Tocilizumab in the Treatment of Graves Orbitopathy

Tocilizumab no Tratamento da Orbitopatia de Graves

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ABSTRACT

INTRODUCTION: Graves orbitopathy (GO) is an autoimmune inflammatory disease with a challenging and somewhat controversial treatment. Therapeutic options in moderate to severe active disease may include intravenous (iv) corticosteroid therapy, other immunomodulators, radiotherapy or surgical decompression of the orbit. The Clinical Activity Score (CAS) is a clinical scale that quantifies signs and symptoms of the disease, allowing the evaluation of the degree of activity and prediction of clinical response to treatment. Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor. Recent studies report its effectiveness in treating active GO refractory to IV corticosteroid therapy. The purpose of this study is to present fourteen cases of GO resistant to IV corticosteroid therapy treated with tocilizumab.

METHODS: We conducted a retrospective analysis of fourteen patients with active GO, with a CAS ≥ 4, resistant to IV methylprednisolone treatment. The patients were then submitted to monthly IV treatment with tocilizumab (8 mg/kg weight) for 4 to 8 months. We recorded and analysed visual acuity, CAS, Hertel exophthalmometry, ocular motility, and Trab levels (anti-TSH receptor antibodies) before and after treatment.

RESULTS: We included fourteen patients, with a median age of 47 years (range 37 – 72 years) at the beginning of treatment, and a mean follow-up period of 37 months (range 4 to 48 months). Thirteen of the fourteen patients showed gradual anatomical and functional improvement of GO, with a reduction of the CAS score, decrease Trab levels (median reduction of 5.77 U/L), and decreased (10 of 14 patients) or stabilized proptosis (3 of 14 patients). One patient maintained active disease (CAS ≥ 3) requiring more tocilizumab sessions. However, there are adverse events such as abnormalities in the lipid profile or liver function and increased risk of serious infections. Two patients developed transient neutropenia, which did not require treatment cessation.

CONCLUSION: Therapeutic options used for moderate to severe active GO, such as corticosteroid therapy or radiotherapy, may provide disappointing results, only offering partial response with the recurrence of the disease. Therefore, the use of new immunosuppressive drugs, such as tocilizumab, with more targeted therapeutic action may show promising results. Despite the reduced sample, our results suggest that tocilizumab can be effective in the treatment of thyroid disease in patients with active GO refractory to corticosteroids.

KEYWORDS: Antibodies, Monoclonal, Humanized/therapeutic use; Graves Ophthalmopathy/drug therapeutic; Tocilizumab.

RESUMO

INTRODUÇÃO: A orbitopatia de Graves (GO) é uma doença inflamatória autoimune com tratamento desafiante e algo controverso. As opções terapêuticas na doença ativa moderada a grave podem incluir a terapêutica endovenosa com corticoides, outros imunomoduladores, radioterapia ou descompressão cirúrgica da órbita. O *Clinical Activity Score* (CAS) é uma escala clínica que quantifica os sinais e sintomas da doença, permitindo avaliar o grau de actividade e prever a resposta clínica ao tratamento. O tocilizumab é um anticorpo monoclonal humanizado contra o receptor da interleucina-6. Estudos recentes relatam a sua eficácia no tratamento da GO ativa refractária à terapêutica com corticosteróides IV tratados com tocilizumab.

MÉTODOS: Foi realizada uma análise retrospetiva de catorze doentes com GO activo, com um CAS ≥ 4, resistente ao tratamento com metilprednisolona IV. Os doentes foram submetidos a tratamento IV mensal com tocilizumab (8 mg/kg de peso) durante 4 a 8 meses. Foi analisado e registado a acuidade visual, o CAS, a exoftalmometria de Hertel, a motilidade ocular e os níveis de Trab (anticorpos anti-receptor de TSH) antes e depois do tratamento.

