Sanja Klet[1], Bojan Marković[1], Tamara Janić[1], Mirjana Stojković[1,2], Jasmina Ćirić[1,2], Biljana Nedeljković Beleslin[1,2], Miloš Žarković[1,2]

KORTOKOREZISTENTNA GREJVSOVA ORBITOPATIJA – TERAPIJSKE OPCIJE

Sažetak: Grejvsova orbitopatija je najčešća ekstratiroidna manifestacija autoimunskog hipertiroidizma, mada se retko može javiti i kod eutiroidnih i hipotiroidnih pacijenata. U patogenezi orbitopatije značajnu ulogu imaju TSH-receptorska antitela i insulinu-sličan faktor rasta-1, a centralno mesto njihovog delovanja predstavljaju orbitalni fibroblasti. Pored navedenih autoantitela, u ovom kompleksnom imunološkom procesu učestvuju T i B limfociti, kao i različiti citokini. Krajnji produkt ove imunološke kaskade je indukcija proliferacije fibroblasta, sekrecije glikozaminoglikana, diferencijacije fibroblasta u miofibroblaste i adipocite, što je zaslužno za pojavu kliničke slike orbitopatije. Pre započinjanja terapije potrebno je uraditi kliničku procenu orbitopatije koja se zasniva na proceni aktivnosti i težine bolesti, kao i procenu kvaliteta života pacijenata. Aktivnost orbitopatije procenjuje se na osnovu skora kliničke aktivnosti, težina bolesti može na osnovu NOSPECS klacifikacije, a kvaliteta života pomoću specifičnog upitnika Evropske grupe za Grejvsovu orbitopatiju. Na osnovu dobijenih podataka orbitopatija se klasifikuje kao aktivna/neaktivna, blaga/srednje-teška/teška. Lečenje Grejvsove orbitopatije može biti specifično ili suportivno. Specifičan tretman zavisiće od stepena kliničke aktivnosti i težine bolesti, a kao dodatan faktor pri izboru individualne terapije uzima se i stepen narušenog kvaliteta života. Intravenski glukokortikoidi su najčeće korišćena prva linija terapije za aktivne, srednje-teške orbitopatije, međutim, određen broj pacijenata slabo reaguje na primenjenu terapiju. Kod takvih pacijenata indikovana je primena druge linije lečenja. Najčešće korišćena druga linija terapije kod nas za aktivne, srednje-teške glukokortikoid - rezistentne Grejvsove orbitopatije je tocilizumab. Prikazali smo pacijentkinju sa autoimunskom tiroidnom bolešću, koja se prezentovala primarnom hipotireozom, kod koje se, uprkos primeni intravenskih glukokortikoida u dva navrata, održavala aktivna, srednje-teška orbitopatija, te je u nastavku lečenja

[1] Sanja Klet, Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Univerzitetski klinički centar Srbije.

[2] Medicinski fakultet Univerziteta u Beogradu

primenjena biološka terapija (tocilizumab). Primenjenom terapijom postignut je značajan povoljan terapijski efekat.

Ključne reci: Grejvsova orbitopatija, kortikosteroid-rezistentna Grejvsova orbitopatija, biološka terapija, tocilizumab

