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Teprotumumab as a Breakthrough in Thyroid Eye Disease Therapy: A Comprehensive Review

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ABSTRACT

Background. Thyroid Eye Disease (TED) is a complex autoimmune condition associated with Graves' disease, causing disfigurement, visual impairment, and reduced quality of life. For decades, options were limited to non-specific anti-inflammatory treatments like glucocorticosteroids and radiotherapy, often failing to address symptoms like proptosis and diplopia. Identifying the insulin-like growth factor-1 receptor (IGF-1R) as a driver of TED pathophysiology led to targeted therapies.

Aim. This study reviews teprotumumab as a breakthrough TED therapy, analyzing its mechanism, efficacy, and place in treatment algorithms relative to traditional methods.

Material and methods. A literature review was conducted using databases (PubMed, Embase, ClinicalTrials.gov) for articles up to November 2025. Analysis prioritized pivotal trials (OPTIC, OPTIC-X), meta-analyses, and reviews focusing on TED pathophysiology and IGF-1R inhibition.

Results. TED pathogenesis involves crosstalk between TSHR and IGF-1R on orbital fibroblasts, triggering inflammation and adipogenesis. While traditional treatments offer limited relief with side effects, teprotumumab, the first FDA-approved IGF-1R inhibitor, targets these

mechanisms. Clinical data shows superior efficacy in reducing proptosis and improving diplopia compared to palliative care.

Conclusions. Teprotumumab is a breakthrough in TED management, shifting from symptomatic to targeted disease modification. By addressing orbital remodeling causes, it offers distinct advantages over traditional therapies, fulfilling a major unmet need.

Keywords: targeted therapy, graves' ophthalmopathy, teprotumumab, grave´s orbitopathy, thyroid eye disease (ted), active thyroid eye disease

1. Introduction

Thyroid Eye Disease (TED) is a complex, autoimmune, inflammatory disease of the orbital tissues, representing the most common extrathyroidal manifestation of Graves' disease (GD) [1, 2]. Although it most frequently accompanies hyperthyroidism, it can also occur in patients who are euthyroid (10%), hypothyroid, or even in the course of Hashimoto's thyroiditis [1, 3, 4]. This condition, leading to significant disfigurement, impaired quality of life, and often threatening vision loss, has long been a major diagnostic and therapeutic challenge [3, 5]. For decades, the therapeutic arsenal was limited to non-specific methods, which were often associated with serious adverse effects and did not satisfactorily modify the course of the disease, especially concerning key symptoms such as proptosis (exophthalmos) and double vision (diplopia) [3, 6]. The long-standing search for an effective drug highlighted a huge, unmet medical need in this patient group. It was only the breakthrough discoveries regarding the pathophysiology of TED, particularly the identification of the key role of the insulin-like growth factor-1 receptor (IGF-1R), that paved the way for targeted therapies. The result of this research is teprotumumab-the first and, to date, the only drug approved by the U.S. Food and Drug Administration (FDA) specifically for the treatment of Thyroid Eye Disease, regardless of its activity [1, 7, 8].

Aim

The aim of this study is to present a comprehensive review of teprotumumab as a breakthrough therapy for Thyroid Eye Disease (TED), analyzing its mechanism of action, clinical efficacy, and placement in current treatment algorithms relative to traditional methods. The paper will discuss the pathophysiology of TED, emphasizing the critical role of the insulin-like growth factor-1 receptor (IGF-1R) pathway. It will also evaluate data from pivotal clinical trials regarding the drug's safety profile and its ability to reduce proptosis and diplopia compared to conventional, non-specific treatments. The collected data were carefully analyzed to identify consistent findings, clinical implications, and the shift in the therapeutic paradigm for patients with Graves' orbitopathy.

2. Research materials and methods

2.1. Participants (Literature Search Strategy)

A comprehensive literature review was conducted to identify relevant studies regarding the use of teprotumumab in Thyroid Eye Disease (TED). Electronic databases, including PubMed, Embase, and ClinicalTrials.gov, were searched for articles published up to November 2025. The search strategy focused on identifying pivotal clinical trials, meta-analyses, systematic reviews, and key publications elucidating the pathophysiology of TED, with a specific emphasis on the role of the insulin-like growth factor-1 receptor (IGF-1R).

2.2. Procedure/Measure/Instruments

The selection criteria prioritized high-quality evidence, including data from the OPTIC and OPTIC-X clinical trials. Articles were included if they provided significant data on the mechanism of action, clinical efficacy, safety profile, and the placement of teprotumumab in current treatment algorithms. Both historical context regarding non-specific therapies and recent breakthrough discoveries in targeted therapies were considered to provide a comprehensive overview.

