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Long-term remission of corticosteroid-resistant Graves' orbitopathy after therapy with tocilizumab

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The management of Graves' orbitopathy (GO) remains a challenge. High-dose, intravenous glucocorticoid (GC) therapy is still considered in many countries to be the treatment of choice in patients with active, moderate-to-severe GO. However, GCs are effective in only 45–80% of patients, with a high probability of disease relapse (10–40%) [1, 2]. According to current guidelines, the use of tocilizumab (TCZ), a monoclonal antibody against interleukin 6 (IL-6) receptor, has been proposed as on of the second-line therapies [1–3].

A 40-year-old female with a 3-year history of GO was referred to our combined GO centre (Fig. 1). She had previously received 2 courses of intravenous methylprednisolone therapy, with cumulative doses of 4.25 g and 7.5 g, respectively. Radiotherapy (20 Gy in 10 fractions) and oral GCs were also administered. A year prior to referral, she underwent bilateral endoscopic orbital medial wall decompression combined with lateral wall decompression of the right eye. The patient had an 8-year history of Graves' hyperthyroidism. She had received 2 courses of radioiodine therapy and underwent a total thyroidectomy. On the referral, she was on adequate substitution with L-thyroxine. She had quit smoking 3 years ago. On admission to our department, the patient presented with active, moderate-to-severe GO. She experienced spontaneous retrobulbar pain and pain upon attempted up or lateral gaze, while a physical examination revealed soft tissue signs of active GO, resulting in a total Clinical Activity Score (CAS) of 6/7 (Tab. 1). Exophthalmometry measurements showed proptosis in both eyes (28 mm in the right eye, 27 mm in the left eye) associated with significant lagophthalmos. Restriction of eye movement during upward gaze was observed, along with intermittent diplopia. The patient received low score in the GO quality-of-life (GO-QOL) questionnaire for visual functioning (17/100) and appearance (31/100).

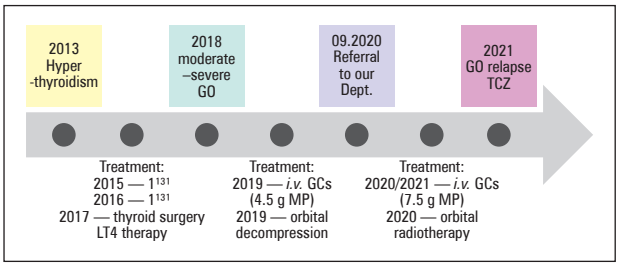

Figure 1. *Patient's journey throughout the course of her Graves' Orbitopathy treatment. GO — Graves' orbitopathy; TCZ — tocilizumab; GCs — glucocorticoids; MP — methylprednisolone; i.v. — intravenous*

In May 2021, after obtaining approval from the Local Bioethics Committee and the patient's written informed consent for off-label use, TCZ therapy was initiated according to a protocol used in a previous clinical trial [4]. The treatment involved intravenous infusion of TCZ at a dose of 8 mg per 1 kg of body weight, and was repeated once-monthly for 4 months. Therapy was well tolerated. Over the following four months, the patient exhibited significant and rapid improvement in signs and symptoms of GO. The pain resolved, and the CAS score decreased to 2/7. Exophthalmos was notably reduced, with only minor lagophthalmos remaining. The patient experienced remission of diplopia (Fig. 2, Tab. 1). Dry eye syndrome improved. A significant improvement in the GO-QOL questionnaire was observed.

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Table 1. *Evaluation of clinical findings during 2 years after tocilizumab administration in a patient with Graves' orbitopathy*