Prikaz slučaja

Pacijentkinja, 52 godine, primljena je na Kliniku za endokrinologiju, dijabetes i bolesti metabolizma UKCS zbog perzistentne Grejvsove orbitopatije (GO). Dijagnoza primarne hipotireoze na terenu autoimunske tiroidne bolesti postavljena je 2015. godine kada je u terapiju uveden levotiroksin. Promene na očima javile su se tokom 2018. Godine, najpre unilateralno na levom oku, u vidu izbočenosti očne jabučice, crvenila konjunktive, otoka gornjih i donjih kapaka i bola pri pokretu očne jabučice, a kasnije i pojavom hemoze i edemom plike i karunkula. Tokom 2021. godine dolazi do pojave otoka gornjeg kapka i konjunktivalne hiperemije na desnom oku. Prvi put hospitalizovana na našem odeljenju oktobra 2021. Godine, kada se prezentovala aktivnom, srednje-teškom Grejvsovom orbitopatijom. Objektivno na prijemu, na levom oku dominirao je edem gornjih i donjih kapaka, konjunktivalna hiperemija, hemoza, edem plike i karunkula, izbočenost i bol pri pokretu očne jabučice, dok je na desnom oku bila prisutna konjunktivalna hiperemija i edem gornjeg kapka (Tabela 1). Učinjen je MR orbita, koja je ukazala na uvećanu gornju grupu mišića na levom oku (gornjeg pravog mišića i mišića podizača gornjeg očnog kapka), sa propagacijom procesa u retrobulbarno masno tkivo, lakrimalnu žlezdu i delom u medijalni i lateralni pravi mišić, kao i na laku proptozu bulbusa. Obavljen oftalmološki pregled (Tabela 1). Lečenje je započeto 12-nedeljnim kortikosteroidnim (KS) protokolom, metilpredizolonom (MP), u dozi 6x500mg+6x250mg, koji je sproveden u periodu oktobar 2021 – januar 2022. godine. Evaluacija postterapijskog efekta terapije sprovedena je januara 2022. godine. Objektivno, postojao je edem i hiperemija gornjih i donjih kapaka, konjunktivalna hiperemija, hemoza, edem plike i karunkula i izbočenost levog oka, dok je na desnom oku bila prisutna konjunktivalna hiperemija i edem gornjeg kapka. Izmerene su povišene vrednosti TSH receptorskih antitela (TRAb). Na kontrolnom oftalmološkom pregledu nije bilo poboljšanja vidne oštrine (Tabela 1). S obzirom na to da je na primenjenu terapiju i dalje postojala aktivna, srednje-teška GO ponovljeno je lečenje 12-nedeljnim KS protokolom u istoj dozi MP u periodu februar 2022 – april 2022. godine. Retestiranje nakon primenjena dva dvanaestonedeljna KS protokola učinjeno je novembra 2022. godine. Objektivno, peristirao je otok i hiperemija gornjeg i donjeg kapka, crvenilo konjunktiva, hemoza, edem plike i karunkula, izbočenost levog oka, a na desnom oku bila je prisutna konjunktivalna hiperemija, edem i hiperemija gornjeg kapka (Tabela 1). TRAb antitela su i dalje bila povišena (Tabela 1). Na oftalmološkom pregledu zabeleženo je delimično poboljšanje

vidne oštrine (Tabela 1). Na osnovu rezultata funkcionalnog i morfološkog ispitivanja zaključeno je da na do tada primenjenu KS terapiju nije došlo do značajnijeg poboljšanja i da i dalje perzistira aktivna, srednje-teška GO, zbog čega je lečenje nastavljeno biološkom terapijom, tocilizumabom, u dozi 8mg/kg, jednom mesečno, u trajanju od 4 meseca. Terapija je sprovedena u periodu februar 2023 – maj 2023. godine. Tokom reevaluacije efekta terapije juna 2023. godine na levom oku zaostao je edem gornjeg kapka i diskretan edem plike i karunkula, a na desnom oku samo diskretna hiperemija konjunktive. Širina palpebralnih apertura i stepen proptoze bio je manji, a izmerena TSH receptorskih antitela u padu. Na oftalmološkom pregledu zabeleženo je značajno poboljšanje vidne oštrine na oba oka (Tabela 1). Zaključeno je da je na primenjenu biološku terapiju došlo do značajnog poboljšanja orbitopatije u vidu smanjenja stepena kliničke aktivnosti bolesti, redukcije proptoze i širine palpebralnih apertura na oba oka. Takođe, zabeleženo je značajno poboljšanje vidne oštrine i pad titra TSH receptorskih antitela (Tabela 1).