RESULTADOS: Foram incluídos catorze doentes, com idade mediana de 47 anos (variação de 37 a 72 anos) no início do tratamento e um período médio de acompanhamento de 37 meses (variação de 4 a 48 meses). Treze de catorze doentes apresentaram uma melhoria anatómica e funcional gradual da GO, com redução do *score* CAS, diminuição dos níveis de Trab (redução mediana de 5,77 U/L) e diminuição (10 de 14 doentes) ou estabilização da proptose (3 de 14 doentes). Um doente manteve a doença ativa (doença CAS ≥ 3) necessitando de mais sessões de tocilizumab. No entanto existem efeitos adversos associados, como anormalidades no perfil lipídico ou na função hepática e aumento do risco de infeções graves. Dois doentes desenvolveram neutropenia transitória, mas não implicou a suspensão do tratamento.

CONCLUSÃO: As opções terapêuticas utilizadas para a GO ativa moderada a grave, como a terapêutica com corticoides ou a radioterapia, podem ter resultados dececionantes, oferecendo apenas uma resposta parcial com a recorrência da doença. Assim, a utilização de novos fármacos imunossupressores, como o tocilizumab, com uma ação terapêutica mais direcionada, pode apresentar resultados promissores. Apesar da amostra reduzida, os nossos resultados sugerem que o tocilizumab pode ser eficaz no tratamento da doença tiroideia em doentes com GO ativo refratário aos corticoides.

PALAVRAS-CHAVE: Anticorpos Monoclonais Humanizados/uso terapêutico; Oftalmopatia de Graves/tratamento farmacológico; Tocilizumab.

INTRODUCTION

Graves orbitopathy (GO) is an inflammatory autoimmune disease that affects the extraocular muscles (EOM) and orbital fat. It is a major extrathyroidal manifestation of Graves' disease and moderate to severe forms of GO affect 5% of these patients.[1,2] At the time of Graves' disease diagnosis, about 20%-25% of patients have clinically apparent GO.[3] However, GO may also occur in euthyroid patients or in patients with chronic autoimmune thyroiditis (Hashimoto thyroiditis).[4] The pathogenesis of GO disease is documented. Lymphocytes B recognize an autoantigen, the thyroid stimulating hormone (TSH) receptor, present in the orbit and thyroid follicular cells, and secrete cytokines, such as interleukin-6 that stimulate fibroblasts to produce glycosaminoglycan.[5-7] Immunological cross-reactivity between antigens expressed in the thyroid and orbit plays a crucial role in the GO pathogenesis. The expression of the TSH receptor and the insulin growth factor-1 (IGF-1) receptor on orbital fibroblasts is responsible for this cross-reactivity.[8,9]

GO is usually bilateral, but it can also be asymmetric or unilateral.[6] The main signs and symptoms of GO include hypertrophy of EOM, swollen eyelids, and an increase in intraorbital fat volume, leading to eyelid retraction, proptosis, redness of conjunctiva, diplopia, decreased visual acuity and optic nerve compression.[2,3,5,6,10] Ocular comorbidities are responsible for marked decrease in the quality of life of these patients.[1] Controlling factors known to exacerbate the disease such as cigarette smoking are critical.[6,9] The clinical activity score (CAS) is a clinical scale that quantifies the activity of the disease, and it is related to the presence of inflammatory signs.[11] A scale of 0 to 10 items is used, and a score of ≥ 3 suggests active GO (Table 1). The CAS is the best validated scoring system, although it has limitations, such as its binary (yes/no) response.[11,12] According to the

Table 1. Clinical Activity Score (CAS).	
For initial CAS, only score item 1-7	**Patients assessed after follow-up can be scored out of 10 by including items 8-10**
1. Spontaneous orbital pain	8. Increase of >2 mm in proptosis
2. Gaze evoked orbital pain	9. Decrease in uniocular ocular excursion in any one direction of >8º
3. Eyelid swelling that is considered to be due to active GO	10. Decrease of acuity equivalent to Snellen line
4. Eyelid erythema	
5. Conjunival redness that is considered to be due to active GO	
6. Chemosis	
7. Inflammation of caruncle	

A scale of 0 to 10 items; for each item present, 1 point is given. A score ≥ 3 suggests active GO.