2.3. Data collection and analysis

2.3.1. Statistical Software

As this study is a comprehensive narrative review of existing literature, no primary statistical software was utilized for meta-analysis or new statistical calculations. Data synthesis was performed qualitatively based on reported results in the included studies.

2.3.2. AI

Artificial Intelligence (AI) tools were utilized in the preparation of this manuscript. Specifically, a Large Language Model (LLM) was employed to assist in editing the text for better comprehension, clarity, and adherence to academic English standards. The AI tool served strictly as an assistive instrument for linguistic refinement; the final interpretation of data, selection of literature, and conclusions were determined solely by the authors.

2.3.3. Statistical Methods

The review analyzes descriptive statistics and efficacy outcomes (such as proptosis reduction and diplopia improvement) as reported in the primary source documents. No new statistical tests were applied to the aggregated data.

3. Research results

3.1. Epidemiology and Pathophysiology of Thyroid Eye Disease (TED)

Thyroid Eye Disease (TED) develops clinically in approximately 25-40% of patients with Graves' disease, while subclinical thickening of the extraocular muscles is found in nearly 70% on imaging studies [1, 3, 5]. The annual incidence in the general population is estimated at 16 cases per 100,000 women and 2.9 cases per 100,000 men [1, 3]. Although the disease is

2.5 to 6 times more common in women, its course is typically more severe in men and the elderly, more frequently leading to optic neuropathy [3, 4].The main risk factors include female sex, genetic predispositions (e.g., polymorphisms of HLA, CTLA-4, PTPN22 genes), uncontrolled thyroid dysfunction, high titers of antibodies against the thyrotropin receptor (TRAb), and smoking, which is the strongest modifiable risk factor, increasing the risk 7- to 8-fold, especially in patients undergoing radioiodine therapy [1, 3, 9]. The pathogenesis of TED is a multifactorial process centered on an autoimmune reaction against antigens shared by the thyroid and orbital tissues, particularly orbital fibroblasts (OFs) [3, 10]. For years, the TSH receptor (TSHR) was considered the primary autoantigen due to its expression on the surface of OFs [7]. However, more recent studies have established the critical importance of a physical and functional interaction between the TSHR and the insulin-like growth factor-1 receptor (IGF-1R). In patients with Graves' disease and TED, both receptors are overexpressed and form a signaling complex on the surface of orbital fibroblasts [5, 9]. Activation of this complex by autoantibodies, including both TSHR-stimulating immunoglobulins (TSI) and potentially IGF-1R-activating antibodies, triggers a cascade of pro-inflammatory and metabolic events in the orbit via signaling pathways such as PI3K/Akt and MAPK/ERK [2, 3, 7, 10]. The stimulation

of orbital fibroblasts initiates a complex pathological cascade. It provokes a potent inflammatory response through the release of pro-inflammatory cytokines (e.g., IL-6, IL-8, IL-16, TNF-α) and chemokines (e.g., RANTES/CCL5), which recruit and activate T and B lymphocytes, macrophages, and mast cells, leading to the formation of an inflammatory infiltrate in the orbital tissues [2, 3, 9]. Concurrently, this stimulation drives cell proliferation and differentiation, wherein a subpopulation of fibroblasts (CD34+) differentiates into mature adipocytes (adipogenesis) and myofibroblasts, resulting in an expansion of orbital fat volume and fibrosis of the extraocular muscles [3, 5, 10]. This tissue remodeling is further amplified by the excessive production of glycosaminoglycans (GAGs), predominantly hyaluronic acid. Due to its hydrophilic properties, hyaluronic acid sequesters water in the extracellular space, causing profound soft tissue edema and a consequent rise in intraorbital pressure and volume [4, 5]. Collectively, these pathological processes lead to the characteristic anatomical and physiological changes that define the clinical presentation of TED.

