and improvement in upper eyelid retraction, these approaches are associated with risks such as elevated intraocular pressure, orbital lipomatosis, and retrobulbar hemorrhage [37].

In summary, intravenous GCs are more effective and safer in the treatment of active GO, especially when using moderate-dose protocols. Oral GCs remain a therapeutic option but should be used cautiously due to a higher risk of adverse effects. Local glucocorticoid therapy, due to its associated risks, is typically considered only for patients who are unable to tolerate systemic treatment. The choice of treatment depends on disease severity, patient age, and the risk of side effects [46,37].

Efficacy of glucocorticoids in controlling TED activity

According to the "Consensus Statement by the American Thyroid Association and the European Thyroid Association" [7], clinical studies have demonstrated the efficacy of GCs in controlling disease activity in TED, with intravenous glucocorticoids (IVGCs) outperforming oral glucocorticoids. IVGCs have shown improvement in disease activity, as measured by the CAS, in 58–83% of treated patients, compared to 51% with OGCs. For instance, a RCT involving 70 patients with active moderate-to-severe TED reported a reduction in median CAS from 5 to 2 in the IVGC group, versus a decrease from 5 to 3 in the OGC group. Overall, 77% of IVGC-treated patients achieved a CAS improvement of 3 points, compared to 51% in the OGC group. Another RCT found a reduction in mean CAS from 3.66 to approximately 1.65 in both eyes after 36 weeks of IVGC therapy.

In additional studies, 75% of patients treated with IVGCs achieved a CAS improvement of ≥2 points at 24 weeks, and 69% experienced disease inactivation (CAS <3). Furthermore, an RCT comparing different IVGC cumulative doses (2.25 g, 4.98 g, and 7.47 g) found that higher doses were associated with greater improvements, with CAS reductions of >2 points in 81–83% of patients at 12 weeks, compared to 58% in the low-dose group. These findings highlight the effectiveness of GCs, particularly IVGCs, in reducing inflammation and lowering the risk of disease progression in active TED [7].

Limitations and optimization of glucocorticoid therapy in TED

While corticosteroids remain the cornerstone of therapy for moderate-to-severe thyroid eye disease, their use is not without significant limitations. Systemic administration, particularly via intravenous routes, is preferred due to its higher efficacy compared to oral or local applications. However, IV glucocorticoid therapy is associated with several risks and potential adverse effects that necessitate careful consideration and monitoring.

Relapses occur in approximately 20% of patients following the completion of treatment, and compressive optic neuropathy (CON) may develop in a minority of cases (around 7.5%). The treatment's efficacy in reducing inflammation and improving ocular motility is generally observed within one to two weeks, but rare severe complications, such as acute liver failure, have been documented. Cases of liver failure were typically linked to cumulative doses of methylprednisolone exceeding 10 g, particularly in patients with pre-existing liver conditions. It is recommended to limit the cumulative dose to 6–8 g to minimize the risk of liver damage and screen patients for liver abnormalities and autoimmune conditions prior to initiating therapy [50].

Other reported risks include cerebrovascular and thromboembolic events, with deaths attributed to liver failure, cerebrovascular complications, and pulmonary embolism occurring in patients receiving higher cumulative doses (>8 g). Factors such as age over 53 years, high daily doses, and pre-existing hepatitis increase the likelihood of adverse effects. A 2011 review revealed a morbidity rate of 6.5% and a mortality rate of 0.57% among patients treated with IV steroids [50].

Steroid-induced bone loss is another concern, making it advisable to initiate preventive measures such as administering bisphosphonates like alendronate. Moreover, cumulative doses exceeding 4.5 g can potentially suppress the hypothalamic–pituitary–adrenal axis, further emphasizing the need to tailor therapy based on individual risk factors and disease severity. Despite their efficacy, glucocorticoid therapy requires a balance between benefits and potential risks, highlighting the importance of patient-specific treatment planning and vigilant monitoring during and after therapy.

Recent analyses reinforce the importance of adherence to European Guidelines, which recommend weekly IV glucocorticoid applications and a maximum cumulative dose of 8 g per treatment cycle. Adverse events, particularly severe cardiovascular and hepatic complications, were predominantly associated with cumulative doses exceeding these guidelines or daily, rather than weekly, administrations, as mentioned before [51]. Furthermore, pre-treatment screening of liver function, blood pressure, blood sugar, and cardiovascular health significantly reduces the likelihood of severe complications.

