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STEROID-RESISTANT GRAVES' ORBITOPATHY – THERAPEUTIC OPTIONS

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Abstract: Graves orbitopathy is the most common extrathyroidal manifestation of autoimmune hyperthyroidism, although it can rarely occur in euthyroid and hypothyroid patients. TSH-receptor antibodies and insulin-like growth factor-1 play a significant role in the pathogenesis of orbitopathy, and orbital fibroblasts are the central site of their action. In addition to the mentioned autoantibodies, T and B lymphocytes, as well as various cytokines, participate in this complex immune process. As the final product of this immune cascade, there is proliferation of fibroblasts, secretion of glycosaminoglycans, differentiation of fibroblasts into myofibroblasts and adipocytes, which is responsible for the appearance of the clinical presentation of orbitopathy. Before starting the therapy, it is necessary to perform a clinical assessment of orbitopathy, which is based on an assessment of the activity and severity of the disease, as well as an assessment of the patient's quality of life. The activity of orbitopathy is assessed based on the clinical activity score. For the severity of the disease the NOSPECS classification, and for the quality of life assessment the specific questionnaire of the European Group for Graves' Orbitopathy can be used. Based on the obtained data, orbitopathy is classified as active/inactive, mild/moderate-to-severe/severe. Treatment of Graves orbitopathy can be specific or supportive. The specific treatment will depend on the degree of clinical activity and severity of the disease, and the degree of impaired quality of life is taken as an additional factor when choosing individual therapy. Intravenous glucocorticoids are the most frequently used first-line therapy for active, moderate-to-severe Graves'

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orbitopathy, however, a certain number of patients respond poorly to the applied therapy. In such patients, the use of a second line of treatment is indicated. The most commonly used second line of therapy in our country for active, moderate-to-severe glucocorticoid-resistant GO is tocilizumab. We presented a patient with autoimmune thyroid disease who presented with primary hypothyroidism, in whom, despite the use of intravenous glucocorticoids on two occasions, maintained active, moderate- to-severe orbitopathy, and therefore the treatment was continued with biological therapy (tocilizumab). A significant beneficial therapeutic effect was achieved with the applied therapy.

Keywords: Graves' orbitopathy, corticosteroid-resistant Graves' orbitopathy, biological therapy, tocilizumab

Case report

The 52 year-old patient was admitted to the Clinic for Endocrinology, Diabetes and Metabolic Diseases of the University Medical Center of Serbia, due to persistent Graves orbitopathy (GO). The diagnosis of primary hypothyroidism on the basis of autoimmune thyroid disease was established in 2015, when levothyroxine was introduced into therapy. Changes in the eyes occurred during 2018, at first unilaterally on the left eye, in the form of protrusion of the eyeball, redness of the conjunctiva, swelling of the upper and lower eyelids and gaze evoked orbital pain, followed by chemosis and edema of caruncle and plica. During 2021, swelling of the upper eyelid and conjunctival hyperemia appeared in the right eye. She was hospitalized for the first time in our department in October 2021 when she presented as active, moderate-to-severe Graves orbitopathy. Objectively, on admission to the hospital, in the left eye, there was prominent swelling of the upper and lower eyelids, conjunctival hyperemia, chemosis, swelling of the plica and caruncle, protrusion of the eyeball, and gaze evoked orbital pain, while in the right eye there was conjunctival hyperemia and swelling of the upper eyelid (Table 1). An MRI of the orbit was performed, which indicated an enlarged upper muscle group in the left eye (superior rectus muscle and elevating muscle of upper eyelid), with extension of the process into the retrobulbar fat tissue, lacrimal gland, and partially into the medial and lateral rectus muscles, as well as mild proptosis of the eyeball. An ophthalmological examination was conducted (Table 1). A 12-week course of corticosteroid (CS) treatment was started, methylprednisolone (MP) in a dose of 6x500mg+6x250mg, which was carried out in the period October 2021 - January 2022. The evaluation of the post-therapeutic effect of the therapy was carried out in January 2022. Objective findings on the eyes then - in the left eye, there was prominent swelling of the upper and lower eyelids, conjunctival hyperemia, chemosis, swelling of the plica and caruncle, protrusion of

