Update on the medical treatment of Graves’ ophthalmopathy

Gregory J Griepentrog
James A Garrity
Department of Ophthalmology, Mayo Clinic, Rochester, MN, USA

Purpose: To review recent advances in the understanding of Graves’ ophthalmopathy (GO) pathogenesis as well as discuss current and future medical management strategies.

Design: Interpretive essay.

Methods: Literature review and interpretation.

Results: Medical treatment of GO has slowly evolved during the past few decades and has been hampered by a poor understanding of the disease at a cellular and molecular level. Current treatment recommendations and guidelines therefore focus on nonspecific immuno-suppression. Newer classes of treatment agents hold promise to more selectively target underlying cellular and molecular alterations in GO.

Conclusion: Cooperation between individual patients, physicians and between differing medical centers, together with a refined understanding of the pathogenesis of GO, will lead to newer more-effective treatments for the disease and improve patient quality of life.

Keywords: Graves’ ophthalmopathy, thyroid eye disease, thyroid-associated ophthalmopathy

Introduction
Graves’ ophthalmopathy (GO) is the most common cause of orbital disease in adults and develops in 25% to 50% of patients with Graves’ disease (GD).1 Although thyroid manifestations of GD can be effectively managed, the prevention and ultimately treatment of GO has remained challenging. Most patients can be managed with nonsurgical treatment, which will be the focus of this article.2 The surgical rehabilitation of GO has been reviewed by others.3,4 Here, we briefly review recent advances in the understanding of GO pathogenesis as well as discuss current and future medical management strategies.

Disease pathogenesis
Depending on the diagnostic criteria utilized GO can be seen in 25% to 50% of patients with GD. The annual incidence of GO is approximately 16 in 100,000 women and 3 in 100,000 men.1 The clinical course of GO differs from most autoimmune disorders in that there is typically an active phase with remission.6 Symptoms and signs of GO range from periorbital pain, conjunctival injection, chemosis, photophobia, diplopia, grittiness, lid lag and retraction, to proptosis, ophthalmoplegia, corneal ulceration, optic nerve dysfunction, and vision loss. Expansion of the orbital tissue (extraocular muscles, connective tissue, and orbital fat) within the confines of the rigid bony orbit, can explain the majority of these observed findings.
A complex interplay between genetic and environmental factors contributes to susceptibility to GD. Although genetic predisposition to GD is well established in the literature, the precise role of genetic factors in the development of GO is unknown. Hereditary studies of GD have demonstrated a 30% to 40% concordance rate for monozygotic twins, while dizygotic twin studies reveal a lower concordance rate of approximately 5%. Non-twin siblings of patients with GD also have been noted to have an elevated risk when compared to the general population. Numerous case-controlled studies examining the role of genetic factors in the development of both GD and GO have been performed. Multiple loci for GO have been proposed including human leucocyte antigen (HLA, 6p21-3), cytotoxic T-lymphocyte antigen-4 (CTLA-4, 2q33), tumor necrosis factor (TNF, 6p21-3), interferon-γ(12q14), intercellular adhesion molecule 1 (ICAM-1, 19p13), and thyroid stimulating hormone receptor gene (TSH-R, 14q31). These results have not been confirmed or replicated in larger studies. It may be that both GD and GO are clinically heterogenous disorders making large-scale studies difficult. The possibility that GO may be predominantly influenced by environmental factors, rather than genetic predisposition, remains.

A unified theory to explain the pathogenesis of GO does not exist. GO is often (>90%), but not exclusively, associated with the onset of Graves’ hyperthyroidism, thus suggesting a common autoimmune pathogenic mechanism. Once viewed as a bystander, orbital fibroblasts have been identified as a potential autoantibody target cell within the orbit. Thyroid-stimulating hormone receptors (TSHr) have been identified in orbital fibroblasts of normal individuals and GO patients. At the mRNA level, patients with active GO have increased expression of TSHr versus patients with inactive disease. Furthermore, orbital fibroblasts show increased TSHr expression after adipocytic differentiation. Insulin-like growth factor-1 (IGF-1), another receptor on the orbital fibroblast cells, has also been shown to induce hyaluronan synthesis, while thyroid-specific antigens such as thyroid peroxidase and thyroglobulin have been detected in orbital tissues. Finally, autoantigens in extraocular muscles (calsequestrin) and orbital fibroblasts (collagen XIII) were reported to be specific and sensitive diagnostic markers of GO. It should be noted that although the autoantibody theory of GO pathogenesis is speculative as the evidence is thus far insufficient to link it fully to the clinical manifestations of GO.