Following these recommendations ensures that IVGCs therapy remains both effective and well-tolerated for the majority of patients with active and severe TED [42, 52].
In conclusion, when tailored to individual patient needs and guided by current European recommendations, glucocorticoids offer a highly effective and well-tolerated treatment for moderate-to-severe TED, playing a pivotal role in improving patient outcomes while minimizing the risk of serious complications. Despite the potential for side effects, they remain the recommended therapy, with data strongly supporting the superiority of IVGCs over OGCs. Moreover, the response rate to immunosuppressive therapy, the therapeutic effectiveness of glucocorticoids, and health-related quality of life can be substantially enhanced by combining IVGCs with mycophenolate, a safe and effective drug [53], or by pairing oral GCs with cyclosporine, intravenous immunoglobulins, or orbital radiotherapy. [42]

Alternative Pharmacological Therapies for moderate-to-severe TED

In addition to GCs, several alternative pharmacological therapies are available for the treatment of moderate-to-severe thyroid eye disease, particularly for patients who are unresponsive, partially responsive, or intolerant to GCs. Rituximab, targeting CD20 on B cells, helps reduce antibody production and immune cell activation, offering potential for disease inactivation [54]. Tocilizumab, an interleukin-6 receptor blocker, decreases inflammation by inhibiting pro-inflammatory cytokine signaling [55]. Teprotumumab, a monoclonal antibody against the IGF-1 receptor, directly addresses orbital fibroblast activation, reducing proptosis and disease activity [56]. [7,37]
These therapies provide important alternatives for patients who do not respond to standard GC treatment, though further studies are needed to confirm their long-term efficacy, safety, and cost-effectiveness compared to glucocorticoids.

Pharmacotherapy for sight-threatening TED

Sight-threatening Graves' orbitopathy constitutes a medical emergency requiring immediate intervention. Vision impairment or loss may result from dysthyroid optic neuropathy (DON), severe corneal exposure and breakdown, or, in rare instances, eyeball subluxation leading to acute optic neuropathy. This can occur due to optic nerve stretching, elevated intraocular pressure, or corneal damage. [37] Based on the studies, the ETA has identified high-dose IVGCs as the first-line treatment for DON. Specifically, intravenous methylprednisolone (single doses of 500 to 1000 mg) is administered for three consecutive days or, preferably for safety reasons, on alternate days during the first week. This regimen can be repeated for a second week if necessary. If there is no response or if visual acuity or visual fields continue to deteriorate, non-pharmacological interventions become essential, with urgent orbital decompression surgery being mandatory.[37] Moreover, recent evidence suggests that mycophenolate, TEP, and TCZ may be effective in treating DON; however, their efficacy requires confirmation through randomized controlled trials. [7]

Conclusions

The management of thyroid eye disease (TED) requires a severity-based approach, with glucocorticoids playing a central role in moderate-to-severe and sight-threatening cases. For mild TED, selenium supplementation remains the recommended first-line therapy, offering measurable improvements in oxidative stress and quality of life. In moderate-to-severe TED, intravenous glucocorticoids (IVGCs) have demonstrated superior efficacy and safety profiles compared to oral administration, making them the treatment of choice. In sight-threatening TED, IVGCs are indispensable for their ability to rapidly control inflammation and prevent irreversible vision loss.

Although alternative therapies such as teprotumumab, rituximab, and tocilizumab are emerging options for glucocorticoid-resistant patients, their application remains secondary in clinical practice. Ensuring adherence to established glucocorticoid dosing protocols and pre-treatment evaluations is essential to minimizing risks, such as hepatotoxicity and cardiovascular complications. When used appropriately, glucocorticoids remain a highly effective and reliable treatment for managing TED, particularly in its more severe forms.

Disclosure

Author's contribution

Conceptualization: Julia Ryniecka and Maciej Wojszczyk; Methodology: Karol Dziedzic; Software: Filip Arczewski; Check: Michalina Wójcikiewicz and Marta Chuncia-Ileczko; Formal analysis: Julia Kacperczyk and Damian Zys; Investigation: Piotr Pasek and Julia Kulbacka; Resources: Julia Kulbacka; Data curation: Julia Ryniecka; Writing - rough preparation: Julia Ryniecka and Maciej Wojszczyk; Writing - review and editing: Julia Kacperczyk and Marta Chuncia-Ileczko; Visualization: Piotr Pasek; Supervision: Damian Zys; Project administration: Filip Arczewski and Karol Dziedzic; Receiving funding - no specific funding. 10 All authors have read and agreed with the published version of the manuscript.

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