European Group on GO (EUGOGO), the severity of GO, defined as the degree of functional deficit, may be classified as mild, moderate to severe and sight-threatening.[4]

GO treatment is challenging and somewhat controversial. In the treatment of moderate to severe and active GO, intravenous methylprednisolone alone or in combination with oral mycophenolate sodium (or mofetil) represents the first-line treatment, due to their anti-inflammatory properties.[13,14] However, some patients report systemic side effects, disease recurrence (8%) or lack of response at the end of therapy.[2,15,16] Radiotherapy, when used in combination with corticosteroids or as isolated treatment, has been shown to be an effective in preventing compressive optic neuropathy, improving motility restriction, and decreasing clinical activity in thyroid eye disease. Orbital radiation also may facilitate a corticosteroid taper. However, there are some side effects related to this therapy, such as retinopathy, neuropathy or cataracts.[5,17] Other treatment possibilities like azathioprine, cyclosporine, ciamexone or somatostatin analogues, have unproven beneficial effects on GO.[6,13]

Therefore, in cases of resistance or non-responders, other immunomodulators should be tried as an alternative. Teprotumumab is a fully humanized immunoglobin (Ig) G1 monoclonal inhibiting antibody, which binds to the extracellular portion of IGF-1R and blocks its activation and signalling by endogenous ligands. It has become the first drug approved by the US Food and Drug Administration for the treatment of adult GO. However, its incorporation into routine clinical practice is currently limited by the lack of comprehensive long-term efficacy and safety data, absence of comparison with i.v. glucocorticoids, restricted geographical availability, reimbursement, and costs. Additionally, hearing impairment has been in recipients of teprotumumab (2 patients with hypoacusis, 1 with deafness, 1 with autophony and 1 with a patulous Eustachian tube, which all resolved).[24,25] Interesting results have been recently published using tocilizumab (anti-interleukin-6 (IL-6) receptor antibody, rituximab (anti-CD20 antibody) or teprotumumab (IGF-1 receptor antibody), in the treatment of active GO refractory to corticotherapy.[2]

An alternative therapy is tocilizumab (anti-IL-6 receptor monoclonal antibody). IL-6 has an important role in the activation of B cells and the development of antibody producing plasma cells.[26] Consequently, tocilizumab can reduce the concentrations of memory B cells and immunoglobulin levels.[26] In 2009 tocilizumab was first introduced as an treatment for severe glucocorticoid-resistant GO, with the initial outcomes published in a small case series.[5] The efficacy of tocilizumab was later supported by randomized clinical trial in patients with active steroid-resistant GO.[27]

The main purpose of our study is to present fourteen cases of GO resistant to treatment with i.v. methylprednisolone, treated with tocilizumab, and to evaluate effectiveness and long-term safety.

METHODS

This was a retrospective case series conducted at the Ophthalmology Department of Coimbra Hospital and University Centre. Informed consent was obtained from all patients, and the study followed the assumptions of the Helsinki Declaration.

Patients with Graves orbitopathy, exhibiting moderate to severe activity (CAS >=4), and who had not responded to previous treatment with intravenous pulses of methylprednisolone were included in the study. Patients with a history of recent hepatitis, liver dysfunction, cardiovascular or pulmonary disease, haematological disorders (anaemia, neutropenia, or thrombocytopenia), oncological disease, tuberculosis infection, severe hypertension or uncontrolled diabetes mellitus, patients were excluded. A complete blood analysis was performed on all patients to rule out active infectious disease.