3.1.1 Clinical Presentation and Impact on Quality of Life

The clinical presentation of Thyroid Eye Disease (TED) is heterogeneous, with symptoms varying based on the phase and severity of the disease. Eyelid retraction is the most common sign, affecting over 90% of patients, and results from sympathetic overstimulation of the Müller's muscle combined with fibrosis and contraction of the levator palpebrae superioris muscle [3, 4]. Proptosis (exophthalmos), a characteristic axial protrusion of the eyeballs due to increased orbital tissue volume, is observed in approximately 60% of cases [3]. Other common manifestations include inflammatory signs of soft tissues, such as orbital pain (particularly with eye movements), eyelid edema and erythema, conjunctival edema (chemosis), and hyperemia at the insertion points of the extraocular muscles [6]. Diplopia (double vision), which affects about 40% of patients, is caused by restricted eye motility resulting from inflammation, edema, and subsequent fibrosis of the extraocular muscles, most frequently the inferior and medial rectus muscles [3]. The most serious complication is Dysthyroid Optic Neuropathy (DON), a vision-threatening condition that occurs in approximately 6% of patients. DON arises from the compression of the optic nerve at the orbital apex by enlarged muscles, leading to impaired color vision, decreased visual acuity, and visual field defects. It is considered a medical emergency requiring urgent intervention [1, 3, 6]. The natural course of TED, as first described by Rundle, is typically divided into two distinct phases [8]. The active (inflammatory) phase, which can last from 6 to 36 months, is characterized by prominent inflammatory signs. This period represents a critical "therapeutic window" where pharmacological interventions,

particularly immunomodulatory therapies, have the greatest potential to alter the disease's progression [1, 11]. Following this is the inactive (fibrotic or "burnt-out") phase, during which the inflammatory process subsides. However, established structural changes such as proptosis, muscle fibrosis, and eyelid retraction often persist, necessitating multi-stage surgical interventions [3, 5]. It is important to note that the disease can reactivate, with a relapse of the inflammatory phase occurring even after many years, which presents an additional therapeutic challenge [8]. Standardized scales are utilized for the objective assessment of disease activity and severity. The Clinical Activity Score (CAS) evaluates seven signs of inflammation, with a score of ≥3/7 indicating an active disease state [7]. For assessing severity, classifications such as the European Group on Graves' Orbitopathy (EUGOGO) or the NOSPECS scale are employed [4]. The disease has a profoundly negative impact on patients' quality of life (QoL), frequently leading to social isolation, depression, anxiety, and difficulties with daily activities like reading or driving. This is substantiated by specific questionnaires, such as the Graves' Orbitopathy Quality of Life (GO-QOL) survey, which consistently show significant impairment in both visual functioning and appearance-related domains [3, 5, 11].

3.1.2 Traditional Treatment Methods and Their Limitations

Before the era of targeted therapies, the treatment of TED was largely non-specific, palliative, and focused on suppressing the inflammatory process and alleviating symptoms.

Table 1: Comparison and Limitations of Conventional Therapies for Thyroid Eye Disease (TED)

Treatment	Indications and Mechanism	Efficacy and Limitations	References
Symptomatic treatment	Artificial tear preparations, lubricating gels, UV-filter glasses. Selenium (in mild TED)	Alleviation of ocular surface symptoms; no effect on the disease course	[4]
Glucocorticosteroids (GCS)	Treatment of active, moderate-to-severe TED. Anti-inflammatory and immunosuppressive action	Minimal effect on proptosis, numerous systemic adverse effects, high relapse rate after treatment cessation (up to 50%)	[6, 7, 8]

Orbital radiotherapy	Second-line therapy in active TED, often combined with GCS. Inhibition of fibroblast and lymphocyte proliferation	Limited and delayed efficacy, no effect on proptosis, risk of retinopathy (especially in diabetics) and cataracts	[3, 7]
Surgical treatment	Mainly in the inactive phase of the disease (decompression, strabismus surgery, eyelid correction) or as an emergency (DON)	Invasiveness, risk of complications, often requiring multi-stage procedures, does not treat the cause of the disease	[5, 8]
Other immunosuppressive drugs	Mycophenolate mofetil, rituximab, tocilizumab. Used off-label	Variable and often unconfirmed efficacy in large trials, potential for serious adverse effects	[6, 9]

Source: authors' own work.

The main, fundamental limitation of traditional methods was the lack of a therapy that could effectively, safely, and durably modify the course of the disease, particularly by reducing proptosis and diplopia-the symptoms most burdensome for patients and most strongly affecting their quality of life [3, 11]. The need to develop a targeted drug that acts directly on key pathogenetic mechanisms was urgent [7]. The identification of the IGF-1R/TSHR complex as a central point in the pathogenesis of TED became a milestone that enabled the development of teprotumumab. This drug, for the first time in history, demonstrated in randomized, placebo-controlled clinical trials the ability to achieve effects (especially in proptosis reduction) previously comparable only to invasive surgical treatment, revolutionizing the treatment paradigm for this debilitating disease [3, 10].

