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The Evaluation and Treatment of Graves Ophthalmopathy

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Keywords

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Graves ophthalmopathy (GO) is an inflammatory disorder of the orbit that occurs in association with autoimmune thyroid disease.¹ Although most patients with GO have a history of Graves disease (GD) with hyperthyroidism, some are euthyroid with no such history or have hypothyroidism primarily caused by Hashimoto thyroiditis.² A close temporal relationship exists between the onset of Graves hyperthyroidism and the onset of GO. Regardless of which condition occurs first, the other condition develops within 18 months in 80% of patients, although GO may occasionally precede or follow hyperthyroidism by many years.³ The common manifestations of the disease vary considerably from patient to patient in expression, severity, and duration. Such signs include proptosis, upper eyelid retraction, and swelling with or without erythema of the periocular tissues, lids, and conjunctivae. The natural history of GO is characterized by fairly steady deterioration over 3 to 6 months, followed by a plateau phase of often between 1 and 3 years, then gradual improvement toward the baseline.⁴ Whereas the inflammatory signs and symptoms generally resolve over time, proptosis, lid retraction, and extraocular dysfunction may persist. A cohort of patients with GO followed for a median of 12 months showed spontaneous improvement in ocular manifestations in approximately two-thirds, stability in 20%, and worsening in 14%.⁵

PATHOPHYSIOLOGY

As with hyperthyroidism of GD, GO likely evolves from an autoimmune process primarily directed against the thyrotropin receptor (TSHR).⁶ However, rather than TSHR on thyroid follicular cells being the autoimmune target, this same receptor expressed on orbital fibroblasts is recognized by TSHR autoantibodies (TRAb) directed against this receptor (Fig. 1).⁷ As a result, these cells are stimulated to produce hydrophilic hyaluronan,⁸ and a subset differentiates into mature adipocytes.⁹ This process leads to enlargement of the extraocular muscles and to expansion of the orbital adipose tissue. Many of the clinical manifestations of GO can be explained in a mechanical sense by this increase in tissue volume within the bony orbit that displaces the globe forward and hinders venous outflow. Cytokines and other mediators of inflammation, produced by infiltrating mononuclear cells and resident macrophages, accumulate within the orbit and contribute to the local inflammatory process.¹⁰ No unique genetic associations have been identified that distinguish

individuals with GO from those having GD without evident GO. However, environmental factors, including smoking, radioactive iodine (RAI) therapy for hyperthyroidism, and posttreatment hypothyroidism, may play an important role in disease development and progression.¹¹

EPIDEMIOLOGY

The annual adjusted incidence rate of Graves hyperthyroidism is 0.50 per 1000 population,¹² with some 25% to 50% of these patients having clinical eye involvement. Most patients with GO show mild signs and symptoms including corneal irritation, periocular swelling, eyelid retraction, conjunctival erythema/chemosis, and mild extraocular muscle dysfunction. A much smaller proportion of patients (approximately 5%) experience severe disease including significant inflammation/congestion, excessive proptosis, and sight-threatening corneal ulceration or optic neuropathy. Although GO is overall more frequent in women than in men, men are overly represented in severe forms of the disease, with a female-to-male ratio of 1:4.¹³ Subclinical eye involvement is common, with approximately 70% of hyperthyroid patients showing evidence of GO on magnetic resonance imaging (MRI) or orbital computed tomography (CT) scanning.¹⁴ The overall incidence of GO varies depending on the diagnostic criteria; the annual adjusted incidence rate of clinically significant GO in Olmsted County, Minnesota is 16 women and 3 men per 100,000 population.¹⁵ A bimodal age distribution is followed, with peak incidence of GO in women occurring between age 40 to 44 years and 60 to 64 years, and in men between 45 to 49 years and 65 to 69 years. The other peripheral manifestations of GD, dermopathy and acropachy, occur with lower frequency and almost always develop in patients with more severe GO.¹⁶

