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New therapeutic strategies for Graves' Ophthalmopathy

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New therapeutic strategies for Graves' Ophthalmopathy

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Abbreviations

ATD	Antithyroid drugs
BAFF	B-lymphocyte activating factor
CAS	Clinical Activity Score
CCL	C-C motif ligands
CD	Cluster of differentiation
COX-2	Cyclooxygenase-2
CTLA-4	Cytotoxic T lymphocyte antigen 4
CXCL	C-X-C motif ligands
DHR-E	Dihydrofolate reductase enzyme
DON	Dysthyroid optic neuropathy
ECM	Extracellular matrix
EOM	Extraocular muscles
EUGOGO	European Group On Graves' Orbitopathy
GAGs	Glycosaminoglycans
GCs	Glucocorticoids
GD	Graves’ disease
GO	Graves’ ophthalmopathy or orbitopathy
HA	Hyaluronic acid
HAS2	HA synthase 2
ICAM	Intercellular adhesion molecule
IFN	Interferon
IGF-1	Insulin-like growth factor 1
IGF-1R	Insulin-like growth factor 1 receptor
IL	Interleukin
IMD-E	Inosine monophosphate dehydrogenase enzyme
MMF	Mycophenolate mofetil
NSAIDs	Nonsteroidal anti-inflammatory drugs
OFs	Orbital fibroblasts
PDGF	Platelet-derived growth factor
PGE2	Prostaglandin E2
PI3K	Phosphatidylinositol 3-kinase
QoL	Quality of life
RAI	Radioactive iodine
RANTES	Regulated upon Activation, Normal T cell Expressed, and Secreted
RCT	Randomized controlled trial
RTX	Rituximab
S1P	Sphingosine-1-phosphate

SST-R	Somatostatin receptor
SSTA	Somatostatin analogue
TCZ	Tocilizumab
TGF	Transforming growth factor
Th cells	T-helper cells
TNF	Tumor necrosis factor
TRAb	Thyroid-stimulating hormone receptor autoantibody
Treg cells	Regulatory T cells
TSH	Thyroid-stimulating hormone
TSH-R	Thyroid-stimulating hormone receptor
α-SMA	Alpha-smooth muscle actin

Abstract

Introduction: Graves' ophthalmopathy (GO) is an inflammatory autoimmune condition that affects approximately 30% of patients with Graves' disease, representing its main extrathyroidal manifestation. Although it is self-limited in the majority of patients, it may be severely disabling because of its effect on vision and appearance, leading to significant decrease in patients' quality of life. Diagnosis is mostly clinical and its management is based on assessment of activity and severity. Glucocorticoids have been the mainstay of treatment for GO since the 1950s. However, 20-30% of patients are poorly responsive or unresponsive and responders may present relevant morbidity and mortality rates. Increasing evidence about pathophysiology of GO has provided a basis to explore other drug classes to find a more efficient and specific treatment. Therefore, the main goal of this project is to review the pathophysiology of GO in order to explain the mechanism of action and potential use of the new drugs proposed for the treatment of this pathology.

Methods: In order to write this review, it was performed a literature search during December 2018 in Pubmed and ISI Web Of Science, using MeSH terms or equivalent terminology. Results were narrowed to English language, date of publication in the last ten years and type of publication including reviews, congresses, meta-analysis, clinical studies and clinical trials.

Results: GO diagnosis is mainly clinical, but a complete assessment of disease activity, severity and impact on patients' quality of life is critical to determine further approach. Sight-threatening complications require urgent treatment, but correction of modifiable risk factors in association to other therapeutic options can be used to achieve remission of the disease. Patients with active mild disease generally benefit from local therapies and selenium, while patients with moderate-to-severe disease benefit most from therapy with glucocorticoids. As GO is an inflammatory autoimmune condition, several strategies that include orbital radiotherapy, surgery and medical targeted therapies have been proposed. These last ones focus on orbital fibroblasts, B cells, T cells and cytokines as they are effectors in disruption of autoimmune tolerance in GO patients.

Conclusion: In the incoming years, it is expectable that more immunomodulatory agents are going to be proposed and challenged as an alternative to stablished first and second-line therapies for GO management. Better disease characterization and combination therapy using suitable drugs with different mechanisms of action could allow the use of minimal doses to achieve effectiveness and minimize adverse events favouring a safe and successful therapeutic outcome.

Keywords: Graves' ophthalmopathy, Orbital fibroblasts, B cells, T cells, Cytokines, Immunotherapy.

Resumo

Introdução: A oftalmopatia de Graves (GO) é uma condição autoimune inflamatória que afeta aproximadamente 30% dos doentes com doença de Graves, representando a sua manifestação extra-tiroideia mais frequente. Embora autolimitada na maioria dos casos, a doença pode ser severamente incapacitante devido ao seu efeito na visão e na aparência, levando a uma diminuição significativa na qualidade de vida. O diagnóstico é geralmente clínico e a abordagem baseada na avaliação da atividade e severidade da doença. Os glucocorticoides têm sido o tratamento de eleição desde a década de 1950. No entanto, 20-30% dos doentes não respondem ou respondem pouco ao tratamento e aqueles sensíveis ao tratamento apresentam morbilidade e mortalidade relevantes devido aos efeitos secundários associados. Os avanços no conhecimento da fisiopatologia da doença têm permitido explorar tratamentos que possam ser mais eficientes e específicos. Portanto, o objetivo principal deste projeto é rever a fisiopatologia da GO de modo a explicar os mecanismos de ação e aplicabilidade potencial das novas estratégias terapêuticas propostas.

Métodos: Para a escrita desta revisão, foi realizada uma pesquisa na literatura em dezembro de 2018 nas bases de dados *Pubmed* e *ISI Web Of Science*, usando terminologia *MeSH* ou equivalente. Os resultados foram filtrados para língua inglesa, publicações nos últimos dez anos, sendo admitidas publicações do tipo revisão, congressos, meta-análises e estudos ou ensaios clínicos.

Resultados: O diagnóstico da GO é sobretudo clínico, mas uma avaliação completa da atividade da doença, severidade e impacto na qualidade de vida do doente é crucial para determinar a abordagem consequente. Complicações comprometedoras da visão requerem tratamento urgente, no entanto a correção de fatores de risco modificáveis em associação com outras opções terapêuticas pode ser útil para atingir a remissão da doença. Os doentes com doença ativa moderada geralmente beneficiam de terapêuticas locais e selénio, ao passo que os doentes com GO moderada-a-severa beneficiam mais do tratamento com glucocorticoides. Como a GO é uma condição inflamatória autoimune, têm sido pospostas várias estratégias que incluem a radioterapia local, a cirurgia e as imunoterapias dirigidas. Estas últimas têm como alvo os fibroblastos do olho, as células B, as células T e as citocinas, uma vez que que estes funcionam como efetores na disrupção da tolerância imunitária nos doentes com GO.

Conclusão: Nos próximos anos, é expectável que mais agentes imunomoduladores sejam propostos e testados como alternativa ao tratamento de primeira e segunda linha da GO. Uma melhor caracterização da doença e a associação de medicamentos adequados que tenham diferentes mecanismos de ação poderão permitir a utilização de doses mais baixas de modo a manter a efetividade e minimizar os efeitos adversos associados ao tratamento, favorecendo assim um resultado terapêutico mais seguro e eficaz.

Palavras-chave: Oftalmopatia de Graves, Fibroblastos da órbita, Células B, Células T, Citocinas, Imunoterapia.