3.2 Teprotumumab: Mechanism of Action

Teprotumumab (TEPEZZA®) represents a breakthrough in the pharmacotherapy of Thyroid Eye Disease (TED), being the first and only targeted drug approved by the U.S. Food and Drug Administration (FDA) specifically for the treatment of this disease [7, 12]. It is a fully human monoclonal antibody of the IgG1 class that shifts the therapeutic focus from non-specific suppression of inflammation to a precise impact on the key pathophysiological mechanisms of TED [13]. The molecular target of teprotumumab is the insulin-like growth factor 1 receptor (IGF-1R). This receptor is overexpressed on the surface of orbital fibroblasts

(OFs) and circulating fibrocytes in patients with TED, making it a central point in the pathogenetic cascade [12, 13]. Studies have shown that orbital fibroblasts from patients with Thyroid Eye Disease can exhibit up to a threefold greater expression of IGF-1R on their surface compared to cells from healthy individuals [14]. This mechanism is twofold: it not only inhibits signal transduction but also induces the internalization and degradation of the antibody-receptor complex, which further weakens the pathological cellular response [14]. The inhibition of IGF-1R by teprotumumab effectively interrupts the signaling cascade that drives the two main processes underlying TED: inflammation and remodeling of orbital tissues. Anti-inflammatory action: The activation of IGF-1R, often in synergy with the thyrotropin receptor (TSHR) with which it forms functional complexes, leads to increased production of pro-inflammatory cytokines [7, 13]. By blocking this pathway, teprotumumab inhibits the orbital fibroblast-dependent production of potent chemoattractants for T-lymphocytes, such as interleukin 16 (IL-16) and the chemokine RANTES (CCL5). This leads to a reduction in the recruitment of immune cells to the orbital tissues, which in clinical trials translates to a rapid and significant reduction in the Clinical Activity Score (CAS) [5, 14]. Limitation of tissue remodeling: The pathological activation of orbital fibroblasts stimulates them to overproduce glycosaminoglycans (GAGs), including hyaluronic acid, and to differentiate into adipocytes and myofibroblasts [15]. The accumulation of hydrophilic GAGs and the proliferation of adipose tissue lead to an increase in the volume of soft orbital tissues, which clinically manifests as proptosis. By blocking IGF-1R, teprotumumab inhibits these processes, directly leading to a reduction in the volume of extraocular muscles and orbital fat, and consequently, a decrease in proptosis [5, 14]. The uniqueness of the therapeutic approach with teprotumumab lies in its precise targeting of the central molecular mechanism of the disease, rather than merely alleviating its symptoms. In contrast to historically used glucocorticosteroids, which act non-selectively as immunosuppressants and often fail to provide satisfactory improvement in proptosis reduction, teprotumumab directly targets the IGF-1R/TSHR pathway, which is crucial for the activation of orbital fibroblasts [7, 13]. As a result, this drug effectively reduces both inflammation and its long-term consequences in the form of tissue remodeling, offering for the first time the possibility of modifying the natural course of the disease.

3.3 Clinical Evidence: Key Studies

The efficacy and safety of teprotumumab in the treatment of Thyroid Eye Disease (TED) have been thoroughly evaluated in a series of key clinical trials. This subsection discusses the

most important of these, which formed the basis for the drug's approval by the Food and Drug Administration (FDA) and revolutionized the therapeutic approach to TED.

3.3.1 Phase II Study: First Evidence of Efficacy

The first breakthrough study that provided evidence of teprotumumab's efficacy was a randomized, double-blind, placebo-controlled Phase II clinical trial [7]. It enrolled patients with active, moderate-to-severe TED, with a disease duration not exceeding 9 months and a Clinical Activity Score (CAS) of at least 4. The primary endpoint was the overall response to treatment at week 24, defined as a simultaneous reduction in proptosis of at least 2 mm and a decrease in the CAS score of at least 2 points. The results were unequivocal: as many as 69% of patients in the teprotumumab group achieved this goal, compared to only 20% in the placebo group ($p < 0.001$) [16]. This study also demonstrated a significant improvement in secondary endpoints, such as proptosis reduction, decrease in inflammation (CAS), and improvement in quality of life, paving the way for further, larger-scale studies [7, 16].