The initial treatment, in accordance with recommended guidelines, consisted of intravenous methylprednisolone 500 mg weekly for six weeks, followed by a reduced dose of 250 mg weekly for another six weeks (EUGOGO protocol). [2,4,14,18]

As there was no clinical or analytical response, and no recurrence of active phase, we began treatment with intravenous tocilizumab, administered monthly at a dose of 8 mg/kg weight (minimum dose of 480 mg/session). A 30-minute infusion of 100 mL saline was given while monitoring blood pressure. The treatment was discontinued when clinical activity score was between 0 and 1. For symptomatic relief of irritation and dryness, topical treatment with artificial tears was recommended.

Clinical and analytical data was collected, including visual acuity with Early Treatment Diabetic Retinopathy Study (ETDRS) charts, biomicroscopy and fundoscopy examination, Goldmann applanation tonometry, assessment of CAS, Hertel exophthalmometry, ocular motility, diplopia, eyelid retraction, and Trab Levels (antibodies anti-TSH receptor) before and after each treatment. Additionally, monthly monitoring of complete blood cell count, liver chemistry, blood glucose, and blood pressure was performed on all patients.

RESULTS

STUDY POPULATION

Our sample included fourteen patients (6 male and 8 female), with a median age of 47 (41- 61 IQR) years old (range 37 to 72 years) in the beginning of treatment and with a median follow-up period of 37 (12.5-48 IQR) months (range 4 to 48 months; from the start of treatment) (Table 2).

Table 2. Demographic data of study population.

n=14	Median (IQR)	Range
Age (Years)	47 (41 – 61)	37 – 72 years
Gender (M:F)	6 : 8	
Follow-up time (months)	37 (12.5 – 48)	4 – 48 months
Treatment sessions	8 (8-8)	4 – 8 sessions

IQR, interquartile range; M, male; F, female.

All patients had moderate to severe GO (initial CAS ranged 4 to 7), resistant to steroid treatment (EUGOGO protocol). Specifically, two patients developed optic neuropathy, and another four were smokers. Fig. 1 shows the optical coherence tomography (OCT) of the optic disc, showing optic disc oedema of the left eye of a 46-year-old woman before treatment with tocilizumab.

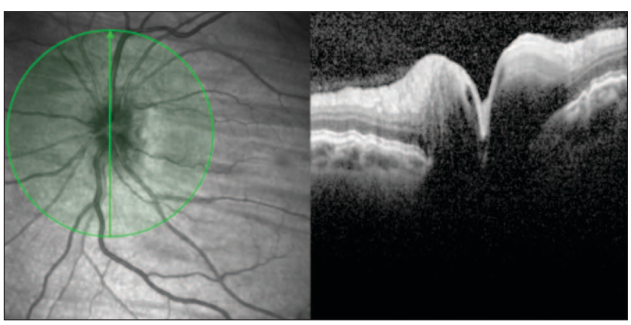

Figure 1. OCT of the left optic disc, showing optic disc edema, of a 46-year-old woman, before treatment with tocilizumab.

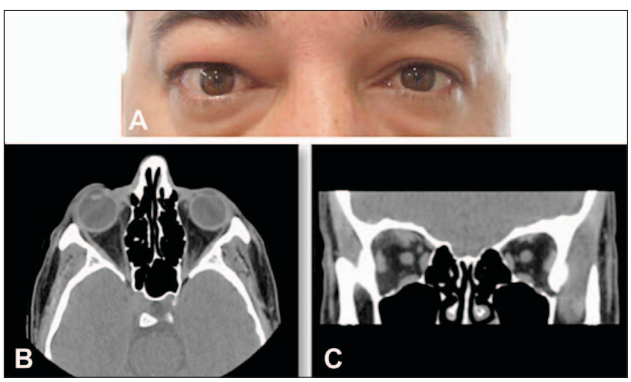

Figure 2. 40-year-old man OCT, with active GO, before treatment with tocilizumab (A). Orbit CT shows right eye proptosis (B), as well as thickening of the right periorbital soft tissues and of the superior rectus muscle (C).