the eyeball, and gaze evoked orbital pain. In the right eye, there was conjunctival hyperemia and swelling of the upper eyelid. Elevated values of TSH receptor antibodies were measured (TRAb). At the follow-up ophthalmological examination, there was no improvement in visual acuity (Table 1). Considering that active, moderate-to-severe GO persisted after the applied therapy, it was decided to reintroduce the 12-week CS treatment protocol with the same dosage, which was carried out in the period February 2022 - April 2022. The follow-up examination after two 12-week CS treatment protocols was done in November 2022. Objectively, changes in the left eye persisted - swelling and hyperemia of the upper and lower eyelids, redness of the conjunctiva, chemosis, edema of the plica and caruncle, protrusion of the left eye, and in the right eye - conjunctival hyperemia, edema and hyperemia of the upper eyelid were present (Table 1). TRAb antibodies were still elevated (Table 1). Ophthalmological examination revealed partial improvement of visual acuity (Table 1). Based on the results of functional and morphological testing, it was concluded that there was not significant improvement after applied CS therapy, and that moderate-to-severe GO persisted, therefore tocilizumab was then introduced in therapy, once a month, in dose of 8mg/kg, for four months. The therapy was carried out in the period February - May 2023. In June 2023 the effect of therapy was reevaluated, when swelling of the upper eyelid and discrete edema of the plica and caruncle persisted in the left eye, and in the right eye there was only discrete conjunctival hyperemia present. The palpebral aperture width and the degree of proptosis was reduced, and measured TSH receptor antibodies were lower. Ophthalmological examination revealed significant improvement of visual acuity in both eyes (Table 1). It was concluded that applied biological therapy led to significant improvement of orbitopathy, which was reflected in improvement of the degree of disease clinical activity, reduction of proptosis and palpebral aperture width. Significant visual acuity was noted, and also lower titres of TSH receptor antibodies (Table 1).

Discussion

Graves orbitopathy is the most common extrathyroidal manifestation of autoimmune hyperthyroidism, although it can rarely occur in euthyroid and hypothyroid patients (1). TSH receptor antibodies (TRAb) and insulin-like growth factor-1 (IGF-1) play an important role in the development of orbitopathy, and the central site of action of these autoantibodies are orbital fibroblasts. Activation of the receptor (TSHR/IGF-1R complex) triggers an immune cascade that leads to fibroblast proliferation, secretion of glycosaminoglycans (water retention, tissue swelling), fibroblast differentiation into myofibroblasts (increasing muscle mass) and adipocytes (enlargement of retrobulbar fat tissue). T and B lymphocytes, as well as various cytokines such as interleukin-1β (IL-1β), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-8 (IL-8),

interleukin-16 (IL-16), tumor necrosis factor-α (TNF-α), also participate in this complex immunological process (2,3,4,5,6). The spectrum of clinical presentation of the disease can vary from eyelid retraction, proptosis, ophthalmoplegia, diplopia, eyelid swelling, hyperemia of eyelid, swelling of caruncle or plica, chemosis, conjunctival hyperemia and all the way to corneal ulcers and loss of vision (2,5). Therefore, before deciding on therapy, it is necessary to perform a clinical assessment of the GO. Clinical assessment is based on an assessment of disease activity and severity, as well as an assessment of the quality of life of patients with GO (4,7). Based on this assessment, a decision is made on an individual therapeutic approach. The clinical activity score (CAS) is used to assess activity of GO, in which the following seven parameters are scored with one point each: spontaneous retrobulbar pain, gaze evoked orbital pain, hyperemia of eyelids, conjunctival hyperemia, swelling of eyelids, swelling of caruncle or plica and chemosis. A score of ≥ 3 is considered to represent active GO (7,8). Severity is assessed based on the degree of soft tissue involvement, the width of the palpebral aperture, the degree of proptosis, the type of diplopia, involvement of the cornea and optic nerve, for what NOSPECS classification could be used, and the severity is then classified as mild, moderate-to-severe and severe (sight-threatening orbitopathy). Based on the obtained data, GO is classified as active/inactive, mild/moderate-to-severe/severe. The quality of life of patients with GO is assessed by the specific questionnaire of the European Group on Graves orbitopathy (GO-QOL) (7). Treatment of GO can be specific or supportive. Some supportive methods include artificial tears, eye gels (protection for the cornea during the night), dark and prism glasses (help with double vision), sleeping with the head elevated (reduce swelling of the eyelids), treatment of hypercholesterolemia, smoking cessation, as well as causal treatment of hyperthyroidism (5). The choice of specific GO treatment will depend on the activity and severity of the disease and the degree of impaired quality of life is taken into account as an additional factor for assessment. Patients with mild GO who live in selenium-deficient areas may benefit from taking oral selenium supplements for 6 months at a dose of 200 μg per day (2,4,5,7). Low-dose of intravenous glucocorticoids (ivGC) can be considered for active mild GO with significantly impaired quality of life, while surgery can be considered for inactive mild forms with significantly impaired quality of life (5,7). Treatment of active moderate-to-severe GO begins with the administration of ivGC, which is among the first-line drugs. Oral glucocorticoids can also be administered, however, ivGC are preferred because of their better effectiveness, fewer side effects and because they are better tolerated in comparison with oral route of administration. IvGC are most commonly administered as 12 weekly infusions of methylprednisolone (MP), once a week, usually for the first six weeks at 500mg of MP and then for the next six weeks at 250mg of MP which makes the cumulative dose 4.5g. Higher doses can be used for more severe forms, but the cumulative dose should not exceed 8g per cycle, and individual doses should not exceed 750mg of MP (4,5,7). About 20-30% of patients with active moderate-to-se-