Once activated, sub-populations of orbital fibroblasts may release cytokines, produce glycosaminoglycans (GAGs), and/or increase orbital fat through adipogenesis. Interleukin-6 fibroblast secretion promotes B-cell development and differentiation, while other chemokines recruit (IL-16, CXCL10, and IL-16) and activate (IL-8 and CXCL10) T-cells. Activated T cells trigger cytokine release (INFγ, TNFα, PGD2, and 15dPGJ2), thus potentiating further inflammation. One sub-population of activated orbital fibroblasts found predominantly in the orbital fat compartment termed “preadipocytes,” displays the ability to differentiate into mature adipocytes. A separate orbital fibroblast sub-population found in connective tissues, that invests the extraocular muscles, may produce GAGs such as hyaluronic acid. Accumulation of these GAGs within the body of extraocular muscles leads to edema and muscle swelling. These changes may be observed radiographically (Figure 1). Volume measurement abnormalities of orbital adipose tissue and/or the extraocular muscles using computerized tomography, may be detected in 87% of Graves’ patients with clinically detectable ophthalmopathy. Conceptually the orbit has two compartments; a fat compartment and a muscle compartment. It has been noted that some patients with GO display adipose expansion as the primary manifestation of their disease, while others exhibit predominantly expansion of the muscle component. The predominance of one sub-population of orbital fibroblasts within the orbit may help to explain this observation.

Fibroblasts also have a number of tissue-specific phenotypes, which likely affects the selective involvement of the skin of the anterior lower legs, known as pretibial myxedema. Also termed Graves’ dermopathy, this autoimmune extrathyroidal manifestation of Graves’ disease is usually mild, and is seen in approximately 15% of patients with GO. Pretibial myxedema has been found to be a clinical marker of severe ophthalmopathy. Stimulation of local fibroblasts with a resulting production of significant amounts of GAGs, leads to the observed clinical manifestations.
Current medical treatment of Graves’ ophthalmopathy

The medical treatment of GO has gradually evolved during the past few decades. The relatively slow evolution of treatment may be explained partly by a poor understanding of GO at a cellular and molecular level, as well as challenges of disease classification at a clinical level. This has led to controversy and a wide variety of medical and surgical recommendations.

Graves’ disease and Graves’ ophthalmopathy are chronic disease processes with both physical and psychological manifestations. Education plays an important role to help with understanding patient concerns along with setting and aligning expectations. At times, patient concerns are very different than physician concerns. “Clinical success” in the treatment of GO has been a moving target. What is defined as “success” in the literature may in fact have little bearing on patients’ perception of improvement. Current tools to evaluate quality of life (QOL) unfortunately lack questions on multiple issues that are important to most patients. An updated QOL survey will be a useful outcome measurement tool in future clinical trials.

Clinical grading

There is no gold standard for grading the severity or activity of GO. This has led to difficulty comparing treatments for GO due to the wide variety of models used in clinical studies. Examples of severity grading systems include the modified NOSPECS (No symptoms or signs, Only signs, Soft tissue symptoms and signs, Proptosis, Extraocular muscle involvement, and Sight loss due to optic neuropathy) and the American Thyroid Association (ATA) grading systems. The American Thyroid Association (ATA) grading system divides patients according to clinical features and severity. Class I solely involve lid retraction or stare. Patients in Class II have soft tissue symptoms and signs (chemosis/edema), while patients in Class III have proptosis. Decreased motility and/or diplopia are characteristic of patients in Class IV. Finally, corneal exposure symptoms/signs or optic neuropathy are found in patients with Class V and Class VI disease, respectively. Used to assess disease activity, the Clinical Activity Score (CAS) is comprised of local manifestations of inflammation. They include spontaneous retrobulbar pain, pain with eye movements, redness of the eyelids, redness of the conjunctiva, swelling of the eyelids, swelling of the caruncle and/or plica, and conjunctival edema. A score of 3 or greater is considered active GO. The VISA classification system combines aspects of both the CAS and NOSPECS systems. Core components include Vision (presence of absence of optic neuropathy), Inflammation (0–8 or mild, moderate, or severe), Strabismus/motility (0–3), and Appearance/exposure (mild, moderate, or severe).

The recent release of The Consensus Statement of the European Group on Graves’ Orbitopathy (EUGOGO) has added refined recommendations to the management of GO. Although the authors do not advocate a detailed clinical grading or scoring system, they do recommend an initial segregation of patients into “mild,” “moderate to severe,” or “sight-threatening” categories, as well as an attempt to determine disease activity (Table 1).