Introduction

Graves' ophthalmopathy or orbitopathy (GO), also known as thyroid-associated orbitopathy and thyroid eye disease, is an inflammatory autoimmune condition that affects approximately 30% of patients with Graves' disease (GD), representing its main extrathyroidal manifestation. (1)

However, GO is not due to the thyroid disorder itself, rather due to an autoimmune antibody reaction. Although 90% of GO cases are associated with hyperthyroidism, it can also be rarely observed in patients with euthyroidism, hypothyroidism (namely a third of patients with Hashimoto's thyroiditis), other autoimmune disorders, thyroid cancer, and neck irradiation. (1)

GO, like GD, is more common in women than men and has an annual adjusted incidence rate of 16 women and 3 men per 100,000 population with a female:male ration of 5:1. (2) It usually starts between the third and fourth decades of life and tends to be more severe in older patients and men and milder in Asian people. Other risk factors have been associated with development and progression of GO, including tobacco use, ethnicity, biochemically more severe hyperthyroidism, high thyroid-stimulating hormone receptor autoantibodies (TRAbs) and radioactive iodine (RAI) treatment. (3,4) Tobacco use is the most important modifiable risk factor and it has been associated with more severe and progressive GO, worsening of symptoms after RAI treatment and worse response to intravenous glucocorticoids (GCs) or immunosuppressant therapies. Several polymorphisms have been proposed to be associated with GO susceptibility, but further investigation is required. (5)

Diagnosis of GO is clinical, typically based on manifestation of ocular signs and symptoms due to expansion of extraocular muscles and fat in the orbit. Although it is mostly a self-limited condition, severe effects on vision and appearance may occur and lead to significant decrease in patients' quality of life. (6) Its management must then be based on the correct assessment of activity and severity. (7) While mild GO is treated mainly with local measures and sight-threatening GO requires a surgical approach, moderate-to-severe disease requires also systemic therapy.

GCs have been the mainstay of treatment for GO since the 1950s. (8) However, 20-30% of patients are poorly responsive or unresponsive at all and the responders present morbidity and mortality rates of 6.5 and 0.6%, respectively. Disease relapse after drug withdrawal occurs in 10-20% of patients. (7) Increasing evidence about pathophysiology of GO has provided a basis to explore other drug classes to find a more efficient and specific treatment.

Therefore, the main goal of this project is to review the pathophysiological mechanisms of GO in order to explain the mechanism of action and potential use of the new drugs proposed for the treatment of this pathology.

Methods

In December 2018, it was performed a literature search in PubMed using the following MeSH terms - "Graves ophthamopathy/drug therapy", "Graves ophthalmopathy/physiopathology" and " Graves ophthalmopathy/therapy" - and also in ISI Web Of Science using equivalent terminology. Results were narrowed with filters of language (English), publication type (review, congress, meta-analysis, clinical studies and clinical trials) and publication dates (last ten years). A total of 216 articles were screened and 92 excluded because they did not match the main objective of this article or had repetitive information. After full text assessment of the remaining articles, 74 were eligible for inclusion in this review. Additional articles considered relevant were also included.

Results

1. Pathophysiology

Disruption of autoimmune tolerance is the hallmark in the pathophysiology of Graves ophthalmopathy (GO) (**Fig. 1**). In fact, thyroid-stimulating hormone receptor (TSH-R), the main autoantigen in Graves' disease (GD), is expressed primarily in the thyroid but also in adipocytes, fibroblasts, and a variety of additional sites. (9) When TSH-R on orbital fibroblasts (OFs) is recognized by antigen-presenting-cells, they lead to activation of T cells. As simultaneously B cells migrate to the orbit and recognize TSH-R through B cell receptor, B cell activation also occurs. The combination of CD40L on T cell surface and CD40 on B cell surface acts as a second signal of B cells activation with subsequent release of IL-4 by T cells. IL-4 leads to clone proliferation of B cells, differentiation into plasma cells and production of autoantibodies. (10)

Thyroid-stimulating hormone receptor autoantibodies (TRAbs) and activated T cells are then able to recognize TSH-R on retroocular fibroblasts and adipose connective tissues in the orbit. (11) When TRAbs in the orbital cavity bind TSH-R on these cells, they mimic the action of thyroid-stimulating hormone (TSH), causing excessive thyroid hormone production, (12) and trigger an autoimmune reaction leading to lymphocytic infiltration into the orbital tissues. The interaction of B7 on B cell surface with CD28 on T cell surface provides a second signal for T cell activation, leading to production of several adhesion molecules and chemokines by OFs and recruitment of more lymphocytes. (10,13)

In early GO, diffuse infiltration of primarily CD4+ T cells is the predominant microenvironmental effector in the orbit but CD8+ T cells, macrophages, plasma cells and B cells are also evident in the extraocular muscles (EOM) and adipose tissue. (14,15) Recent studies suggest that elevated levels of miR-4443 found in CD4+ T cells result in an increased expression of proinflammatory effectors with a greater impact in all orbit-resident cells, including stromal fibroblasts and the vascular system. (16,17) In fact it is known that several CD4+ T-helper (Th) subsets play an important role in the pathophysiology of GO: Th1 cells mainly in the induction and initial stages of GO (cell-mediated immune response), Th2 cells in a more chronic stage (humoral-mediated immune response) and, more recently, Th17 cells were closely associated to the progression and clinical course of the disease. (14,15,18) Regulatory T (Treg) cells, which account for 5-10% of peripheral blood CD4+ T cells, also have crucial immunoregulatory functions in GO pathogenesis.

Th1 cells are found in a higher percentage in the peripheral blood of GO patients compared to GD patients and the frequency of Th1 cells and the Th1/Th2 ratio are positively correlated with the inflammatory activity of the disease. (19) These cells release or stimulate OFs production of proinflammatory cytokines that were detected in extraocular myocytes and adipocytes of GO patients, (15) including interferon (IFN)-γ, tumor necrosis factor (TNF)-α and interleukin (IL)-1β. (8) IFN-γ is a cell

signalling protein released by activated Th1 and natural killer (NK) cells to activate/enhance macrophage phagocytosis, stimulate OFs to secrete monocyte chemotactic factors such as C-C motif ligands (CCL), and stimulate release of T cell chemokines, including C-X-C motif ligands (CXCL) 9, CXCL10 and CXCL11. TNF-α, also secreted by activated macrophages, increases the production of acute phase reactants and other proinflammatory cytokines, stimulating OFs expression of CCL2, CCL5, CCL7, IL-6, IL-8 and IL-16, which are involved in further T, B and mast cells activation. The infiltration of these cells on orbital tissues depends on expression of intercellular adhesion molecule (ICAM)-1 on OFs, which is increased by IFN-γ, TNF-α, IL-1α and IL-1β. IL-1β is an endogenous pyrogen that activates the insulin-like growth factor-1 (IGF-1) pathway in CD34+ OFs, a subset of OFs specifically found in GO patients, and upregulates the expression of cyclooxygenase-2 (COX-2) by enhancing its gene promoter activity and mRNA stability in OFs. Consequent release of more proinflammatory cytokines and synthesis of prostaglandin E2 (PGE2) leads to vasodilation and infiltration of inflammatory cells.

