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EFFICACY OF TOCILIZUMAB IN RESISTANT FORMS OF THYROID EYE DISEASE

Abstract: Thyroid Eye Disease (TED), formerly known as Graves' orbitopathy, is an autoimmune disorder affecting orbital tissues. The Clinical Activity Score (CAS) is used to evaluate TED activity. A score ≥3 indicates active disease, warranting immunomodulatory therapy. Intravenous corticosteroids (IVCS) are the first-line treatment. However, studies show 20–30% of patients with moderately severe active TED have an inadequate response to corticosteroids. For patients with poor response or tolerance to steroids, tocilizumab offers an effective alternative. We present a case of a 49-year-old female with moderately severe, active, corticosteroid-resistant TED. After failure of two corticosteroid regimens (4.5 g and 5 g), biological therapy with tocilizumab (6 cycles of 600 mg every 4 weeks) was initiated. Clinical response was monitored using NOSPECS, CAS, and the Gorman-Bahneman diplopia classification. This case confirms the potential efficacy of tocilizumab in managing corticosteroid-resistant, moderately severe active TED.

Keywords: TED, Tocilizumab, orbitopathy

CASE REPORT:

A 49-year-old female jeweler presented in July 2023 with bilateral eyelid swelling and significant ocular irritation (burning, scratching, photophobia). Concurrently, she was diagnosed with hyperthyroidism (TRAb 6.3) and initiated on Thiamazole. Due to intolerance, the drug was switched to Propylthiouracil (PTU). By December 2023, she began experiencing intermittent diplopia, mainly in extreme left, right, and upward gaze, followed by painful eye movements. Diplopia gradu-

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ally worsened and became constant (Gorman-Bahneman grade 2). TRAb levels increased (TRAb 8.4).

In March 2024, during her first hospitalization at the Clinic for Endocrinology, Diabetes and Metabolic Diseases (University Clinical Center of Serbia), moderately severe, active TED was diagnosed (PAOD 13 mm; PAOS 11 mm; Hertel OD 19-20 mm, OS 21 mm; CAS 4; VOD 0.5 corrected to 0.9; VOS 0.7 corrected to 0.9). An initial corticosteroid protocol (4.5 g cumulative) was applied. Disease progression was noted (constant diplopia in all directions – grade 3; CAS 5), and a second high-dose protocol (6 × 750 mg + 500 mg methylprednisolone) was administered. Clinical symptoms persisted, prompting initiation of biological therapy with six doses of tocilizumab (600 mg every 4 weeks). Significant improvement followed (NOSPECS: OD 2 0; 3 0; 4 ; 5 0; 6 0; OS: 2 0; 3 0; 4 0; 5 0; 6 0; CAS OU 0; Gorman-Bahneman grade 2; VOD 0.8 corrected to 0.9; VOS 0.6 corrected to 0.9), along with >2 mm reduction in proptosis (Table 2).

DISCUSSION:

TED, or Graves' orbitopathy, is a complication of thyroid disease, most commonly associated with hyperthyroidism. However, ~10% of TED patients are euthyroid or hypothyroid. TED is more prevalent in females and tends to have a poorer prognosis after age 50. Epidemiological data varies, with TED occurring in 25–50% of patients with Graves' disease. Tanda et al. reported an incidence of 16 per 100,000 women and 2.9 per 100,000 men. Subclinical TED cases may go undetected without imaging, despite active orbital inflammation.

Two hallmark clinical signs are eyelid retraction and "lid lag" (delayed upper eyelid descent in downward gaze). CAS evaluates disease activity using seven parameters:

1. Spontaneous retrobulbar pain (1 point)
2. Pain during eye movement (1 point)
3. Eyelid erythema (1 point)
4. Eyelid edema (1 point)
5. Conjunctival redness (1 point)
6. Conjunctival edema – chemosis (1 point)
7. Swelling of caruncle and plica (1 point)