3.3.2 Phase III Study - OPTIC

The OPTIC study (Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study) was a pivotal, multicenter Phase III trial that confirmed and solidified the results obtained in Phase II [5]. This was a randomized, double-blind, placebo-controlled clinical trial in which patients received eight intravenous infusions of teprotumumab or placebo over 24 weeks [5]. The inclusion criteria for the patient population were similar to the Phase II study, with eligible participants being adult patients (18-80 years old) with active TED (CAS ≥ 4) of recent onset (≤ 9 months) who had moderate-to-severe disease [5, 17]. The primary endpoint was to assess the percentage of patients who achieved a reduction in proptosis of at least 2 mm in the more affected eye from baseline at week 24 of therapy [5]. The study met its primary endpoint with high statistical significance, as 83% of patients treated with teprotumumab achieved the required reduction in proptosis, whereas in the placebo group, this rate was only 10% ($p<0.001$) [7, 13]. The mean reduction in proptosis in the study group was 3.32 mm compared to 0.53 mmin the placebo group [16]. Furthermore, analysis of secondary endpoints showed that teprotumumab also demonstrated a significant advantage over placebo across all key secondary outcomes; specifically, 59% of patients in the teprotumumab group achieved a CAS score of 0 or 1 (indicating no or minimal inflammation) compared with 21% in the placebo group [5]. Among

patients with baseline diplopia who received teprotumumab, 68% experienced an improvement of at least one grade on the Gorman scale, versus 29% in the placebo group [5]. Finally, patients treated with teprotumumab reported a significant improvement in quality of life as measured by the disease-specific GO-QoL (Graves' Ophthalmopathy Quality of Life) questionnaire [7, 16].

3.3.3 Extension Study - OPTIC-X

The OPTIC-X (Open-Label Extension Study) was designed to evaluate the long-term efficacy and safety of the treatment, as well as to investigate the effects of therapy in patients who had initially received a placebo in the OPTIC study [17].The primary objective was to allow patients from the OPTIC study who did not respond to treatment (including all from the placebo group) or who experienced a disease relapse to receive a full, 24-week course of teprotumumab in an open-label setting [17]. Results demonstrated strong efficacy in placebo-group patients, as those who had previously received a placebo, after switching to teprotumumab therapy, achieved results comparable to those observed in the active treatment group of the original OPTIC study; specifically, as many as 89.2% of them met the primary endpoint (proptosis reduction of ≥2 mm) [17]. Importantly, the median duration of TED in this crossover group was longer (12.9 months), suggesting that teprotumumab is also effective in patients in a later phase of the active disease [17]. Furthermore, the durability of the therapeutic effect was confirmed by long-term analysis of patients who responded to treatment in the Phase II and III trials, which showed that at 51 weeks after the end of therapy (week 72 visit), approximately 67% of patients maintained a proptosis reduction of ≥2 mm, and nearly 90% maintained an improvement in the composite ophthalmic index [18].During the 99-week period following the end of treatment, only 17.9% of patients required additional therapeutic interventions (including surgery) for TED [18]. The results of these key studies unequivocally confirmed that teprotumumab is a highly effective and breakthrough therapy that not only alleviates inflammatory symptoms but, most importantly, modifies the course of the disease, leading to a significant and lasting reduction in proptosis and diplopia, which translates into a fundamental improvement in patients' quality of life.

3.4 Current Treatment Strategies with Teprotumumab

The introduction of teprotumumab, the first drug approved by the U.S. Food and Drug Administration (FDA) specifically for the treatment of Thyroid Eye Disease (TED), marked a

breakthrough in the therapeutic approach to this condition [19, 20]. As a human monoclonal antibody targeting the insulin-like growth factor-1 receptor (IGF-1R), teprotumumab offers a mechanism of action aimed at the key pathophysiological processes of TED, including inflammation and tissue remodelling [19, 21].

3.4.1 Indications for Treatment

Teprotumumab is indicated for the treatment of patients with active, moderate-to-severe Thyroid Eye Disease [21]. Qualification for therapy is based on a comprehensive clinical assessment, in which the evaluation of disease activity and severity plays a crucial role. The Clinical Activity Score (CAS) is most commonly used to assess TED activity. A patient with a CAS of 3 or more (out of 7) at the initial visit or 4 or more (out of 10) in subsequent examinations is considered to be in the active phase of the disease [22]. A high CAS score, indicating a significant inflammatory process (e.g., retrobulbar pain, eyelid edema and erythema, conjunctival edema), is one of the main criteria for qualifying for teprotumumab treatment. In addition to the CAS scale, the clinical assessment includes the classification of symptom severity according to guidelines such as those developed by the European Group on Graves' Orbitopathy (EUGOGO). The moderate-to-severe category is characterized by, among other things, significant eyelid retraction (≥2 mm), proptosis (≥3 mm above normal), and persistent diplopia, which significantly impact the patient's daily functioning and quality of life [19, 22].