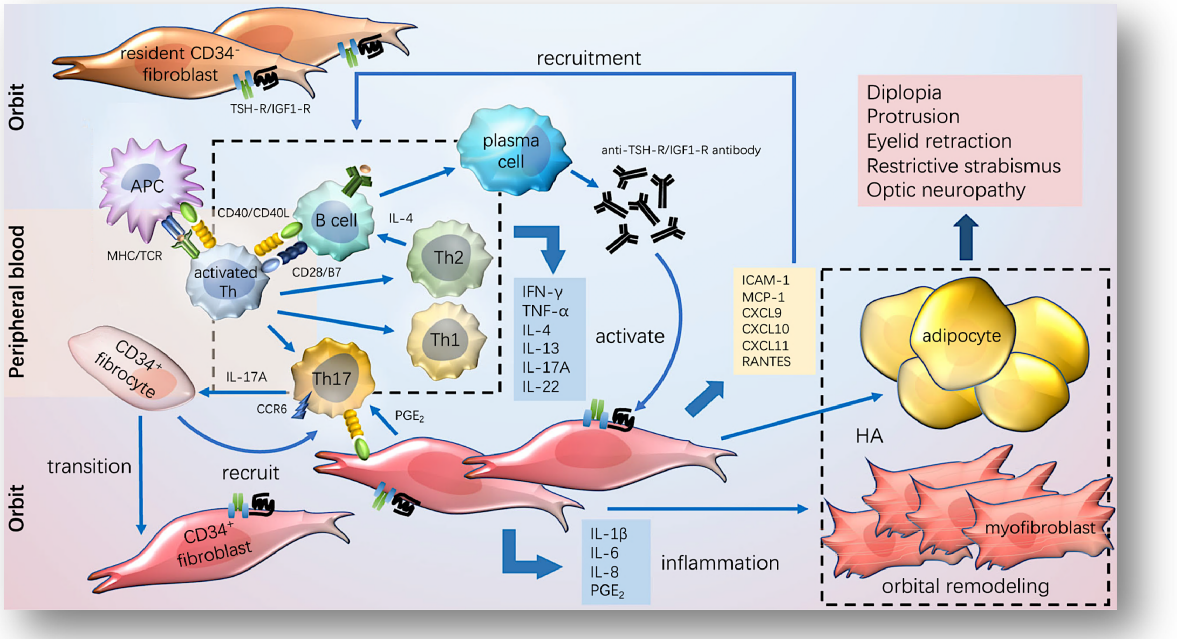

Figure 1 Pathogenesis of Graves Ophthalmopathy (GO). T cells, B cells, and CD34+ fibrocytes infiltrate into the orbit. Antigen-presenting cells (APC) present self-antigens to T cells. Activated T cells differentiate into T helper (Th) subtypes, producing several proinflammatory cytokines, which activate orbital fibroblasts (OFs) and stimulate their proliferation and differentiation. Two signals are needed to activate B cells, the self-antigen recognition and interaction with activated T cells. Activated B cells then differentiate into plasma cells and secrete autoantibodies. Both CD34+ and CD34– OFs express thyroid stimulating hormone receptor (TSH-R) and insulin-like growth factor 1 receptor (IGF-1R). When activated, these cells secrete proinflammatory factors and chemokines that allowed recruitment of more lymphocytes. They can also differentiate into adipocytes or myofibroblasts and promote the synthesis of hyaluronic acid (HA), leading to increased volume of the orbital tissues, remodeling of the orbit and ultimately to the clinical manifestations of GO (Adapted from Huang *et al.*, 2019).

Th2 cells also produce additional inflammatory cytokines, which are important to induce humoral-mediated immune responses. They release IL-4, which promotes differentiation of *naive* CD4+ T cells to produce additional Th2 cells (positive feedback), and IL-10, which also inhibits the secretion of Th1 cytokines (negative feedback), suppressing activated macrophages and dendritic cells. Additional release of IL-5, IL-6 and IL-13 contributes to differentiation of B cells and cytotoxic T cells.

Th17 cells, especially when driven by IL-1β, IL-6, IL-23 and TGF-β, are known by its major contribution to autoimmune inflammation. (18,20) These cells are related to various autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, psoriasis, inflammatory bowel disease, Behcet's disease, systemic sclerosis, systemic lupus erythematosus, and high IgE syndrome. (21) These proinflammatory cytokines are increased in the serum and the orbits of patients with GO (22) and it is thought that they guide Th17 cells toward a more pathogenic phenotype: IFN-γ- and IL-22-expressing CD3+CD82RORγt+CCR6+IL-17A+ cells. (18) CD44 is highly expressed on surface of a subpopulation of these cells, being associated to a more activated state of GO Th17 cells capable of produce IL-17A. CD44 is also a major receptor for hyaluronic acid (HA), mediating T cell adhesion to OFs (18) and serving as an important signal to recruit themselves into the orbits. (22) Increased levels of IL-17A amplify the proinflammatory response of OFs and Regulated upon activation, and normal T-cell expressed and secreted (RANTES), inhibits adipogenesis in those expressing CD90 (18) and promotes α-SMA expression and ECM deposition leading to fibrotic changes in GO. (22) CD90 is a surface marker, also known as Thy-1, highly expressed in a subpopulation of fibroblasts that produces PGE2, IL-8 and HA. When exposed to TGF-β, which is strongly expressed in the orbit of patients with mild and severe GO, these fibroblasts also differentiate into myofibroblasts and increase their expression of sphingosine-1-phosphate (S1P), a known profibrotic effector, and plasminogen activator inhibitor-1 (PAI-1), a serine protease inhibitor present at higher levels in tears of GO patients. (14,23,24) So, it is thought that high levels of IL-17A, TGF-β and enhanced CD90+ expression in GO orbits would ultimately determine the clinical manifestation and progression of GO to a more or less fibrotic phenotype. (18)

Treg cells reduction or dysfunction is also an important risk factor for the pathogenesis of various autoimmune diseases and, in fact, it was found that its levels in peripheral blood of GO patients can be used as a predictor of clinical course and severity of the disease. Cytotoxic T lymphocyte antigen 4 (CTLA-4), also known as CD152, is constitutively expressed on Treg cells and acts as an immunological checkpoint for negative regulation of T cell activation. Indeed, it was found that low levels of CTLA-4 mRNA and high levels of forkhead box P3 (a transcriptional factor of Treg cells) mRNA in orbital tissues of GO patients due to activation of phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway may be associated with the expansion of the orbital inflammation and GO severity. (25,26)

CD8+ T cells are mature cytotoxic T cells primarily responsible for immune defence against intracellular pathogens and tumor monitoring. However, it is known that their reduction or dysfunction leads to impaired immune surveillance and increased autoimmune responses. In such cases, GO included, there

is an increased CD4/CD8 ratio and the Th cells response to autoantigens is thought to be amplified. (19,25) Different subsets of CD8+ T cells are able to secrete IFN-γ, IL-5, IL-9, IL-17 and TGF-β, having a synergistic profibrotic effect of OFs. However, the complete understanding of CD8+ T cells contribution to GO remains unclear. (15)

Weakened regulatory mechanisms play also an important role in the pathogenesis of GO. In fact, besides Treg cells reduction, it was found significantly lower TIM-3 and galectin-9 expression on Th1 and Th17 cells in patients with GO. By binding to its ligand, galectin-9, TIM-3 serves as a negative regulator in Th1 mediated immune responses. Impaired expression or blockade of TIM-3 on these cells leads to failure of peripheral tolerance and enhanced inflammatory activity which may be associated with the susceptibility of GO in GD patients. (27)

These various stimuli lead to activation of OFs and their subsequent differentiation into mature adipocytes and myofibroblasts with production of HA, a non-sulfted glycosaminoglycan (GAG), through activation of HA synthase 2 (HAS2). (8,14) The accumulation of this high-hydrophilic GAG in turn leads to fluid accumulation (osmotic effect), muscle swelling and an increase in pressure within the orbit. (12) These changes, together with retroocular adipogenesis and the continuous migration and inflammatory cell influx, displace the eyeball forward, leading to extraocular muscle dysfunction, impaired venous drainage and ultimately to the typical clinical features of GO.