Table 1. NOSPECS Classification of Thyroid Eye Disease

Grade	Description	Subgrades (if applicable)
0	**No signs or symptoms**	-
I	**Only signs (no symptoms)**	Usually lid retraction or lid lag
II	**Soft-tissue involvement**	
a	Absent	
b	Minimal	Mild periorbital edema, conjunctival injection
c	Moderate*	Obvious edema, redness, chemosis
d	Marked*	Severe soft-tissue signs, inflammation
III	**Exophthalmos (Proptosis)**	
a	Absent	
b	Minimal	Slight bulging
c	Moderate	Easily visible proptosis
d	Marked	Severe protrusion of globe
IV	**Extraocular muscle involvement**	
a	Absent	
b	Limitation of motion in extremes of gaze	
c	Evident restriction of motion	Diplopia in primary gaze
d	Fixation of globe(s)	Very restricted or absent motion
V	**Corneal involvement**	
a	Absent	
b	Stippling of cornea	Punctate keratopathy
c	Ulceration	
d	Clouding, necrosis, or perforation	Severe vision-threatening condition

VI	Sight loss (due to optic nerve compression)	
a	Absent	
b	Visual acuity 0.63 – 0.5	Mild reduction
c	Visual acuity 0.4 – 0.1	Moderate to severe impairment
d	Visual acuity <0.1 or no light perception	Legal blindness or worse

A CAS score ≥3 indicates active TED warranting immunomodulatory therapy. Alongside diplopia, which severely impairs quality of life, optic neuropathy occurs in ~5% of patients. Imaging typically shows spindle-shaped enlargement of affected muscles with tendon sparing. TRAb is a key marker in TED but TRAb-negative euthyroid patients present diagnostic challenges and require differentiation from other orbital pathologies.

The GO-QOL (www.eugogo.eu) questionnaire assesses quality of life in TED. Imaging (CT/MRI) supports diagnosis and is essential in atypical cases or optic nerve compression. CT is particularly important pre-decompression surgery.

First-line therapy includes IV methylprednisolone: 500 mg weekly for 6 weeks, followed by 250 mg weekly for another 6 weeks (total dose: 4.5 g). IV is preferred over oral for better efficacy and fewer side effects. Patients must be monitored for adverse effects and given gastroprotection during this 12-week protocol. The 2021 EUGOGO guideline (Bartalena et al.) allows for higher doses in severe cases but advises a cumulative limit of 8 g per treatment cycle. Response rates are 70–80%, but some patients are steroid-refractory or worsen.

In our center, the most commonly used second-line therapy in steroid-resistant TED is tocilizumab – a monoclonal IL-6 receptor antibody. IL-6 enhances TSH receptor expression in fibroblasts; tocilizumab blocks this pathway. It is administered intravenously at 4–8 mg/kg every 4 weeks. Subcutaneous administration (162 mg weekly) has also shown efficacy in several cases.

The systematic review “Efficiency and Safety of Tocilizumab for the Treatment of Thyroid Eye Disease” showed the highest efficacy in reducing clinical activity (up to 3 points), with a recurrence rate of 8.2%. The meta-analysis highlighted the drug’s notable effect on proptosis reduction.

Table 2. Clinical Response Monitoring During TED Treatment

Parameter	Before 4.5g Steroids	Before Tocilizumab	After Tocilizumab	3 Months Post-Tocilizumab
1. Retrobulbar pain	No (0)	No (0)	No (0)	No (0)
2. Pain with eye movement	No (0)	No (0)	No (0)	No (0)
3. Eyelid redness	Yes (1)	Yes (1)	No (0)	No (0)
4. Conjunctival redness	No (0)	Yes (1)	No (0)	No (0)
5. Eyelid edema	Yes (1)	Yes (1)	No (0)	No (0)
6. Chemosis	Yes (1)	Yes (1)	No (0)	No (0)
7. Plica/Caruncle swelling	Yes (1)	No (1)	No (0)	No (0)
CAS score	4	5	0	0
Diplopia (Gorman-Bahneman)	Grade 2	Grade 3	Grade 0	Grade 0
Hertel (OD/OS)	20 / 21 mm	23 / 23 mm	19 / 19 mm	16 / 17 mm
TRAb	4.5	2.1	1.5	1.7

Legend: GK – glucocorticoids; TOCI – Tocilizumab; CAS – Clinical Activity Score; OD – right eye; OS – left eye

CONCLUSION:

This case presents a patient with moderately severe, active corticosteroid-resistant TED who achieved significant therapeutic improvement with tocilizumab. This IL-6 receptor blocking agent may serve as a viable alternative in persistent, progressive, or relapsing TED, including vision-threatening forms (e.g., dysthyroid optic neuropathy). In this case, CAS was reduced to 0, diplopia resolved, and proptosis reduced by 4 mm. Despite promising results, further studies are needed to establish clear indications for biological therapy in TED.

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