3.4.2 Dosing Regimen

The standard treatment protocol for teprotumumab, which was established and used in pivotal clinical trials, consists of a course of eight intravenous infusions administered every three weeks [20]. The dosing regimen begins with an initial dose (first infusion) of 10 mg/kg of body weight, followed by the subsequent seven infusions, each administered at a dose of 20 mg/kg of body weight. The total duration of therapy is approximately 21 weeks, and this specific regimen was designed to achieve an optimal clinical response, including a reduction in proptosis and diplopia, and a measurable improvement in the patient's overall quality of life [19, 21].

3.4.3 Safety Profile and Adverse Effects

Teprotumumab is generally well-tolerated, but its use is associated with the risk of adverse effects resulting from the systemic inhibition of the IGF-1R signaling pathway [20]. The most commonly reported adverse effects include: muscle spasms, nausea and

gastrointestinal disordersAlopecia (usually transient), fatigue, hyperglycemia and hearing impairment. Particular attention should be paid to hyperglycemia, which is an effect of the disruption of the growth hormone (GH)-IGF-1 axis and can lead to insulin resistance. This risk is higher in patients with pre-existing diabetes or pre-diabetes. Close monitoring of blood glucose is recommended for these patients before and during therapy, as well as modification of hypoglycaemic treatment if necessary [20]. Another significant adverse effect is hearing impairment, the spectrum of which includes a feeling of ear fullness, tinnitus, and, in rare cases, sensorineural hearing loss (SNHL) [19, 20]. Due to the potentially irreversible nature of some of these changes, audiological monitoring of patients is crucial before starting and during treatment, especially if they report any hearing-related symptoms.

3.4.4 Contraindications and Warnings

Teprotumumab is contraindicated in pregnancy due to potential fetal risk. Female patients of reproductive potential must use effective contraception during therapy and for a specified period after its completion. Caution should also be exercised in patients with inflammatory bowel disease (IBD), as exacerbations of the disease have been reported during treatment [20]. When deciding on therapy, the balance of potential benefits and risks should be considered on a case-by-case basis, taking into account the patient's individual circumstances and preferences [20].

3.5 The Place of Teprotumumab in the TED Treatment Algorithm

The introduction of teprotumumab, the first drug approved by the Food and Drug Administration (FDA) specifically for the treatment of Thyroid Eye Disease (TED), represents a turning point in the therapeutic approach to this condition [7, 23]. As a targeted inhibitor of the insulin-like growth factor 1 receptor (IGF-1R), teprotumumab offers a novel mechanism of action that distinguishes it from previously used, non-specific treatment methods [7, 24]. Its emergence necessitates a re-evaluation of traditional algorithms and opens a discussion about a new paradigm in the treatment of TED.

3.5.1 Comparison of Teprotumumab with Traditional Treatment Methods

The efficacy and safety profile of teprotumumab should be considered in the context of the previous standard of care, which was primarily based on intravenous glucocorticosteroid therapy in the active phase and surgical interventions in the chronic (inactive) phase [23, 25]. The table below presents the key differences between these approaches.

Table 2: Comparison of teprotumumab with traditional methods of TED treatment.

Feature	Teprotumumab	IV Glucocorticosteroids	Surgical Decompression	References
Mechanism	Targeted (IGF-1R inhibitor)	Non-specific, anti-inflammatory	Mechanical expansion of orbital volume	[7, 23, 25]
Disease Phase	Active (clinical trials), growing evidence in chronic phase	Active	Mainly inactive (or urgent indications, e.g., optic neuropathy)	[7, 23, 24, 25]
Main Effect	Reduction of proptosis, inflammation, diplopia	Reduction of inflammation	Reduction of proptosis, optic nerve decompression	[7, 23, 24, 25]
Reversibility	Potentially modifies the course of the disease	Suppresses symptoms, frequent relapses after discontinuation	Irreversible anatomical change	[23, 25]
Key Risks	Hyperglycemia, hearing disorders (tinnitus, hearing loss), muscle complaints	Metabolic disorders, psychosis, liver damage	Diplopia, vision loss, infections	[23, 24, 26]

Source: authors' own work.