DIAGNOSIS

There is no single clinical finding or laboratory test that is diagnostic of GO. A careful history and physical examination often allows for a firm diagnosis of GO to be made. Although the diagnosis is generally straightforward without the need for additional laboratory or imaging data in a thyrotoxic patient with bilateral proptosis, it can be more difficult in a euthyroid patient with unilateral proptosis. In this instance, CT scanning or MRI with special attention paid to the orbits is indicated, and may identify an orbital mass lesion, an infiltrative process, idiopathic orbital inflammation (pseudotumor), or other orbital abnormality. If the imaging is compatible with GO, the finding of elevated TRAb is helpful in making the diagnosis in a euthyroid patient.² Although the absence of elevated TRAb in this setting does not rule out the diagnosis of GO, it makes the diagnosis less likely and necessitates further evaluation and/or observation over time. The differential diagnosis of GO regarding particular findings on physical examination is outlined in Table 1.

CLINICAL EVALUATION

The clinical evaluation and management of GO, as well as any accompanying hyperthyroidism, is optimally performed in a multidisciplinary clinic having both endocrine and ophthalmologic expertise in the condition as well as access to ancillary specialties.¹⁷ All patients with GO, except for the mildest cases, should be examined by both an ophthalmologist and an endocrinologist. Proper management of GO is based on accurate determination of both the severity of the disease, or extent of ocular dysfunction or involvement, and its clinical activity, or degree of active inflammation present. Although severity and activity may peak simultaneously, often the two are not congruent, with peak activity preceding the most significant clinical expressions of the disease.¹⁸

The degree of severity can be classified as mild, moderate to severe, or sight-threatening, following quantitative assessment of lid aperture width, proptosis measurement, diplopia

score (1 = intermittent [ie, when tired or on awakening]; 2 = inconstant [ie, only at extremes of gaze]; 3 = constant), degrees of abduction in eye muscle movement, examination of the cornea for evidence of exposure keratitis or ulceration, and assessment of optic nerve function (Table 2).¹⁷

The activity of GO can be graded using a clinical activity score (CAS) that ranges from 0 to 10 and predicts response to anti-inflammatory therapies.¹⁸ The CAS is generated by the addition of 1 point for the presence of each the following features: chemosis, eyelid swelling, eyelid erythema, conjunctival erythema, caruncular swelling, pain in primary gaze, and pain with ocular movement. In addition, if the patient has been examined within the 3 months prior, additional points may be given for decreased visual acuity, worsened diplopia, and increased proptosis compared with that visit. GO is considered active in patients with a CAS of 3 or more out of 7 (if no previous assessment is available), or 4 out of 10 on the complete scale.

Dysthyroid optic neuropathy (DON) is a severe complication of GO that affects approximately 5% of GO patients, and may lead to loss of vision. The condition may present as unexplained deterioration in vision or change in intensity or quality of color vision.¹⁹ Corneal breakdown with subsequent ulceration is another sight-threatening complication, and may be found in patients who experience corneal exposure in the setting of poor blinks, excessive upper lid retraction, and/or lagophthalmos (inability to fully close the eye), which can be exacerbated with greater amounts of proptosis. Globe subluxation is a form of partial displacement of the globe from the orbit whereby the eyelids are repositioned behind the protruding globe. It is typically seen with greater amounts of proptosis and lid retraction, and is associated with pain and risk of loss of vision caused by optic nerve compromise with repeated episodes. As immediate treatment is essential for each of these conditions, patients in whom they occur or are suspected should be referred urgently to an ophthalmologist.

Clinical assessment of GO also includes evaluation of the impact of the disease on the patient's quality of life (QOL). The QOL has been shown to be impaired in GO, with both physical and mental health being adversely affected. Patients have poorer self-image, more sleep disturbance, and more impaired social and work functioning than controls.²⁰ Several QOL questionnaires have been developed and validated for use in patients with GO.^{20–22} While being essential for treatment evaluation in clinical studies, such instruments may also be useful in clinical practice to aid in decisions regarding disease intervention.