2. Diagnosis

GO diagnosis is mainly based on clinical presentation of ocular signs and symptoms. Patients may manifest unilateral or bilateral exophthalmos, retropulsion, ocular motility disturbances (binocular diplopia, poor convergence, restriction of extraocular muscles), lid retraction, ocular discomfort, conjunctival injection and chemosis. (28,29) In 30% of cases GO patients have a previous diagnosis of GD from months to years, however, it is important to keep in mind that hyperthyroidism, euthyroidism or hypothyroidism can be present. (1) Decreased levels of TSH and increased levels of free T3 and T4 in laboratory analysis may be found and indicate hyperthyroidism, but TRAbs detection is the sensitive and specific maker for GO. (30) In uncertain cases, orbital imaging techniques may be helpful for reveal abnormalities associated with GO in 90% of cases. Computerized tomography is a confirmatory test that shows exophthalmos, increased fat density, inflammation and enlargement of extraocular muscles, and may help to monitor progression of disease. Magnetic resonance imaging is an alternative option to tomography that can show similar findings and additional compression of the optic nerve. (31)

GO has a self-limiting natural course, characterized typically by a first phase of active inflammation of the orbital tissues, in which signs and symptoms worsen rapidly up to a peak of maximum severity, and a second phase of stabilization and regression of the inflammatory process, which may lead to fibrosis and requirement of rehabilitative surgery (Rundle's curve) (**Fig. 2**). (7,32,33) The first phase of GO

generally lasts for 18 to 36 months and the second one for 12 to 18 months, but it is known that inflammatory activity precedes the severity peak by a few months. As the therapeutic approach depends on the correct assessment of GO activity and severity, rigorous clinical examination of the patient must be performed. (28,32)

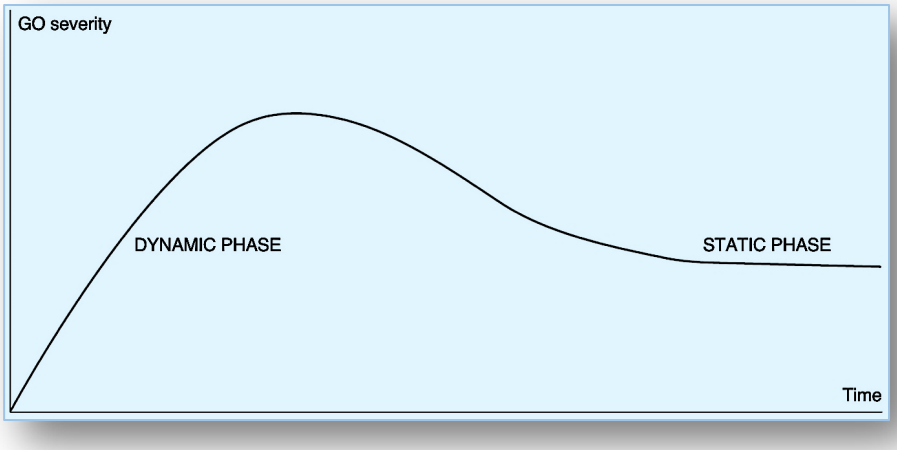

Figure 2 Rundle's curve from Kalmann and Mourits describes the biphasic course of Graves Ophthalmopathy (GO): a first phase of active inflammation and a second phase of stabilization and regression of the inflammatory process (Adapted from Bartley, 2011).

Several classification schemes have been conceived to assess the clinical manifestations of GO. (6) The first one, NO SPECS classification (No physical signs or symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle signs, Corneal involvement, and Sight loss), was created in 1969 but it grades exclusively for clinical severity of GO. For that reason, alternative assessment schemes have been developed, including CAS (Clinical Activity Score), VISA (Vision, Inflammation, Strabismus, and Appearance) and EUGOGO (European Group On Graves' Orbitopathy) classification. As different schemes have their own limitations and are not interchangeable, it is recommended to monitor consistently each patient on one or the other. (28)

Modified CAS (**Table 1**) and EUGOGO classification (**Table 2**) are widely used in Europe to assess activity and severity of GO. An active phase is diagnosed with modified CAS score of at least 3/7 at first examination or 4/10 on follow-up visits. The disease severity assessment is based in evaluation of modified CAS items for soft tissue inflammation (except pain), eyelid measurements, proptosis, ocular motility, corneal integrity and optic neuropathy. (6) The disease severity is then graded in mild, moderate-to-severe or very severe (sight-threatening) GO. This is a critical point because application of CAS items cannot always be adjusted to the different phenotypes of the disease. (7,32)

Quantification of quality of life (QoL) in GO is another step that should be done for a correct evaluation of patient status. Despite general health-related QoL questionnaires, there is a specific-disease scale

created in 1998 for GO patients. It consists of 16 questions focusing on visual impairment due to decreased visual acuity or diplopia and on psychosocial effects of facial disfigurement in the patient. The use of this scale has several advantages because it is easy to calculate, self-administered, reproducible, and it correlates to severity of disease. Moreover, this score is a reliable measure of disease changes over time, including changes after medical or surgical treatment. (34)

Table 1 Clinical Activity Score (CAS), according to Mourits *et al.*. One point is given for the presence of each parameter and the sum ranges from 0 to 10. An active phase of GO is defined when the score is at least 3/7 at the first examination or 4/10 in successive examinations.

Spontaneous retrobulbar pain or oppressive feeling during the past 4 weeks
Pain on attempted upward or downward gaze during the past 4 weeks
Redness of the eyelid(s)
Diffuse redness of the conjunctiva, covering at least one quadrant
Swelling of caruncle or plica
Swelling of eyelid(s)
Swelling of conjunctiva (chemosis)
Exophthalmos increase of ≥2 mm during a period of 1-3 months
Decrease of eye movements in any direction ≥8º during a period of 1-3 months
Decrease of visual acuity of ≥1 line(s) on the Snellen chart during a period of 1-3 months

Table 2 Assessment of severity with European Group On Graves' Orbitopathy (EUGOGO) classification. GO is classified as mild when patients have one or more features that have only a mild impact on daily life and moderate-to-severe when patients have two or more features that impact on daily life sufficiently to justify the risks of immunosuppression or surgical intervention.

Mild GO	Minor lid retraction (<2 mm) Minor soft-tissue involvement Exophthalmos <3 mm above normal for race and gender No or intermitent diplopia Corneal exposure responsive to lubricants
Modera-to-severe GO	Lid retraction >2 mm Moderate or severe soft-tissue involvement Exophthalmos ≥3 mm above normal for race and gender Inconstant or constant diplopia
Very severe (sight-threatening) GO	Dysthyroid optic neuropathy (DON) Corneal breakdown

3. Treatment

Treatment of patients with GO is based on a general approach and on specific measures according to activity and severity of disease. Even if it is commonly a self-limiting condition, intervention may be necessary not just because of recurrence of symptoms or risk of complications but also because it has a negative impact in patients' QoL.