Initial management

The initial management of patients with GO flows from widely accepted guidelines. These include the correction of thyroid dysfunction, smoking cessation counseling, and local symptomatic treatments for corneal exposure (lubricants and ointments), diplopia (prisms), and photophobia (dark lenses). Patients with uncontrolled hyperthyroidism are more likely to have severe GO than euthyroid patients. Although treatment modalities (thyroidectomy, antithyroid medications) of hyperthyroidism have similar outcomes in regards to GO, treatment with radioiodine has been associated with progression in some patients with GO or newly diagnosed eye disease (~15%). This risk may be mitigated with a short course (3 months) of oral glucocorticoids (GCs), along with avoidance of post-operative hypothyroidism. Patients with risk factors such as smoking along with greater than mild GO are most likely to benefit from pretreatment. It has been suggested by some that only patients with preexisting moderate to severe GO should be pretreated with GCs.

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<th>Table 1 Severity classifications in Graves’ ophthalmopathy (GO)</th>
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<td>1. Sight-threatening GO: patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown. This category warrants immediate intervention.</td>
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<td>2. Moderate to severe GO: patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients with moderate to severe GO usually have any one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and gender, inconstant or constant diplopia.</td>
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<td>3. Mild GO: patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually only have one or more of the following: minor lid retraction (&lt; 2 mm), mild soft tissue involvement, exophthalmos &lt; 3 mm above normal for race and gender, transient or no diplopia, corneal exposure responsive to lubricants.</td>
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There is a strong association between smoking and GO. Patients who smoke are more likely to have more severe GO,\textsuperscript{36,37} as well as an increased likelihood of GO progression after radioiodine therapy for hyperthyroidism.\textsuperscript{39} In addition, there appears to be a dose-related response between the number of cigarettes smoked per day and the probability of developing GO.\textsuperscript{39} Therefore, counseling to promote smoking cessation should take a central role in the management of all patients with GD. The precise mechanism underlying this association remains obscure, but free radical formation has been shown to stimulate orbital fibroblast proliferation.\textsuperscript{39}

**Glucocorticoids**

Used for their immunosuppressive and anti-inflammatory actions, glucocorticoids (GCs) are often utilized in the treatment of active GO.\textsuperscript{31} Since the early 1950s, GCs have been administered through oral, local (retrobulbar or subconjunctival) or intravenous routes. Retrobulbar or subconjunctival GC injections have been found to be less effective than oral GCs.\textsuperscript{40} However, this route of administration is reasonable when oral or intravenous GCs are contraindicated.

Oral glucocorticoids have been a mainstay in the management of GO for many years. Recent randomized clinical trials have compared the efficacy of oral versus intravenous glucocorticoids (IVGCs). A recent prospective, single-blind, randomized study of 70 patients, directly compared oral GCs (initial dose 0.1 g/day tapering 0.01 g/week) versus IVGCs (0.5 g, then 0.25 g, 6 weeks each) for the treatment of euthyroid patients with untreated, active, severe GO.\textsuperscript{43} The authors were able to use a lower cumulative dose of IVGCs (4.5 g) than previous studies, and they reported a treatment response rate (77 vs 51%) favoring IVGCs.

A major concern of high-dose GC treatment is the risk of adverse side effects. Although GCs effectively suppress inflammation, they may be associated with a number of potential side effects including immunosuppression, hyperglycemia, osteoporosis and necrosis, together with weight gain. Cushing’s syndrome is an almost unavoidable side effect of long-term use of oral glucocorticoids. The use of pulse IVGCs and large cumulative doses may result in serious liver toxicity and even death. Reporting of fatal acute liver failure led some authors to recommend a cumulative dose of no more than 6 g.\textsuperscript{42} The European consortium recommends pulse IVGCs as the treatment of choice for patients with moderate to severe and active GO.\textsuperscript{31} In an accompanying editorial, concern was raised that for some patients with “moderate” disease and active GO, the risk-benefit ratio for IVCG may be weighted toward the unacceptable risk side.

The statement was given within the context that many patients will spontaneously improve, albeit not as quickly in the untreated group, given the natural history of the disease.\textsuperscript{44} Monitoring of liver function, along with other potential side-effects such as hyperglycemia and increased blood pressure, during and after treatment is mandatory.