RISK FACTORS FOR GO DEVELOPMENT OR PROGRESSION

Several risk factors have been identified that predispose to the development or progression of GO (Table 3). Among the most carefully studied factors in randomized trials have been the various treatment options for Graves hyperthyroidism. Risks in these studies ranged from 33% for radioactive iodine (RAI) compared with 10% for antithyroid drugs and 16% for surgery,³¹ to 39% for RAI compared with 21% for antithyroid drugs.³² In one large randomized study, patients were treated with RAI with or without concurrent corticosteroid (to determine whether this might be preventive), or methimazole.³⁷ Within 6 months of treatment, progression was seen in 15% of patients treated with RAI alone, in approximately 3% of patients treated with methimazole, and in no patients treated with RAI plus corticosteroid. By 1 year most patients with progression had improved, with only 5% of the RAI group experiencing persistent worsening that required additional treatment. Overall, studies suggest that antithyroid drug therapy or thyroidectomy do not affect the course of GO, whereas there is a small but significant increased risk of worsening following RAI therapy in patients with active disease. By contrast, it appears that patients with inactive GO may be treated with RAI without increased risk.^{17,38}

Smoking is the risk factor most strongly and consistently linked with the development or progression of GO and with poorer response to therapy.^{32,39,40} Several studies suggest that smokers develop more severe GO, that the risk is proportional to the number of cigarettes smoked per day, and that former smokers have significantly lower risk than current smokers.^{33,41} In a recent randomized trial of patients with newly diagnosed GD treated with either RAI or antithyroid drugs, smoking was found to be a more important risk factor for GO than was RAI.³² Regardless of which therapy they received, more than 40% of smokers either developed GO or experienced deterioration of their eye involvement. This rate was almost double that of nonsmokers. In another study wherein hyperthyroid patients with established GO were treated with RAI, smoking was found to add additional risk for GO over that conferred by RAI alone, and GO progression was prevented when RAI was combined with steroids in only 14.9% of smokers compared with 63.8% of nonsmokers.⁴² Second-hand smoking has also been linked, albeit indirectly, with GO development.³⁴ Although no intervention trial of smoking cessation has been successfully undertaken, there is retrospective evidence that quitting is associated with a better outcome.³³ Counseling and aiding GO patients to stop smoking is the standard of care.^{17,43}

The relationship between TRAb level and disease activity or progression has been studied by several groups. TRAb level was found in one study to be strongly correlated with the CAS or degree of proptosis in euthyroid patients with untreated GO of moderate severity.³⁶ In another study, 159 GO patients were followed for 1 to 2 years, with TRAb levels recorded every 3 months.³⁵ Using specific levels of TRAb as threshold points at various times following the diagnosis of GO, the prognosis of GO was predictable as being either mild or severe in 50% of patients. Both hyperthyroidism and hypothyroidism have also been shown in multiple reports to be associated with increased risk for development or deterioration of GO. When GO patients in a referral population were stratified into groups using a severity index, approximately twice as many patients with current thyroid dysfunction were identified in the groups having more severe GO than in the more mildly affected groups.²⁷ The impact on GO of early supplementation with levothyroxine (to avoid hypothyroidism following RAI therapy) was studied in a group of patients receiving levothyroxine beginning 2 weeks following RAI.²⁸ The investigators compared GO progression in these patients with a historical cohort of patients who did not receive levothyroxine until they were documented to be hypothyroid following RAI therapy (permissive hypothyroidism). The investigators found the relative risk of GO development or worsening in the permissive hypothyroidism group compared with the early treatment group to be 1.64 (95% confidence interval: 1.1–2.6), and additionally documented more severe GO in the former. The association between hypothyroidism following RAI therapy and progression of GO was later confirmed in a prospective cohort of 114 patients followed for 2 years.²⁹ Based on these studies, it has become widely accepted that hypothyroidism following treatment of Graves hyperthyroidism is a risk factor for GO, warranting active prevention.⁴³ The complication of DON has its own risk factors that include smoking, advanced age, and the presence of diabetes.⁴⁴