3.5.2 Discussion on the New Paradigm: Can Teprotumumab Replace or Postpone the Need for Surgical Intervention?

Traditionally, surgical treatment, such as orbital decompression, was reserved for patients in a stable, inactive phase of the disease to correct permanent consequences like proptosis or diplopia [23, 25]. Interventions in the active phase were limited to cases threatening vision loss, such as in dysthyroid optic neuropathy [23]. Teprotumumab, as the first drug to demonstrate a significant reduction in proptosis in clinical trials, challenges this established division [7]. Its ability to reduce proptosis during the active phase of the disease creates the

possibility of avoiding or postponing the need for orbital decompression [25]. Moreover, reports are emerging about the efficacy of teprotumumab in patients with chronic, inactive TED, for whom surgery was previously the only option [24]. In a study involving patients with chronic disease and a low clinical activity score (CAS ≤1), a clinically and statistically significant reduction in proptosis was observed after teprotumumab therapy [24]. These observations suggest a fundamental shift in the treatment algorithm. Teprotumumab may become a first-line therapy not only for managing inflammation but also for treating the key symptom of proptosis, potentially reducing the number of patients who will require reconstructive procedures in the future.

3.5.3 The Role of Therapy in Preventing Progression to the Fibrotic Phase

The pathogenesis of TED involves an inflammatory phase, characterized by edema and cellular infiltration, which over time transitions into a fibrotic (inactive) phase, leading to permanent changes in the orbital tissues [23, 25]. Traditional treatment with glucocorticosteroids, although effective at suppressing inflammation, often does not prevent the development of fibrosis, and disease activity frequently relapses after its discontinuation [23]. Teprotumumab, by inhibiting the IGF-1R signaling pathway which plays a key role in adipogenesis and the deposition of glycosaminoglycans, can influence the processes underlying tissue remodeling [7, 25]. By acting at an earlier stage of the pathogenetic cascade, this therapy has the potential not only to alleviate symptoms but also to modify the natural course of the disease. By effectively and rapidly suppressing inflammatory activity and reducing soft tissue volume, teprotumumab may limit the degree of fibrosis and prevent the formation of permanent, irreversible changes. Such an intervention could significantly reduce the percentage of patients who develop complications requiring multi-stage surgical treatment in the chronic phase, thereby improving long-term functional and aesthetic outcomes.

4. Discussion

The introduction of teprotumumab into clinical practice represents a fundamental shift in the approach to treating Thyroid Eye Disease (TED), moving the paradigm from symptomatic therapy to disease-modifying treatment. It is the first and, to date, the only FDA-approved drug that has demonstrated efficacy not only in reducing inflammation but also in decreasing the key symptom of proptosis to a degree comparable to surgical orbital decompression [27].

4.1 Synthesis of Results

Previous standards of care, based mainly on intravenous glucocorticosteroids, had a limited impact on proptosis and were characterized by a significant relapse rate [27]. Teprotumumab, as an inhibitor of the insulin-like growth factor-1 receptor (IGF-1R), targets key pathogenetic mechanisms of TED, which translates to its high efficacy. Clinical trials have shown that the therapy leads to a significant reduction in proptosis, improvement in diplopia (double vision), and a decrease in the Clinical Activity Score (CAS) in patients with active, moderate-to-severe TED [27, 28]. Importantly, the drug has also proven effective in a population of patients with chronic, inactive disease, opening new therapeutic possibilities for a group of patients for whom surgical intervention was previously the only option [29]. The benefits of teprotumumab therapy extend beyond objective clinical measures. Studies confirm that the treatment leads to a significant and rapid improvement in patients' quality of life (QoL). Analyses using the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire have shown a significant improvement in both the visual function and appearance subscales after just a few infusions of the drug. This improvement is often greater than that observed after treatment with glucocorticosteroids or even after surgical decompression, which underscores the holistic impact of the therapy on patient well-being [7].

4.2 Long-term Efficacy and Safety

Data on the durability of treatment effects are limited. Although preliminary analyses suggest that improvement is maintained in some patients even one year after completing therapy, rates of relapse and disease reactivation are a concern. One retrospective study showed that 47% of patients who initially responded to treatment experienced disease reactivation, defined as a worsening of proptosis and CAS. Two years after therapy, only 33% of patients maintained a durable response [28]. Particular attention is paid to the profile of adverse events. The most commonly reported include hearing-related disorders, such as hearing loss, tinnitus, and a feeling of fullness in the ear. Recent commentaries suggest that hearing impairment is a significant concern and may be more frequent and chronic than initially reported in clinical trials [27]. Among the known side effects of teprotumumab are ototoxicity (hearing impairment and tinnitus) and hyperglycemia. Another significant adverse event is hyperglycemia, which occurs especially in patients with diabetes or pre-diabetes. This requires close monitoring of blood glucose levels and potential modification of hypoglycemic treatment during teprotumumab therapy [30].

4.3 Treatment of Relapses

The high rate of disease relapse after the standard 8-infusion cycle questions the optimal management strategy. There are no clear guidelines for treating reactivation. Although there are reports of the effectiveness of retreatment with teprotumumab, it is not clear whether this approach is safe and cost-effective in the long term [27]. It is necessary to define predictive markers for relapse to identify patients who may require longer treatment or maintenance therapy.