Characteristics	Before treatment		3 months after treatment		2 years after treatment	
CAS	OD 6/7	OS 6/7	OD 2/7	OS 2/7	OD 2/7	OS 2/7
Spontaneous retrobulbar pain	+	+	–	–	–	–
Pain on attempted upward or lateral gaze	+	+	–	–	–	–
Redness of the eyelids	–	–	–	–	–	–
Redness of the conjunctiva	+	+	–	–	–	–
Swelling of the eyelids	+	+	+	+	+	+
Chemosis	+	+	–	–	–	–
Inflammation of the caruncle	+	+	+	+	+	+
Lid retraction [mm]	OD 2	OS 2	OD 1	OS 1	No retraction	No retraction
Lagophthalmos [mm]	OD 3	OS 4	OD 1	OS 1	OD 1	OS 1
Lid aperture [mm]	OD 12	OS 11	OD 8	OS 8	OD9	OS9
Proptosis [mm]	OD 28	OS 27	OD 25	OS 25	OD 24	OS 24
Diplopia [Gorman score]	Inconstant		Intermittent		No diplopia	
Central and colour vision	Normal		Normal		Normal	
QoL						
Visual functioning	17/100		86/100		83/100	
Appearance	31/100		50/100		43/100	
TRAB [IU/L]	12.2		11.2		11.3	

CAS — clinical activity score; OD — oculus dexter (right eye); OS — oculus sinister (left eye); QoL — quality of life; TRAB — thyroid-stimulating hormone receptor antibodies

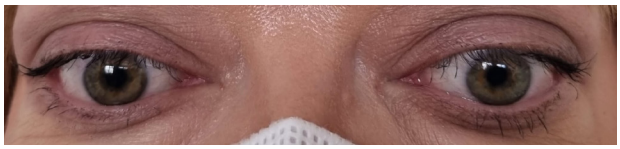

Figure 2. *Patient at one-year follow-up visit with a marked resolution of proptosis and retraction*

Furthermore, 2 years after the administration of TCZ, the patient's clinical improvement in GO was maintained. She remained free of any signs of GO relapse. She also declined additional surgical rehabilitative interventions, being satisfied with the outcomes achieved so far.

Patients with GO often undergo a protracted journey throughout the course of their GO treatment. In the presented case, the patient experienced a long period of active disease and had previously received multiple therapies, which resulted in only partial and transient improvements. The use of TCZ proved to be effective in managing soft tissue inflammatory changes, lagophthalmos, diplopia, and proptosis in our patient, leading to a significant improvement in her quality of life.

Clinical studies evaluating the effects of TCZ in patients with corticoid-resistant GO have shown encouraging results [4–5]. However, published studies differ in terms of the dosage of TCZ, the treatment protocols, and the route of drug administration. Moreover, the data concerning long-term outcomes and safety of TCZ in GO are still scarce. Therefore, more studies are necessary to further confirm the long-term effectiveness of TCZ treatment, to determine its safety profile, and to establish a definitive therapeutic regimen.

In conclusion, this case report confirms the efficacy of TCZ in patients with corticoid-resistant GO. TCZ may be efficient also in patients with longstanding active GO, in whom other treatment modalities have not yielded the desired effects.

Ethics statement

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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Conflict of interest

The authors have no conflicts of interest to disclose.

References

1. Bartalena L, Kahaly GJ, Baldeschi L, et al. EUGOGO † . The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol. 2021; 185(4): G43–G67, doi: 10.1530/EJE-21-0479, indexed in Pubmed: 34297684.
2. Burch HB, Perros P, Bednarczuk T, et al. Management of thyroid eye disease: a Consensus Statement by the American Thyroid Association and the European Thyroid Association. Eur Thyroid J. 2022; 11(6), doi: 10.1530/ETJ-22-0189, indexed in Pubmed: 36479875.
3. Nowak M, Marek B, Kos-Kudła B, et al. Optimization of the treatment of moderate to severe and active thyroid orbitopathy considering the recommendations of the European Group on Graves' Orbitopathy (EUGOGO). Endokrynol Pol. 2022; 73(4): 756–777, doi: 10.5603/EP.a2022.0040, indexed in Pubmed: 36059167.
4. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, et al. Tocilizumab in Graves Orbitopathy Study Group. Efficacy of Tocilizumab in Patients With Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy: A Randomized Clinical Trial. Am J Ophthalmol. 2018; 195: 181–190, doi: 10.1016/j.ajo.2018.07.038, indexed in Pubmed: 30081019.
5. Dorado Cortez O, Grivet D, Perrillat N, et al. Treatment of corticosteroid-resistant Graves' orbitopathy with tocilizumab: a single-centre prospective study. Orbit. 2023; 42(4): 411–417, doi: 10.1080/01676830.2022.2119262, indexed in Pubmed: 36065465.