INITIAL MANAGEMENT

Optimum management of GO requires a partnership between the endocrinologist and ophthalmologist, with the goal of preserving the patient's vision and restoring favorable self-perception and QOL. Although either partner may make the diagnosis, the initial steps in management are generally the purview of the endocrinologist, who evaluates and addresses the reversible risk factors associated with disease progression and severity.¹³ Smokers should be offered participation in a structured smoking cessation program, and patients exposed to second-hand smoke should be identified and advised of its negative impact.⁴⁵ If the patient is hyperthyroid, prompt attention should be directed toward the restoration of

euthyroidism. Whereas RAI therapy with or without concurrent corticosteroid treatment for GO prophylaxis may be considered in nonsmokers with mild active GO, smokers who choose this treatment option should receive oral corticosteroids. A common regimen consists of prednisone (0.4–0.5 mg/kg/d) started 1 to 3 days following RAI administration and continued for 1 month, with tapering over the 2 subsequent months.¹⁷ However, a recent retrospective cohort study suggested that lower doses of prednisone (0.2 mg/kg/d) for 6 weeks may be equally effective.⁴⁶ RAI treatment in patients with active and moderate or severe GO should be avoided in favor of either antithyroid drug therapy or thyroidectomy.⁴⁵

As described earlier, therapeutic decision making hinges on proper evaluation of the clinical activity of the disease and its severity, with particular attention paid to the possible presence of the sight-threatening complications of corneal ulceration and DON. While these elements are addressed by the endocrinologist, a complete evaluation by the ophthalmologist, especially in patients with moderate or severe disease, is essential for appropriate assessment. Generally mild disease is treated with local supportive measures. A patient having moderate or severe active disease may benefit from systemic medical therapy or external radiation therapy, whereas inactive disease of the same severity might be considered for rehabilitative surgery.

LOCAL THERAPY

In both active and inactive GO, the use of local measures can afford good symptomatic relief.¹⁷ Ocular lubrication with artificial tears (administered 4–6 times per day) or gels (applied at nighttime) benefits the corneal symptoms of dryness, photophobia, and grittiness. The application of viscous gels or ointment at bedtime lengthens the duration of action and is useful for patients with nocturnal lagophthalmos, who typically have prominent symptoms on awakening. Cool compresses and sunglasses are also helpful with ocular irritation. Temporary relief from diplopia may be obtained from botulinum toxin A injected in the extraocular muscles, and symptomatic lid retraction may improve with injection into the levator palpebralis.⁴⁷ This effect is temporary, however, and in the authors' experience botulinum injections have not been as helpful as initially hoped.

Approximately two-thirds of patients with mild disease experience spontaneous improvement within about 6 months, and thus need no treatment beyond local measures.⁵ In these patients, observation every few months is appropriate until the inactive stage is reached, and rehabilitative surgery can be performed if needed. However, in some patients with mild disease the QOL is significantly diminished and additional intervention may be warranted.¹⁷

ANTIOXIDANT THERAPY

Antioxidant therapy generally carries with it few side effects and may have a beneficial effect on GO outcome. An early intervention study consecutively assigned patients to allopurinol (300 mg daily) plus nicotinamide (300 mg daily) or placebo.⁴⁸ A promising result was noted in this nonrandomized study, with a total eye score index showing improvement in 82% of treated patients compared with 27% of those receiving placebo. Selenium was recently reported to improve mild GO in a trial conducted by the European Group on Graves Orbitopathy (EUGOGO) consortium.⁴⁹ Patients were randomized to receive selenium (100 µg twice daily), pentoxifylline, or placebo. Evaluation at 6 months, with confirmation at 12 months, documented an improvement not only in several ocular parameters but also in QOL, compared with placebo or pentoxifylline. The selenium-treated group did not experience any significant side effects, and in particular there was no increase in blood glucose levels, as has been noted in studies of selenium treatment in other diseases. An important caveat is that these subjects were from a population with marginally decreased

selenium levels, leaving unanswered the question of selenium-related benefit in patients living in selenium-sufficient regions.