4.4 Use in Other Populations

Initial clinical trials focused on patients with a short duration of active, moderate-to-severe TED. Subsequent data, including a randomized placebo-controlled trial, have confirmed the efficacy of teprotumumab in patients with chronic, inactive disease (CAS $\leq$ 1) and significant proptosis, showing a statistically significant reduction in exophthalmos [29]. This opens a path to treating patients who have passed the inflammatory phase but struggle with permanent morphological changes. Further research is needed to evaluate its efficacy in patients with milder forms of TED and to determine the safety and dosage in the pediatric population.

4.5 Therapy Optimization

The standard treatment protocol involves 8 infusions at 3-week intervals. However, the forced interruption of therapy in some patients due to the COVID-19 pandemic unexpectedly provided data suggesting that shorter treatment courses (an average of 4.2 infusions) can also lead to a significant and sustained reduction in proptosis and CAS [31]. These observations raise the question of whether therapy can be individualized and whether shorter, potentially more cost-effective regimens can be used. The potential benefits of combination therapies, for example with mycophenolate, which is standard with glucocorticosteroids, should also be investigated [29]. Sequential therapies, such as starting with glucocorticosteroids to quickly control inflammation and then introducing teprotumumab, also require evaluation in clinical trials.

4.6 Availability and Cost

One of the biggest barriers to the widespread use of teprotumumab is its extremely high cost, estimated at over $300,000 for a full course of treatment [27]. This poses a serious

challenge to healthcare systems worldwide and leads to inequities in access to treatment. The limited availability of the drug outside the United States further exacerbates this problem [27]. It has been suggested that despite the very high cost of teprotumumab therapy, it may be considered cost-effective in the future. This is based on the hypothesis that its effectiveness in reducing proptosis could allow patients to avoid or reduce the number of multi-stage surgical interventions (e.g., orbital decompression), which could offset the initial treatment costs [27]. However, it is emphasized that there is currently a lack of formal pharmacoeconomic analyses to confirm this.

4.7 Future Therapies

The success of teprotumumab is stimulating research into new therapeutic targets in the pathogenesis of TED. In addition to the IGF-1R pathway, other molecules and receptors involved in the autoimmune and inflammatory process are of interest. Clinical trials are underway for new drugs, such as batoclimab (an FcRn inhibitor) and linsitinib (an oral IGF-1R inhibitor), which may offer alternative or complementary therapeutic options [32, 33]. The development of targeted therapies, potentially with a more favorable safety profile, lower costs, or a more convenient route of administration (e.g., oral or subcutaneous), is crucial for the future of TED treatment[33].

5. Conclusion

Teprotumumab represents a paradigm shift in Thyroid Eye Disease (TED) management as the first approved targeted, disease-modifying therapy. By inhibiting the insulin-like growth factor-1 receptor (IGF-1R), it uniquely addresses both inflammation and proptosis, achieving significant, non-surgical reductions in orbital tissue volume. Its proven efficacy in rapidly improving clinical activity scores, proptosis, and diplopia has established it as a cornerstone therapy for active, moderate-to-severe TED, challenging the traditional first-line role of glucocorticosteroids. This allows for earlier, more effective intervention that can alter the disease's natural course and potentially obviate the need for subsequent corrective surgeries. The success of teprotumumab has validated the targeted therapy approach, catalyzing research into new molecular pathways and promising a future of more personalized, effective, and less burdensome treatments for TED.

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Author contributions

Conceptualization, M.M. and M.P.; Methodology, E.K.; Software, P.B.; Validation, H.D., J.Ż., P.B., E.K., A.O., J.B., J.B., M.M., F.C.; Formal Analysis, H.D., A.O., F.C., J.Ż., P.B., M.P., E.K., J.B., J.B., M.M.; Investigation, H.D. and M.M.; Resources, H.D., A.O., J.Ż., P.B., M.P., E.K., F.C., J.B., J.B., M.M.; Data Curation, H.D., A.O., J.Ż., P.B., F.C., M.P., E.K., F.C., J.B., J.B., M.M.; Writing – Original Draft Preparation, H.D., A.O., J.Ż., P.B., F.C., M.P., E.K., J.B., J.B., M.M.; Writing – Review & Editing, M.M. and M.P.; Visualization, E.K., F.C.; Supervision, J.Ż.; Project Administration, M.M.

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Conflict of interest

The authors declare there are no conflicts of interest.

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