3.1. Standard approach

Once GO is confirmed, it is imperative to exclude the presence of sight-threatening complications such as dysthyroid optic neuropathy (DON), globe subluxation or corneal ulceration. (35) The first situation is treated with high-dose IV GCs and additional orbital decompression in some reference centres, the second one requires surgical repair depending on severity and the third one, due to associated eyelid retraction and proptosis, is treated with surgical repair and additional local measures to improve globe coverage (**Fig. 3**). These measures include artificial tears and the use of sunglasses but some ointments such as carboxymethylcellulose have osmoprotective properties that confer additional epithelial protection and symptomatic control. (35,36)

Even in the absence of these complications, all patients at risk for or with established GO benefit significantly from correction of their own risk factors. Cessation of smoking is indeed a crucial step in the treatment of GO because tobacco use has been strongly linked to higher prevalence of GO among GD patients, more severe clinical course of the disease and poorer responsiveness to standard therapies. (37) Restoration of euthyroid status is also important to prevent further progression of GO and it can be achieved using antithyroid drugs (ATD) as thionamides, RAI ablation or thyroidectomy. (38) These three options seem equally acceptable when the patient has no risk factors for GO, such as cigarette smoking or high baseline serum concentration of T3. However, in cases of active mild GO, it is recommended concomitant short course of oral GCs with a daily dose of 0.3-0.5 mg prednisone/kg to prevent RAI-induced exacerbation of GO when RAI ablation is the chosen therapy because it has been reported to worsen or develop *de novo* GO with higher risk than ATD (38.7% and 21.3%, respectively). (7,39) In cases of active and moderate-to-severe or sight-threatening GO, RAI ablation is contraindicated and therefore the treatment must be based on ATD therapy or surgery. (39) Usually both strategies lead to progressive reduction of serum concentration of TRAbs, suggesting waning of autoimmunity, unlike RAI treatment that causes elevation of TRAbs levels. In patients with low likelihood of complete remission on ATD therapy, thyroidectomy was shown to have the potential to inactivate and significantly decrease severity of disease with no different outcomes between total or subtotal surgical approaches. (40,41) It is important to keep in mind, nonetheless, that reducing thyroid hormone secretion does not improve GO itself, although it does decrease eyelid retraction and stare. Secondary hypothyroidism, in turn, can cause more fluid retention and worsen orbitopathy. Therefore, monitoring of thyroid function every 4-6 weeks is essential during the early stages of treatment. (6)

Activity and severity of GO dictate further treatment. As spontaneous remission can occur within about 6 months, management of mild GO is focused on symptomatic relief. (28) Local therapies above mentioned are of particular importance at this point and additional oral selenium supplementation is indicated in case of active disease due to its anti-inflammatory and antioxidant properties. (42) For most patients with mild active GO, local measures and selenium are efficient controlling symptoms. However, in case of progression or decrease in patients' QoL, the treatment is then decided as in the context of moderate-to-severe GO. The trend of disease progression over the last 3 months is often used as guide to decide the most suitable intervention on a risk-benefit basis. Rehabilitative surgery should be then proposed if moderate-to-severe disease is in an inactive phase, otherwise, IV GCs remain the mainstay treatment. (36)

Several strategies are actually pointed as second-line therapy and the more GO pathophysiology is clarified, more studies have been done to investigate the potential of established treatments of other diseases on GO. Next sections present the most relevant strategies already proposed or under investigation and their potential use for the treatment of this pathology with a special focus on medical targeted therapy (**Table 3**), but also on orbital radiotherapy and surgical approaches.

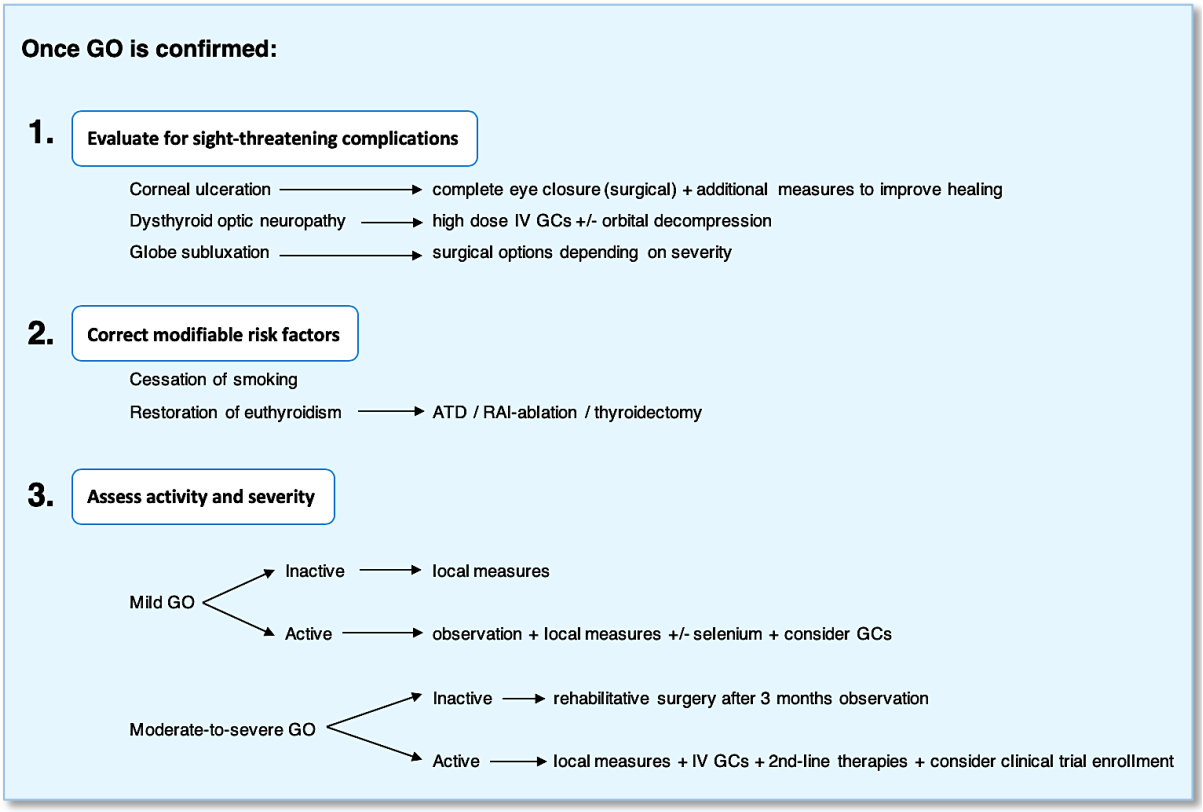

Figure 3 Algorithm for the treatment of Graves Ophthalmopathy (GO). IV, intravenous; GCs, glucocorticoid; ATD, antithyroid drugs; RAI-ablation, radiodine iodine ablation (Adapted from Genere & Stan, 2019).

3.2. Medical targeted therapy

3.2.1. Orbital fibroblasts

Thyroid-stimulating hormone receptor

TSH-R is the main autoantigen of GO and its blockade could be a promising strategy for targeted therapy. (8) Several *in vitro* studies on thyrocytes and OFs have been already done, (8,43) but only few clinical trials have been completed so far and their results are not yet published. K1-70, for example, is an intramuscular TSH-R antagonist actually being tested in an open-label clinical trial phase 1 to assess both safety and dosing scheme in patients with GD (NCT02904330). (43) ATX-GD-59, by its side, is an intradermal injectable peptide-based therapy also tested in patients with GD in a clinical trial phase 1 whose results have not been released yet (NCT02973802).