The median number of treatment sessions was 8 (8-8 IQR) (range 4 to 8 sessions), where one non-smoker was submitted to 4 treatment cycles. At the end of follow-up, almost every patient showed anatomical, functional, and analytical improvement. One patient is still undergoing treatment because he maintained active disease requiring more tocilizumab sessions. There were no relapses; however, two patients developed transient neutropenia, which did not require treatment cessation.

Fig. 2 corresponds to a 40-year-old man with active GO before treatment with tocilizumab, and the respective computed tomography (CT), showing thickening of the right periorbital soft tissues and of the superior rectus muscle.

ANALYSIS OF CAS SCORE PARAMETERS

Almost every patient improved the CAS score, showing a median reduction of 4.14 (range reduction of 2 to 5), with a mean final score of 0.89 (range 0 to 3). One patient maintained active disease (CAS ≥ 4) after 8 sessions requiring more tocilizumab sessions. Resolution of conjunctival hyperaemia, eyelid retraction, and eyelid oedema was reported in seven cases. Regarding the evolution of proptosis, there was a median reduction of 0.63 (range -3 to 2.5 mm) in the Hertel ophthalmometry, although one patient showed maintained of proptosis and is still in treatment. Apart from one patient, all showed complete improvement of ocular motility and full recovery of diplopia. Visual acuity improved on average 0.79 Snellen lines (range 0 to 2.5 lines).

Analysis of palpebral retraction, IOP and TRAB levels

Related to palpebral retraction, there was a median improvement of 1.02 (range 0 to 3.5 mm). Regarding intraocular pressure (IOP), it remained stable in many patients; nevertheless, one patient needed topical hypotensive medication. Similarly, there was a median reduction of Trab levels of 5.77 (range 1.20 to 42.0 U/L) (Table 3).

Table 3. Clinical and analytical evolution.

n=14	Median	Range
CAS reduction	4.14	2 - 5
CAS final	0.89	0 - 3
Proptosis reduction (mm)	0.63	-3 to 2.5
VA improvement (Snellen lines)	0.79	0 – 2.5
Palpebral retraction reduction (mm)	1.02	0 – 3.5
TRABs reduction (U/L)	5.77	1.2 - 42

CAS, Clinical Activity Score; VA, visual acuity; TRABs, thyrotropin receptor antibodies.

Finally, there was a resolution of optic neuropathy on both cases, with normal campimetry.

DISCUSSION

Therapeutic options used for moderate to severe active Graves' orbitopathy (GO), such as corticotherapy or radiotherapy, may have disappointing results and systemic side effects such as acute liver damage, suppression of the hypothalamus-pituitary-adrenal axis, and uncontrolled diabetes. Therefore, the use of new immunosuppressive drugs such as tocilizumab, which are more targeted to the pathogenic mechanisms of the disease, may provide promising results.

Our study demonstrates that treatment with tocilizumab may improve the clinical and analytical manifestations of GO disease refractory to multiple cycles of intravenous corticotherapy. The patients included in the study had moderate to severe GO activity (CAS >= 4) for several months and demonstrated clinical and analytical improvement since the first treatment cycles. Almost all patients decreased their CAS levels to final values between 0 and 3, except for one patient who maintained active disease requiring more tocilizumab sessions, due to partial response. Similarly, there was a progressive improvement in extraocular movements, with resolution of diplopia, avoiding strabismus surgery. Proptosis and eyelid retraction remained stable or slightly improved. Trab levels decreased progressively, and TSH, T3 and T4 ranged normal values at the end of follow-up. There were no relapses, however two patients had transitory neutropenia, which did not require treatment cessation. The most common side effects related to tocilizumab treatment were laboratory abnormalities such as rise in the hepatic function markers, decrease in platelet and white cells counts, rise in blood cholesterol levels, and infections. Cardiac events and solid-organ malignancies were not reported in this retrospective analysis.