Diskusija

Grejvsova orbitopatija je najčešća ekstratiroidna manifestacija autoimunskog hipertiroidizma, mada se retko može javiti i kod eutiroidnih i hipotiroidnih pacijenata (1). Važnu ulogu u nastanku orbitopatije imaju TSH-receptorska antitela (TRAb) i insulinu-sličan faktor rasta-1 (IGF-1), a centralno mesto delovanja ovih autoantitela jesu orbitalni fibroblasti. Aktivacija receptora (TSHR/IGF-1R kompleks) pokreće imunološku kaskadu koja dovodi do proliferacije fibroblasta, sekrecije glikozaminoglikana (zadržavanje vode, otok tkiva), diferencijacije fibroblasta u miofibroblaste (uvećanje mase mišića) i adipocite (uvećanje retrobulbarnog masnog tkiva). U ovom kompleksnom imunološkom procesu učestvuju i T i B limfociti, kao i različiti citokini, poput interleukina-1β (IL-1β), interleukina-4 (IL-4), interleukina-6 (IL-6), interleukina-8 (IL-8), interleukina-16 (IL-16), faktora nekroze tumora α (TNF-α) (2, 3, 4, 5, 6). Spektar kliničke prezentacije bolesti može varirati od retrakcije kapaka, proptoze, oftalmoplegije, duplih slika, otoka kapaka, hiperemije kapaka, otoka plika i karunkula, hemoze, konjunktivalne hiperemije pa sve do kornealnih ulceracija i gubitka vida (2, 5). Zbog toga je pre donošenja odluke o terapiji potrebno uraditi kliničku procenu GO, koja se zasniva na proceni aktivnosti i težine bolesti, kao i proceni kvaliteta života pacijenata sa GO (4, 7). Na osnovu ove procene donosi se odluka o individualnom terapijskom pristupu. Za procenu aktivnosti GO koristi se skor kliničke aktivnosti (Clinical activity score – CAS), u kom se sledećih sedam parametara boduju sa po jednim bodom: retrobulbarni bol u miru, retrobulbarni bol pri pokretima bulbusa, crvenilo kapaka, crvenilo konjunktiva, otok kapaka, edem plika i karunkula i hemoza. Zbir bodova ≥ 3 predstavlja aktivnu GO (7, 8). Težina bolesti procenjuje se na osnovu stepena zahvaćenosti mekih tkiva, širine