Insulin-like growth factor 1 receptor

IGF-1 receptor (IGF-1R) was shown to be co-expressed with TSH-R on OFs of GO patients (44) and also overexpressed on lymphocytes. (45,46) As *in vitro* blockade of IGF-1R showed attenuation of TSH-dependent signalling with decreased expression of IL-6, IL-8 and Akt phosporilation, (47) several studies using teprotumumab were performed. Teprotumumab is a specific human monoclonal antibody that binds to the extracellular subunit domain of IGF-1R and was described as a potential disease-modifying drug in GO. (48) It has shown impressive results in a phase-2 multicentre placebo randomized controlled trial (RCT) published in 2017, where 88 patients received teprotumumab or placebo infusion every 3 weeks for a total of 8 IV infusions (the first one with 10 mg/kg and the remaining doses with 20 mg/kg). (48) All patients developed GO within 9 months of the start of the trial, had CAS ≥4 and had not received any prior therapy with the exception of oral GCs. Group of patients treated with teprotumumab developed significant clinical improvement compared to placebo group (69% vs. 20%, respectively) and tend to respond earlier to therapy, leading to an objective improvement in patients' QoL. Adverse events described were mainly mild, but 5 patients developed more serious complications (diarrhea, inflammatory bowel disease, *Escherichia coli* sepsis, autoimmune encephalopathy and urinary retention) and 7 patients developed hyperglycemia manageable with anti-hyperglycemic medications. Overall, these promising results suggest that teprotumumab could be a safe and effective treatment for patients with active moderate-to-severe GO of recent onset. (48,49) A second RCT (NCT03298867) has already been initiated to validate these findings and further studies are needed to compare its effects with IV GCs.

Platelet-derived growth factor receptor

Platelet-derived growth factor subunit B is an isoform of the platelet-derived growth factor (PDGF) receptor that has been found expressed and increased in the orbital tissues of GO patients. (7) Its signalling can be blocked using tyrosine kinase inhibitors such as imatinib mesylate, nilotinib and dasatinib, leading to decreased expression of HAS2, IL-6 and IL-8. (50) However serious side effects (periorbital edema, peripheral arterial occlusive disease, cerebrovascular events) that have been described with imatinib mesylate and nilotinib may impact their availability as an effective and safe alternative therapy. (51) Dasatinib, the tyrosine-kinase inhibitor for PDGF receptors with the lowest half maximal inhibitory concentration, was shown to be effective in *in vitro* studies and may provide a safer alternative in the future. (50)

Somatostatin receptors

Expression of somatostatin receptors (SST-R) 1, 2, 3 and 5 was found in lymphocytes and fibroblasts of retrobulbar tissue from GO patients. (52) As use of somatostatin analogues (SSTA) has shown to decrease local cytokines production and release of IGF, their potential to treat GO has been tested in clinical studies. (53) Octreotide long-acting release and lanreotide, that act predominantly on SST-R2, have shown improvement of GO symptoms in several uncontrolled trials. However, their beneficial effect compared to placebo has not been associated with clinically relevant reduction in CAS and improvement in patients' QoL in subsequent RCTs. (54,55) It is thought that this lack of efficacy might be explained by the low binding affinities of octreotide and lanreotide for SST-R1 and SST-R5. (8) Of note that results of a phase 2 double-blind RCT (NCT00288522) to evaluate efficacy and safety of lanreotide in patients with active moderate GO have not been released yet. In any case, these drugs still seem an interesting alternative due to their promising *in vitro* results and low rate of severe adverse events, but it is suggested that further study designs should include only patients with short lasting, active disease to effectively understand their therapeutic effect. Pasireotide, by its side, is a SSTA with much higher affinity for STT-R1, STT-R3 and STT-R5, but it has not been tested yet in the context of GO. (53,56)

3.2.2. B cells

CD20

Rituximab (RTX) is a chimeric monoclonal antibody that targets CD20, a human B-lymphocyte-specific antigen expressed on pre-B and mature B-cells but not on plasma cells. (54) It leads to transient augmentation of antibody-dependent cell-mediated cytotoxicity and complement-mediated lysis, causing B-cell depletion and potential blockade of TRAbs and inflammatory cytokines production. RTX is classically used to treat CD20-positive non-Hodgkin lymphoma and CD20-positive chronic lymphocytic leukemia. However, due to its B-cell-depleting action, it has been also tested for the

treatment of moderate-to-severe active rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis. Side effects of RTX are dose-related and most of them are reversible but fatal infusion reactions were also described. It was not found an association between RTX and increased risk of malignancy, but it still to be confirmed its association with increased incidence of progressive multifocal leukoencephalopathy. (7,53) Several studies have been performed to understand the potential benefit of RTX as first or second line therapy in GO and which should be the best dosage and administration protocols. (7) Once previous studies have suggested substantial improvement of CAS in patients with prior GCs failure, two double-blind RCTs were performed to compare efficacy of IV RTX to either placebo or IV GCs. (57,58) These studies had contradictory results because one reported no difference of RTX use (2 g total dose) compared to placebo and another reported CAS improvement even at lower doses of RTX (0.5 g and 2 g), increased disease inactivation and more effectiveness than high-dose IV GCs on motility and QoL of all patients. Nevertheless, it is pointed that patients in the placebo-RCT had significantly longer disease duration, higher proportion of old males and higher TRAb levels, all of which are risk factors for poorer prognosis and may contributed to lower responsiveness to the therapy. (59) Interestingly, IV GC-RTC included more smokers and still there was not a diminished response to RTX. Both studies reported adverse events, specifically DON requiring urgent decompression in placebo-RCT and acute visual loss related to an acute cytokine release reaction in IV GC-RCT. Overall, it is suggested that RTX is more useful in patients with moderate-to-severe GO and eventually in severe cases with short disease duration, but additional trials are warranted to select optimal dosing schedules and ensure efficacy with minimal side effects. Actually, RTX makes part of the second-line therapy recommend according to EUGOGO guidelines in those patients who do not have a satisfactory response to IV GC therapy. (35)

B-lymphocyte activating factor

B-lymphocyte activating factor (BAFF) is a cytokine expressed on neutrophils, monocytes, dendritic cells, lymphoid stromal cells and malignant B cells that belongs to the TNF family. It has receptors expressed on surface of B cells, plasma cells and a subset of activated T cells. (60) Serum BAFF concentrations have been found to be elevated in systemic lupus erythematosus, rheumatoid arthritis and hyperthyroid GD patients, but not in patients with GO, even during the active phase of the disease. (61,62) However, it is thought that inhibition of B cells stimulation by blocking BAFF may reduce disease activity and subsequently have clinical benefits. Belimumab, a fully humanized monoclonal antibody against BAFF, has been approved for treatment of patients with systemic lupus after demonstration of its beneficial effects by RCTs with autoantibody-positive patients. (63) Its potential use in GO is actually being tested in an RCT involving GD patients with detectable serum TRAb and associated active moderate-to-severe GO treated with IV belimumab or methylprednisolone (NCT10057889). (64)

3.2.3. T cells

Cyclophilin

Cyclosporine is a lipophilic cyclic polypeptide extracted from the soil fungus *Beauveria nivea* that is extensively used to prevent rejection of kidney, liver and cardiac allogeneic transplants. It binds to the cytosolic protein cyclophilin of T cells and this complex is able to inhibit calcineurin, which is usually responsible for activating the transcription of IL-2. (65,66) Its use alone or in combination therapy with GCs has been tested in a RCT with patients exhibiting moderate-to-severe GO. Combined therapy was found to be superior, leading to clinical improvement and reduction of disease relapses. However, some side effects of cyclosporine (renal, infectious, hypertension, gingival hyperplasia) that could be tolerated for transplanted patients or in the context of severe systemic autoimmune disorders should be seriously taken into account before its use for GO. For these reasons, cyclosporine is actually seen as a possible but not popular drug to use in association with GCs in patients who had partial response to that agent as monotherapy, making part of second-line therapy according to EUGOGO guidelines. (35,36)