Targeted therapy with different immunomodulators is being tried and has shown encouraging results, not only because it avoids the side effects of GC, but also because it controls active disease that is not responsive to steroid treatment. Tocilizumab is a humanized monoclonal antibody against the receptor of IL-6, which is administered intravenously at dose of 4 to 8 mg/kg every 4 weeks.[16] IL-6 is a proinflammatory cytokine produced by T and B lymphocytes, monocytes, differentiated adipocytes, and fibroblasts; it is present in high concentrations in patients with Graves' disease.[5] IL-6 stimulates B lymphocytes and produces thyroid-stimulating immunoglobulin (TSI), which activates fibroblasts of the orbit to produce glycosaminoglycans, adipogenesis and inflammation.[5] The administered dose of tocilizumab was 8mg/kg intravenously, and patients underwent a median of 8 treatment sessions (range: 4-8), with a follow-up time of 37 months (range: 12.5-48). Almost all patients showed improvement of CAS and Trab levels. Around 72% of patients reduced proptosis, 83% improved ocular motility, and two patient which developed compressive optic neuropathy improved without the need for orbital decompression. No severe side effects or relapse of active GO were reported.

Pérez-Moreira *et al* studied the effectiveness and safety of tocilizumab use for the treatment of active steroid-resistant Graves' orbitopathy. The absolute CAS response was obtained in 74% of patients after the fourth dose of tocilizumab, with a TRAb response being achieved in 55% of patients. While relative CAS response was achieved in 90.9% of patients after the first dose of tocilizumab. Measurements of proptosis and eyelid retraction, and the prevalence of diplopia were significantly reduced after the last dose of tocilizumab. Four patients exhibited disease recurrence, established as an increase in CAS of ≥ 2 points in the six months following the date of investigation. Most adverse drug reactions were mild or moderate in severity. This suggests that a course of at least 4 months of tocilizumab therapy provides a significant benefit to patients with active moderate-to-severe steroid resistant GO.[28]

Furthermore, in an uncontrolled observation study, GO resistant to established therapies, tocilizumab given monthly i.v. or weekly subcutaneously was well tolerated and most patients showed improvement (92%).[18] Subcutaneous administration of tocilizumab has also been reported to be efficacious in thyroid eye disease.[29,30]

Another immunomodulatory drug, rituximab, is a monoclonal antibody that targets the CD20 antigen expressed by B cells but not B-cell precursors. Its action blocks the antigen presentation by B cells, resulting in decreased T-cell activation and allowing reductions in serum concentrations of thyroid receptor antibody after treatment.[2,5,19,20] Salvi *et al*, suggested that rituximab could represent an important option for treatment of Graves' orbitopathy. They compared the effect of rituximab therapy (1000 mg IV at 2-week intervals) with glucocorticoids (500 mg iv for 16 weeks), in 20 consecutive patients. They reported a significant improvement in the CAS and inflammation, more significantly in the group treated with rituximab. Relapse was verified in 10% of patients treated with GC.[21] Another promising drug in active GO treatment is teprotumumab, an IGF-1-receptor-blocking antibody.[16] Its principle of action is based on blocking the ligation of IGF-1 receptors expressed on orbital fibroblasts with IGF-1, preventing hyaluronan production and adipogenesis.[2,8,16]

An additional steroid-sparing agent being studied for the treatment of GO is adalimumab, a TNF-α antagonist that is administered subcutaneously every two weeks.[22,23] In a retrospective study including 10 patients with a severe GO, 60% of patients decreased the inflammatory score, but 30% experienced worsening, and 10% remained the same. It was also reported that there is an increased risk of infection with this treatment.

Teprotumumab has been shown to be effective in the treatment of active Graves' orbitopathy in two randomized clinical trials. Both trails demonstrated that teprotumumab was associated with significantly improvement in proptosis, diplopia and clinical activity score compared to those subjects who received placebo. Overall, these trials provide strong evidence supporting the use of teprotumumab as first line for active GO and have led to its approval by the U.S. Food and Drug Administration.[24,25]

Furthermore, it is important to note that the establishment of a euthyroid state and the control of risk factors that

increase the risk of progression and resistance to treatment, namely smoking habits, are crucial in controlling the disease.