palpebralnih apertura, stepena proptoze, vrste duplih slika, zahvaćenosti kornee i optičkog nerva, za šta se može koristi NOSPECS klacifikacija i može biti blaga, srednje-teška i teška (orbitopatija koja ugrožava vid). Na osnovu dobijenih podataka GO se klasifikuje kao aktivna/neaktivna, blaga/srednje-teška/teška orbitopatija. Za procenu kvaliteta života pacijenata sa GO koristi se specifični upitnik Evropske grupe za Grejvsovu orbitopatiju (GO-QOL) (7). Lečenje GO može biti specifično ili suportivno. U suportivne metode spadaju veštačke suze, gelovi za oči (štite korneu tokom noći), tamne i prizmatske naočare (pomažu kod duplih slika), spavanje na visokom uzglavlju (redukcija otoka), lečenje hiperholesterolemije, prestank pušenja, kao i samo kauzalno lečenje hipertireoze (5). Specifičan tretman GO zavisi od aktivnosti i stepena težine bolesti, a kao dodatan faktor za procenu uzima se stepen narušenog kvaliteta života. Pacijenti sa blagom formom GO koji žive u selen-deficitnom području mogu imati benefit od uzimanja oralnih suplemenata selena tokom 6 meseci u dozi od 200 μg dnevno (2, 4, 5, 7). Međutim, ukoliko postoji znatno narušen kvalitet života mogu se razmotriti niske doze intravenskih glukokortikoida (ivGK) kod aktivnih ili hirurški tretman kod neaktivnih GO (5,7). Prva linija lečenja aktivnih, srednje-teških GO je primena ivGK. Oralni glukokortikoidi se takođe mogu koristiti, međutim, prednost se daje ivGK jer su oni efikasniji, imaju manje neželjenih efekata i bolje se tolerišu. IvGK se najčešće primenjuju u vidu infuzija MP, jednom nedeljno, tokom 12 nedelja, obično prvih šest nedelja po 500 mg MP, a narednih šest nedelja po 250 mg MP, kada kumulativna doza iznosi 4,5 g. Veće doze mogu se koristiti za teže oblike, ali kumulativna doza ne bi trebalo da prelazi 8 g po ciklusu, a pojedinačne doze ne veće od 750 mg MP (4, 5, 7). Oko 20–30% pacijenata sa aktivnom srednje-teškom GO slabo reaguje na glukokortikoidnu terapiju, što dovodi do relapsa ili progresije bolesti (6, 9, 10). Kod takvih pacijenata indikovana je primena druge linije lečenja. Moguće opcije lečenja jesu ponavljanje 12-nedeljnog ivGK protokola, per os pronison, orbitalna radioterapija u kombinaciji sa oralnim ili ivGK, primena biološke terapije (teprotumumab, rituksimab, tocilizumab), hirurško lečenje (7). Najčešće korišćena druga linija terapije kod nas za aktivnu srednje-tešku glukokortikoid-rezistentnu GO je tocilizumab. Tocilizumab je monoklonsko IL-6 receptorsko antitelo. IL-6 kao proinflamatorni citokin igra važnu ulogu u aktivaciji T i B limfocita, a deluje i direktno na orbitalne preadipocite (2, 5, 6, 7, 9, 10). Lečenje tocilizumabom pokazalo je povoljan efekat u vidu smanjenja kliničke aktivnosti bolesti, titra TSH-receptorskih antitela, proptoze, retrakcije kapaka, diplopija, poboljšanja motiliteta bulbusa (6, 9). Teška GO (GO sa značajnom zahvaćenošću kornee, GO sa distiroidnom optičkom neuropatijom (DON)) jeste najteži oblik GO i predstavlja urgentno stanje gde je indikovano hitno započinjanje terapije. Inicijalno se može pokušati sa medikamentnom dekompresijom (visokim dozama ivGK koje mogu preći 750 mg), a ukoliko pacijenti nemaju povoljan odgovor na primenjenu terapiju savetuje se hirurška dekompresija (7).

Zaključak

Terapija kortiko-rezistentnih GO predstvalja veliki izazov. Vodiči sugerišu da se tocilizumab može koristiti kod pacijenata sa aktivnom, srednje-teškom GO rezistentnom na glukokortikoide. Povoljni efekti leka ogledaju se u smanjenju kliničke aktivnosti bolesti, titra TRAb, proptoze, retrakcije kapaka, diplopija, poboljšanju motiliteta bulbusa. U slučaju naše pacijentkinje na primenjenu terapiju došlo je do značajnog poboljšanja orbitopatije u vidu smanjenja stepena kliničke aktivnosti, redukcije proptoze i poboljšanja vidne oštrine na oba oka, kao i do smanjenja titra TSH receptorskih antitela. Primenjenom terapijom postignut je značajan povoljan terapijski efekat, a kvalitet života pacijentkinje znatno poboljšan.

Tabela 1.

	Oktobar 2021. pre terapije	Januar 2022.g. - nakon prvog ciklusa KS th	Novembar 2022.g. – nakon drugog ciklusa KS th, a pre početka biološke th	Jun 2023.g. - nakon biološke th
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 – skor kliničke aktivnosti, OS – levo oko, OD – desno oko, VOS – oštrina vida na levom oku, VOD – oštrina vida na levom oku, TRAb – TSH receptorska antitela, Hertel – egzoftalmoletrija po Hertelu, cc. – sa optičkom korekcijom; *EUGOGO

Literatura

1. Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, Natural History, Risk Factors, and Prevention of Graves' Orbitopathy. Front Endocrinol (Lausanne). 2020; 11: 1.
2. Men CJ, Kossler AL, Wester ST. Updates on the understanding and management of thyroid eye disease. Ther Adv Ophthalmol 2021; 13: 1–14.