3.2.4. Cytokines

TNF-α

Most of TNF inhibitors have been widely and successfully used in rheumatoid arthritis, inflammatory bowel disease and some other autoimmune conditions. As TNF is also involved in Th1 driven autoimmune response in GO, use of etanercept, adalimumab or infliximab could be a reasonable therapeutic alternative. Etanercept is a recombinant fusion protein of extracellular ligand-binding portion of human TNF receptor that binds TNF and blocks subsequent inflammatory cascade. A clinical pilot trial with 25 mg etanercept twice weekly for 12 weeks in 10 patients with mild-to-moderate GO showed significant improvement on CAS and recurrence of 30% after treatment cessation. (67) Adalimumab, by its side, showed only promising results treating GO patients with prominent inflammatory symptoms when its efficacy was retrospectively analysed in a small study. (68) Infliximab was only used in a patient with DON, leading to decrease in CAS and vision improvement. (69) However, even if some benefit in the inflammatory status of GO patients has been reported, no RCTs have been published yet to conclude about their definitive potential in GO treatment. (53)

IL-1

Use of IL-1 inhibitors for the treatment of GO is thought to be interesting given its potential to block one of most important cytokines on GO pathophysiology. In fact, anakinra is an IL-1 receptor antagonist already approved for the treatment of rheumatoid arthritis, but with no clinical trials in context of GD or GO despite *in vitro* reported inhibition of HA production by OFs. (8)

IL-6

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody against IL-6 receptor, that acts as an antagonist and interrupts this inflammatory cascade. It is already an established drug used in the treatment of resistant rheumatoid arthritis, Castleman's disease, systemic and polyarticular juvenile idiopathic arthritis, giant cell arteritis, Takayasu arteritis and cytokine releasing syndrome with successful results and a favourable side effect profile. (70-72) Several studies have been performed to understand its potential role in the treatment of GO. A recent open clinical trial on 18 patients with active GO refractory to GCs showed that 8 mg/kg of TCZ every 4 weeks decreased the activity of disease in all patients, decreased values of proptosis in 72% of them, improved ocular motility in 83% and decreased TRAbs values by approximately 40%. Follow-up period of this study ranged from 9 to 27 months because it was proposed to do it until CAS ≤1 or TRAbs were negative. Side effects were mainly mild (fatigue, musculoskeletal complaints) and only 2 patients who developed neutropenia required a slight dose reduction. (73) Another recent study showed successful treatment of 29 patients who could not tolerate GCs and MTX, leading to reduction of CAS, TRAbs level and laboratory markers of inflammation without severe complications. (74) The first RCT performed revealed significant improvement in proptosis and CAS in 93% of patients treated with 4 monthly infusions of TCZ compared with 59% of patients treated with placebo. Severe adverse events were reported only in 2 patients who developed moderate increase in transaminases and acute pyelonephritis at 9 and 32 weeks of treatment with TCZ, respectively. (75) Nevertheless, the impact on long-term outcome is unknown and subsequent studies should be performed to confirm these promising results.

3.2.5. Others

Purine metabolism

Azathioprine is a purine analogue with immunosuppressive and antiproliferative properties used mainly in transplantation medicine. Its potential has also been proved in some autoimmune disorders, namely rheumatoid arthritis and inflammatory bowel disease. However, when tested as monotherapy in GO, azathioprine showed no benefit compared to control patients and, more recently, when tested in association to GCs in an RCT, it leaded to discontinuation in more than 50% of patients. Those who did not withdraw the treatment with azathioprine had improved clinical outcome at 48 weeks, suggesting that it may have a potential role preventing long term relapse after GCs discontinuation. (36,76)

Dihydrofolate reductase enzyme

Methotrexate (MTX) is a chemotherapeutic and immunosuppressant agent with anti-inflammatory and immunomodulatory properties at lower doses. As an antimetabolite, its main mechanism of action consists in the competitive inhibition of dihydrofolate reductase enzyme (DHR-E) and ultimately of purine

and pyrimidine base biosynthesis. It is thought that MTX is involved in multiple additional mechanisms, including selective down-regulation of B cells and inhibition of T cell activation and IL-1β effect. (77-79) Because of its effectiveness, low-dose MTX is widely used as first-line therapy for the treatment of rheumatoid arthritis and its role as second-line therapy for GO has been studied. (80-83) All retrospective trials performed enhance the beneficial effect of MTX as a safe and effective treatment for active moderate-to-severe GO for patients who cannot tolerate steroids. Mild adverse events were initially described as very common, but no severe side effects were reported with smallest doses (7.5-10 mg weekly) and subcutaneous administration. (82)

Inosine monophosphate dehydrogenase enzyme

Mycophenolate mofetil (MMF) is an immunosuppressive agent that inhibits inosine monophosphate dehydrogenase enzyme (IMD-E), leading to depletion of guanosine nucleotides from T and B cells. Its potential benefit in the treatment of active moderate-to-severe GO has been tested both alone and in association with GCs. It was found an overall clinical improvement in 93% of patients treated with 1 g daily of MMF compared to 71% of those treated also with GCs (IV and oral). Patients from the first group presented higher response rate to therapy (91% vs. 68%) at 24 weeks of treatment, higher CAS reduction and lower adverse events, suggesting that MMF may be more effective and safer. (39,84) Recently is was published by EUGOGO an RCT comparing the use of IV GCs alone or in combination with 360 mg twice daily of MMF in patients also with active moderate-to-severe GO. Most of parameters evaluated were not significantly different between the two groups, however, authors concluded that addition of MMF to IV GCs may be beneficial with longer duration of therapy providing improvement in QoL and ocular patients' symptoms. (85) Taking into account that other studies reported higher rates of adverse events, (86) further investigation should include double-blind RCTs to better understand the real benefit and safety profile of MMF in the treatment of GO.

PIK3-AKTmTOR pathway

Several inhibitors of PIK3-AKT-mTOR pathway have shown a reduction of HA accumulation and adipogenesis in *in vitro* studies. Despite some concerns related to the side effects profile of these drugs, two agents still under recent investigation in GO, namely idelalisib and trifluoperazine. The first one has proven to decrease IL-1β–induced expression of IL-6 and IL-8 in GO OFs but not in non-GO cells. The second one inhibits the nuclear exclusion of transcription factor FOXO1, which represents a convergence point for the signalling cascades, and, at least *in vitro*, it was shown to be an effective inhibitor of adipogenesis and HA accumulation. Trifluoperazine was developed and tested as a cancer therapy, however, it could be interesting test it in the future for the treatment of GO. (87)

Table 3 Prominent clinical studies of medical targeted therapy for Graves Ophthalmopathy.

Target	Drug	Trial	Results
Orbital fibroblasts			
TSH-R	K1-70	Open-label clinical trial (NCT02904330)	To be released
	ATX-GD-59	Open-label clinical trial (NCT02904330)	To be released
IGF-1R	Teprotumumab	RCT, double blind (comparison with placebo) (48)	Superior reduction in CAS and proptosis, causing hyperglycemia in diabetic patients
		RCT, double blind (comparison with placebo) (NCT03298867)	To be released
SST-R	Octreotide long-acting release	RCT, double blind (comparison with placebo) (55)	Superior reduction in CAS, but with no clinical relevance and some gastrointestinal side effects
	Lanreotide	RCT, double blind (comparison with placebo) (NCT00288522)	To be released
B-cells			
CD20	Rituximab	RCT, double blind (comparison with placebo) (57)	Equivalent to placebo, but with serious side effects
		RCT, double blind (comparison with IV MP) (58)	Superior to IV MP reaching GO inactivation
BAFF	Belimumab	RCT, blinding not mentioned (comparison with IV MP) (NCT10057889)	To be released
T-cells			
Cyclophilin	Cyclosporine	RCT, blinding not mentioned (comparison associated with oral GC or oral GC alone) (36)	Superior CAS reduction in combination therapy
Cytokines			
TNF-α	Etanercept	Open-label pilot trial (67)	Significant CAS reduction
	Adalimumab	Retrospective, with varied prior treatments (68)	Significant reduction of inflammation and higher recurrence rate after discontinuation
	Infliximab	Case report (69)	CAS reduction and vision improvement in a patient with DON
IL-6	Tocilizumab	Prospective interventional study (73)	Significant reduction of CAS and proptosis with improved extra-ocular motility and no significant side effects
		Open-label clinical trial (74)	Significant reduction of CAS and proptosis in GC- and MTX-resistant patients
		RCT, double blind (comparison with placebo) (75)	Significant reduction of CAS and proptosis in GC-resistant patients