However, the present study has some limitations, namely its retrospective nature and the small sample size.

In conclusion, it has been proposed that tocilizumab may be a promising drug in near future, effective and safe in treatment of active GO refractory to steroid treatment. Despite the small sample size, our results suggest that tocilizumab can be effective in the treatment of active GO refractory to corticosteroids. Moreover, we raise the possibility of replacing i.v. methylprednisolone pulses with tocilizumab, not only in corticosteroid-resistant cases but also as first-line option. However, new randomized placebo-controlled clinical trials are needed to elucidate whether tocilizumab and other biological drugs could replace GC in active, moderate-to-severe GO.

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PNP and JP: Study design and article writing; Data collection, statistical analysis and interpretation: Writing and approval of the final version.

TQ, FP, GC and JM: Critical review of the manuscript and approval of the final version.

PNP e JP: Desenho do estudo e elaboração do artigo; Recolha, análise estatística e interpretação de dados: Redação e aprovação da versão final.

TQ, FP, GC e JM: Revisão crítica do manuscrito e aprovação da versão final.

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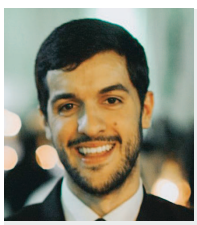
REFERENCES

1. Bartalena L, Lai A, Compri E, Marcocci C, Tanda ML, Novel immunomodulating agents for Graves orbitopathy. Ophthalmic Plast Reconstr Surg. 2008;24:251–6. doi: 10.1097/IOP.0b013e318179f8a5.
2. Wiersinga WM. Advances in treatment of active, moderate-to-severe Graves' ophthalmopathy. Lancet Diabetes Endocrinol. 2017;5:134-42. doi: 10.1016/S2213-8587(16)30046-8.
3. Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, Ezrachi D, Shimon I, Leibovici L. Treatment modalities for Graves' ophthalmopathy: systematic review and metaanalysis. J Clin Endocrinol Metab. 2009;94:2708-16. doi: 10.1210/jc.2009-0376.
4. Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marcocci C, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol. 2008;158:273-85. doi: 10.1530/EJE-07-0666.
5. Pérez-Moreiras JV, Alvarez-López A, Gómez EC. Treatment of active corticosteroid-resistant graves' orbitopathy. Ophthalmic Plast Reconstr Surg. 2014;30:162-7. doi: 10.1097/IOP.0000000000000037.
6. Bartalena L, Tanda ML. Clinical practice. Graves' ophthalmopathy. N Engl J Med. 2009;360:994-1001. doi: 10.1056/NEJMcp0806317.
7. Bahn RS. Current Insights into the Pathogenesis of Graves' Ophthalmopathy. Horm Metab Res. 2015;47:773-8. doi: 10.1055/s-0035-1555762.
8. Salvi M. Immunotherapy for Graves' ophthalmopathy. Curr Opin Endocrinol Diabetes Obes. 2014;21:409-14. doi: 10.1097/MED.0000000000000097.
9. Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010;362:726-38. doi: 10.1056/NEJMra0905750.
10. Pillar AJ, Richa DC. Treatment options for thyroid eye disease. Curr Treat Options Neurol. 2014;16:303. doi: 10.1007/s11940-014-0303-8.
11. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol. 199;47:9-14. doi: 10.1046/j.1365-2265.1997.2331047.x. Erratum in: Clin Endocrinol;47:632.
12. Marcocci C, Marinò M. Treatment of mild, moderate-to-severe and very severe Graves' orbitopathy. Best Pract Res Clin Endocrinol Metab. 2012;26:325-37. doi: 10.1016/j.beem.2011.11.005.
13. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 European Thyroid Association/