3. Tsui S, Naik V, Hoa N, Hwang CJ, Afifiyan NF, Sinha Hikim A, Gianoukakis AG, Douglas RS, Smith TJ. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in Graves' disease. J Immunol 2008; 181(6): 4397–4405.
4. Dosiou C, Kossler AL. Thyroid Eye Disease: Navigating the New Treatment Landscape. J Endocr Soc. 2021; 5(5): 1–13.
5. Bartalena L, Tanda ML. Current concepts regarding Graves' orbitopathy. J Intern Med. 2022; 292(5): 692–716.
6. Boutzios G, Chatzi S, Goules AV, Mina A, Charonis GC, Vlachoyiannopoulos PG, Tzioufas AG. Tocilizumab improves clinical outcome in patients with active corticosteroid-resistant moderate-to-severe Graves' orbitopathy: an observational study. Front Endocrinol (Lausanne). 2023; 14: 1–7
7. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, Marinò M, Vaidya B, Wiersinga WM; EUGOGO. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol 2021; 185: G43–G67.
8. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf). 1997; 47: 9–14.
9. Pérez-Moreiras JV, Varela-Agra M, Prada-Sánchez MC, Prada-Ramallal G. Steroid-Resistant Graves' Orbitopathy Treated with Tocilizumab in Real-World Clinical Practice: A 9-Year Single-Center Experience. J Clin Med. 2021; 10(4): 1–17.
10. Pérez-Moreiras JV, Alvarez-López A, Gómez EC. Treatment of active corticosteroid-resistant graves' orbitopathy. Ophthalmic Plast Reconstr Surg. 2014; 30(2): 162–7.

Sanja Klet[1], Bojan Marković[1], Tamara Janić[1], Mirjana Stojković[1,2], Jasmina Ćirić[1,2], Biljana Nedeljković Beleslin[1,2], Miloš Žarković[1,2]

STEROID-RESISTANT GRAVES' ORBITOPATHY – THERAPEUTIC OPTIONS

1 Clinic of Endocrinology, Diabetes and Metabolic Disease, University Clinical Center of Serbia
2 Faculty of medicine, University of Belgrade

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'

[1] Sanja Klet, Clinic of Endocrinology, Diabetes and Metabolic Disease, University Clinical Center of Serbia.

[2] Faculty of medicine, University of Belgrade

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

References

1. Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, Natural History, Risk Factors, and Prevention of Graves' Orbitopathy. Front Endocrinol (Lausanne). 2020;11:1.
2. Men CJ, Kossler AL, Wester ST. Updates on the understanding and management of thyroid eye disease. Ther Adv Ophthalmol 2021;13:1-14.
3. Tsui S, Naik V, Hoa N, Hwang CJ, Afifiyan NF, Sinha Hikim A, Gianoukakis AG, Douglas RS, Smith TJ. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in Graves' disease. J Immunol 2008;181(6):4397-4405.
4. Dosiou C, Kossler AL. Thyroid Eye Disease: Navigating the New Treatment Landscape. J Endocr Soc. 2021;5(5):1-13
5. Bartalena L, Tanda ML. Current concepts regarding Graves' orbitopathy. J Intern Med. 2022;292(5):692-716.
6. Boutzios G, Chatzi S, Goules AV, Mina A, Charonis GC, Vlachoyiannopoulos PG, Tzioufas AG. Tocilizumab improves clinical outcome in patients with active corticosteroid-resistant moderate-to-severe Graves' orbitopathy: an observational study. Front Endocrinol (Lausanne). 2023;14:1-7
7. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, Marinò M, Vaidya B, Wiersinga WM; EUGOGO. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol 2021;185:G43-G67

8. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf). 1997;47:9-14.
9. Pérez-Moreiras JV, Varela-Agra M, Prada-Sánchez MC, Prada-Ramallal G. Steroid-Resistant Graves' Orbitopathy Treated with Tocilizumab in Real-World Clinical Practice: A 9-Year Single-Center Experience. J Clin Med. 2021;10(4):1-17
10. Pérez-Moreiras JV, Alvarez-López A, Gómez EC. Treatment of active corticosteroid-resistant graves' orbitopathy. Ophthalmic Plast Reconstr Surg. 2014;30(2):162-7.