**Orbital radiation**

Orbital radiation (OR) has been used in the treatment of GO for more than 90 years.\textsuperscript{45} The rationale for the use of orbital radiotherapy stems from its anti-inflammatory effects and the radiosensitivity of activated orbital T-cells and fibroblasts. A common cumulative dose of radiation is 20 Gy per eye, fractionated over a 2-week period. Known complications of orbital radiation are fortunately rare but may include radiation retinopathy and cataract.\textsuperscript{46} There are also theoretic concerns of cancer induction which is estimated at 0.39\%.\textsuperscript{47}

Orbital radiation was initially widely adopted, despite a lack of published data from controlled clinical trials clearly demonstrating its efficacy. To address this, several retrospective controlled clinical trials have been undertaken in the past decade. A controversial study by Gorman et al found that treatment with orbital radiation was no better than the natural history of the disease which is associated with spontaneous improvement.\textsuperscript{48} A recent review by Bradley et al evaluated the role of orbital radiation for GO by identifying 5 observational studies and 9 randomized controlled trials (RCTs) sufficient to meet inclusion criteria.\textsuperscript{49} The RCTs were qualitatively heterogeneous and only three of the 9 randomized trials were sham-controlled.\textsuperscript{45,50,51} The majority of the reviewed RCTs enrolled patients with moderately severe GO, although inclusion criteria ranged from one trial that enrolled patients solely with mild GO to another that enrolled patients with moderate to severe ophthalmopathy, including patients with optic neuropathy. The measured outcomes were similarly heterogenous and included changes in one or more clinical parameters such as lid fissure, proptosis, and extraocular muscle function, change in orbital computed tomography CT volume, change in NOSPECS class or grade, change in American Thyroid Association ophthalmopathy index, and change in major and minor criteria (Donaldson criteria). Two of the 3 sham-controlled trials demonstrated improved vertical range of motion in orbital radiation-treated subjects compared with controls.

There are a wide variety of recommendations for the use of orbital radiation in the treatment for GO. The European consortium recommends that, “Orbital irradiation (OR) should be considered in patients with active disease who have...
Adipogenesis may be inhibited. This is due to the fact that it is a costimulatory or second signal-blocker of T-cell activation. Mimicking endogenous CTLA4, it competes with CD28 for B7.1 (CD80) and B7.2 (CD86) ligand binding, thus blocking a costimulatory signal required for optimal T cell activation.58,59 Abatacept was recently approved by the FDA for treatment of patients with RA, but to date, there are no published studies using the drug in patients with GO.

Anticytokine medications targeting tumor necrosis factor alpha (TNF-α) or IL-1 have been approved for treatment of a number of auto-immune diseases. In particular, anti-TNF-α therapies with agents, such as etanercept and infliximab, have been of clinical value in difficult-to-treat RA. Studies using these agents to treat GO are limited. Etanercept is a TNF-receptor/immunoglobulin fusion molecule that has shown some promise in treating GO in a small pilot study.60 Infliximab, a monoclonal antibody to TNF-α, was used to treat a patient with sight threatening GO.61 Anakinra, an IL-1 receptor antagonist is approved for the treatment of RA, but there are no reports of its use in GO.

**Conclusion**
A close relationship that emphasizes education and cooperation between patients and physicians is crucial to the management of GO. Medical therapy for GO has evolved little during the past few decades and generally focuses on conventional approaches of nonspecific immuno-suppression. This may be explained partly by a poor understanding of GO at a cellular and molecular level, as well as challenges of disease classification at a clinical level. On both fronts, progress is being made. Newer classes of treatment agents hold promise to more selectively target underlying cellular and molecular alterations in GO. Also, cooperation between multiple medical centers, as evidenced by the European Group on Graves’ Orbitopathy (EUGOGO) and the recent formation of the International Thyroid Eye Disease Study Group (ITEDS), have the potential to better standardize the language and tests used in GO.

**Disclosures**
No financial support or grants were utilized for this study. The authors do not have financial disclosure or competing interests in the presented topic.

**References**

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**Figure 2** Proposed targets for agents of potential benefit in the treatment of Graves’ ophthalmopathy. 1) blocking T-cell co-stimulation, 2) depleting B cells, 3) inhibiting cytokine action, 4) targeting the insulin-growth factor-I (IGF-1) receptor or the thyrotropin (TSH) receptor, and 5) preventing connective tissue remodeling. Adapted with permission from Garrity JA, Bahn RS. Pathogenesis of Graves Ophthalmopathy: Implications for Prediction, Prevention, and Treatment. *Am J Ophthalmol*. 2006;142(1):147–153. Copyright © 2008 Elsevier.
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