vere GO poorly respond to glucocorticoid therapy, leading to relapse or progression (6,9,10). In such patients, the use of a second line of treatment is indicated. Second-line treatment options for such patients include repeating the 12-week ivGC protocol, oral prednisone, orbital radiotherapy with oral or ivGC, biological therapy (teprotumumab, rituximab, tocilizumab) and surgical treatment (7). The most commonly used second line therapy in our country for active moderate-to-severe glucocorticoid-resistant GO is tocilizumab. Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor. IL-6 as a proinflammatory cytokine plays a role in the activation of T and B lymphocytes, and also acts directly on orbital pre-adipocytes (2,5,6,7,9,10). Patients treated with tocilizumab showed favorable effects of therapy in the form of reduced clinical activity, titer of TSH receptor antibody, proptosis, eyelid retraction, diplopia and improved bulbar motility (6,9). Severe GO (GO with significant corneal involvement, GO with dysthyroid optic neuropathy (DON)) is the most severe form of GO and is an urgent condition where immediate therapy is indicated. Initially, medical decompression can be tried (high doses of ivGC that can exceed 750 mg), and if patients do not have a favorable response to the applied therapy, surgical decompression is advised (7).

Conclusion

Therapy of cortico-resistant GO represents a great challenge. Guidelines suggest that tocilizumab may be prescribed in patients with active-moderate glucocorticoid-resistant GO. The beneficial effects of the drug are reflected in the reduction of clinical activity of the disease, TRAb titer, proptosis, eyelid retraction, diplopia and improvement of bulbar motility. In the case of our patient, there was a significant improvement of the orbitopathy in the form of a lower degree of clinical activity, decrease in the degree of proptosis and improvements in visual acuity in both eyes as well as a drop in TSH receptor antibodies titers. A significant therapeutic effect was achieved with the applied therapy, and the patient's quality of life improved significantly.

Table 1.

	October 2021 - before therapy	January 2022 - after first cycle of ivGC therapy	November 2022 - after the second cycle of ivGC therapy, and before the biological therapy	June 2023 - after biological therapy
CAS OS	5	5	5	2
CAS OD	2	2	3	1
NOSPECS* OS	2b;3c;4b;50;60;	2b;3c;4b;50;60;	2b;3c;4a;50;60;	2a;3a;40;50;60;

NOSPECS* OD	2a;3b;4a;50;60;	2a;3b;4a;50;60;	2a;3b;4a;50;60;	2a;3a;40;50;60;
PAOS	13mm	13mm	14mm	9mm
PAOD	9mm	9mm	10mm	9mm
HERTEL BAZA	121mm	121mm	110mm	110mm
HERTEL OS	26mm	26mm	23mm	18mm
HERTEL OD	21mm	21m	21mm	19mm
VOS	cc. 0.6	cc. 0.6	cc. 0.7	cc. 1.0
VOD	cc. 0.6	cc. 0.6	cc. 0.7	cc. 1.0
TRAb		2.9 IU/l	2.6 IU/l	1.8 IU/l

CAS - clinical activity score, OS - left eye, OD - right eye , VOS – visual acuity in the left eye, VOD - visual acuity in the right eye, TRAb - TSH receptor antibodies , Hertel - the Hertel exophthalmometer, cc. – with correction; *EUGOGO

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