Others			
Purine metabolism	Azathioprine	RCT, double blind (comparison associated with oral GCs and/or orbital radiotherapy or these alone) (76)	No significant improvement with high discontinuation rate
DHR-E	Methotrexate	Retrospective studies (80-82)	Use as monotherapy showed to improve ocular motility and reduce CAS in GC-resistant patients
		Retrospective study (83)	Combined treatment with IV MP showed superior reduction of CAS and inflammation and improved ocular motility
IMD-E	Mycophenolate mofetil	RCT, single blind (comparison with oral and IV GC) (84)	Superior reduction of CAS and ophthalmic involvement
		RCT, single blind (comparison associated with IV GC or IV GC alone) (85)	Combined therapy improved some symptoms and patients' QoL

BAFF, B-lymphocyte activating factor; CAS, clinical activity score; DHR-E, dihydrofolate reductase enzyme; GC, glucocorticoid; IGF-1R, insulin-like growth factor 1 receptor; IL, interleukin; IMD-E, inosine monophosphate dehydrogenase enzyme; IV, intravenous; MP, methylprednisolone; MTX, methotrexate; QoL, quality of life; RCT, randomized-controlled trial; SST-R, somatostatin receptor; TNF, tumor necrosis factor; TSH-R, thyroid-stimulating hormone receptor.

3.3. Orbital radiotherapy

Orbital radiotherapy has a non-specific anti-inflammatory effect in irradiated tissues and its potential for GO treatment has been extensively studied over years. (28,88) In fact, it is known that low doses radiotherapy leads to increased expression of anti-inflammatory cytokines (IL-10 and TGF-α) with concomitant decreased expression of pro-inflammatory cytokines (TNF-α, IL-1β) and diminished expression of adhesion molecules, nitric oxide and reactive oxygen species generation. (88)

Most of RCTs have reported improvement in some parameters of CAS and severity of disease, while combination with GCs has shown to be more beneficial than monotherapy without any severe adverse events. (36) For that reason, orbital radiotherapy in association to oral GCs makes part of second-line treatment options according to EUGOGO guidelines in those patients who do not have a satisfactory response to IV GC monotherapy. (35) However, documented risk of secondary malignancies and worsening of retinal microvascular abnormalities contraindicates its use in patients under 35 years, with severe hypertension or with diabetic retinopathy. (28,29) Use of lower doses of radiation and new radiation techniques have been investigated in order to obtain both higher efficacy and lower toxicity. (88)

In a recent study, for example, use of phosphorus-32 brachytherapy has shown to improve exophthalmos, reduce tissue swelling and associated symptoms with no significant side effects 3-12 months after treatment. This could be a future option easier to perform and cheaper than traditional technique, however, whether these approaches avoid the need of rehabilitative surgeries or significantly improved QoL remains to be seen. (36)

3.4. Orbital surgery

Orbital surgical interventions are mainly performed for rehabilitative purposes when the disease is in an inactive phase and stable for at least 6 months, with exception for urgent orbital decompression in patients with evidence of compressive optic neuropathy. Orbital decompression could also be considered in case of moderate-to-severe disease when immunomodulatory therapy has failed. (29,39)

However, when disease is an active phase or in case of poor surgical candidates, temporary local treatment for eyelid retraction can be helpful for improvement of patients' QoL. Three major options are available and have been already tested in the context of GO, namely transcutaneous or transconjunctival injection of HA, triamcinolone or botulinum toxin type A. The first option has shown to improve both eyelid retraction and lagophthalmos with an estimated effect lasting 6-12 months and reversion possible with hyaluronidase, the second one is a synthetic GC that can be used by periocular injection and has shown to improve upper eyelid retraction with a standard dose of 20 mg, and the third option is a known neurotoxic protein that causes reversible paralysis lasting 1-6 months and has shown to significantly improve upper eyelid retraction in an active or inactive phase of GO. (89-91)

Once optimized operative conditions are present, a specific sequence of surgeries can be performed for rehabilitative purposes. Orbital decompression, the first one, aims to reduce proptosis and ocular discomfort and it is usually followed by strabismus surgery for symptomatic secondary diplopia and eyelid surgery for eyelid retraction. Depending on patients' symptoms, these more invasive procedures may not be necessary. (29)

Discussion and Conclusion

GO is a rare yet challenging disease that may significantly decrease patients' quality of life. The initial evaluation of all patients with Graves' disease or Hashimoto thyroiditis should so include screening for GO. Diagnosis is mainly clinical and a complete assessment of disease activity, severity and impact on patients' quality of life is critical to determine further approach. Coordinated efforts involving endocrinologists and ophthalmologists are crucial at this point. Sight-threatening complications require urgent treatment as definitive vision impairment can occur, but correction of modifiable risk factors in association to other therapeutic options can be used to achieve remission of the disease. Patients with active mild disease generally benefit from local therapies and selenium, while patients with moderate-to-severe disease benefit most from therapy with GCs. In fact, as GO is an inflammatory autoimmune condition, corticoids have been the mainstay of treatment despite their systemic secondary effects.

Several strategies are actually recommended in EUGOGO guidelines as second-line therapy in those patients who do not have a satisfactory response to IV GC therapy, specifically rituximab as monotherapy and orbital radiotherapy or cyclosporine in association to oral GCs. However, description of some severe adverse events with these agents and specific contraindications in the case of orbital radiotherapy make important further investigation in this area. In fact, the more GO pathophysiology is clarified, more studies have been done to investigate the potential of additional established treatments of other diseases on GO. Despite of orbital radiotherapy and surgery whose new techniques have been recently studied, medical targeted therapies focused on orbital fibroblasts, B cells, T cells and cytokines as they are effectors in disruption of autoimmune tolerance continue to be challenged. Teprotumumab and tocilizumab are not recommended yet as second-line therapy, but their data seem the most promising so far. However, several results of ongoing studies are going to be released during this year. To note that not all clinical trials were double blind and a subjective measurement may be part of the outcome reported in some of them despite rigorous evaluation. It reinforces the need of promising results confirmation in studies with a much larger series of patients and comparison with standard therapy concerning both efficacy and adverse events profile. It is also curious that the trials including placebo reported consistent improvement in that group as well, demonstrating the importance of considering the natural history of GO when designing clinical trials for this pathology.

In the incoming years, it is expectable that more immunomodulatory agents are going to be proposed for GO management. Taking diseases' pathophysiology into account, some drugs being tested in other diseases may reveal interesting in the context of GO, namely those targeting CD40 (CFZ533) and CTLA-4 (abatacept). Combination therapy using drugs with different mechanisms of action also seems reasonable as it allows the use of minimal doses to achieve effectiveness and minimize adverse events. However, as GO may manifest in so different phenotypes, find more proper systems of classification could also be reasonable in order to identify subgroups of patients where the balance between potential benefits and risks of a specific therapy is most likely to favour a safe and successful therapeutic outcome.

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