European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J. 2016;5:9-26. doi: 10.1159/000443828.
14. Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. J Clin Endocrinol Metab. 2011;96:320-32. doi: 10.1210/jc.2010-1962.
15. Bartalena L, Krassas GE, Wiersinga W, Marcocci C, Salvi M, Daumerie C, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. J Clin Endocrinol Metab. 2012;97:4454-63. doi: 10.1210/jc.2012-2389.
16. Salvi M, Campi I. Medical Treatment of Graves' Orbitopathy. Horm Metab Res. 2015;47:779-88. doi: 10.1055/s-0035-1554721.
17. Sobel RK, Aakalu VK, Vagefi MR, Foster JA, Tao JP, Freitag SK, et al. Orbital Radiation for Thyroid Eye Disease: A Report by the American Academy of Ophthalmology. Ophthalmology. 2022;129:450-5. doi: 10.1016/j.ophtha.2021.10.025.
18. Sánchez-Bilbao L, Martínez-López D, Revenga M, López-Vázquez Á, Valls-Pascual E, Atienza-Mateo B, et al. Anti-IL-6 Receptor Tocilizumab in Refractory Graves' Orbitopathy: National Multicenter Observational Study of 48 Patients. J Clin Med. 2020;9:2816. doi: 10.3390/jcm9092816.
19. Salvi M, Vannucchi G, Beck-Peccoz P. Potential utility of rituximab for Graves' orbitopathy. J Clin Endocrinol Metab. 2013;98:4291-9. doi: 10.1210/jc.2013-1804.
20. Persani L, Guastella C, Wall J, Beck-Peccoz P, Salvi M. Rituximab treatment in patients with active Graves' orbitopathy: effects on proinflammatory and humoral immune reactions. Clin Exp Immunol. 2010;161:436-43. doi: 10.1111/j.1365-2249.2010.04191.x.
21. Salvi M, Vannucchi G, Campi I, Currò N, Dazzi D, Simonetta S, et al. Treatment of Graves' disease and associated ophthalmopathy with the anti-CD20 monoclonal antibody rituximab: an open study. Eur J Endocrinol. 2007;156:33-40. doi: 10.1530/eje.1.02325.
22. Ayabe R, Rootman DB, Hwang CJ, Ben-Artzi A, Goldberg R. Adalimumab as steroid-sparing treatment of inflammatory-stage thyroid eye disease. Ophthalmic Plast Reconstr Surg. 2014;30:415-9. doi: 10.1097/IOP.0000000000000211.
23. Ahmadzadeh-amiri A, Ahmadzadeh-amiri A. Steroid-sparing medications in thyroid eye disease. Sudan J Ophthalmol. 2016: 1–4. doi:10.4103/1858-540X.184241
24. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for thyroid-associated ophthalmology. New Engl J Med. 2017;376:1748-61. doi:10.1056/nejmoa1614949
25. Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EZ, Perdok R, et al. Teprotumumab for the treatment of active thyroid eye disease. New Engl J Med. 2020; 382:341-52. doi:10.1056/nejmoa1910434
26. Strianese D, Rossi F, Interruption of autoimmunity for thyroid eye disease: B-cell and T-cell strategy. Eye. 2019;33:191-9. doi: 10.1038/s41433-018-0315-9
27. Perez-Moreira JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo Lopez A, Rodríguez Alvarez FM, Castillo Laguarta JM, Del Estad Cabello A, Gessa Sorroche M, España Gregori E, et al. 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.
28. 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; 11;10:706. doi: 10.3390/jcm10040706.
29. Copperman T, Idowu OO, Kersten RC, Vagefi MR. Subcutaneous tocilizumab for thyroid eye disease: simplified dosing and delivery. Ophthalmic Plast Reconstr Surg. 2019;35:e64-e66. doi: 10.1097/IOP.0000000000001346.
30. Silkiss RZ, Paap MK, Roelofs KA, Agi J, Weis E. Treatment of corticosteroid-resistant thyroid eye disease with subcutaneous tocilizumab. Can J Ophthalmol. 2021;56:66-70. doi: 10.1016/j.jcjo.2020.07.020.



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