IMMUNOMODULATORY THERAPY

Oral glucocorticoids (GC) have long been used as treatment for GO (often in starting doses of between 40 and 100 mg/d with tapering over 10–24 weeks for a cumulative dose of 2–6 g), but more recent evidence suggests that the intravenous (IV) route is more effective. The two modes of GC administration have been assessed separately in several clinical trials and directly compared in 4.⁵⁰ In the largest trial, 70 patients with severe and active GO were randomized to receive either prednisolone (starting at 100 mg/d and tapered by 10 mg daily at weekly intervals for a total dose of 4.0 g) or IV methylprednisolone (500 mg weekly $\times$ 6 weeks then 250 mg weekly $\times$ 6 weeks for a total dose of 4.5 g).⁵¹ After 3 months, the composite outcome (improvement in 3 or more of the following: proptosis, intraocular pressure, diplopia, muscle size, lid fissure width, visual acuity) was met in 77% of patients treated with IVGC and in 51% of those treated with oral GC. More importantly, the use of IVGC was associated with improved QOL and less need for subsequent surgery. Mild side effects were observed in 17% in the IVGC group and included palpitations (the most common), weight gain, gastrointestinal distress, and sleeplessness. By contrast, more significant side effects were reported with the use of oral GC and included cushingoid features, secondary adrenal insufficiency, weight gain, hypertension, myalgias, hirsutism, depression, hyperglycemia, and osteoporosis. Although similar efficacy and an equally favorable side-effect profile for IVGC were found in a comparable trial,⁵² of concern is that fatal acute hepatotoxicity has been reported in 4 GO patients treated with IVGC.⁵³ Severe hepatotoxicity appears to be dose dependent, as it occurs only in patients receiving a cumulative dose of greater than 8 g of methylprednisolone.⁵⁴ Other severe complications of IVGC reported in a recent survey of members of the European Thyroid Association include cardiovascular or cerebrovascular events, autoimmune encephalitis, and liver test abnormalities (>4 -fold upper limit of normal).⁵⁵ In light of these reports, it has been suggested that patients being considered for IVGC therapy be screened for chronic viral infections, underlying autoimmunity, and preexistent hepatic abnormalities, and that liver function be followed during therapy.^{17,56} Retrobulbar injection of GCs was evaluated in a study of triamcinolone compared with placebo, with 25 patients in each arm.⁵⁷ The outcome was improved field of vision without diplopia and decreased muscle size on orbital CT in the triamcinolone group. However, because the effect was small and was associated with a risk of injury to the globe, retrobulbar GC injection is not a recommended therapy for GO.

Nonsteroidal immunomodulators have been studied in an attempt to identify agents that can supplant the need for high doses of GC or prevent GO remission after GC therapy is discontinued. Cyclosporine, the first of these agents to be investigated, showed an additive effect to oral steroids and extended the benefits of discontinued GC.⁵⁸ However, in a direct comparison with GC therapy, cyclosporine was less effective in reducing the total eye score (combination of extraocular muscle thickness, proptosis, and visual acuity), and the side-effect profile was significant (eg, pneumonia, renal failure, hepatitis, hypertension).⁵⁹ As the combination of cyclosporine with oral GC therapy was more effective than either agent alone, cyclosporine is sometimes used with benefit in oral GC-resistant patients or as a steroid-sparing agent. Azathioprine was compared with placebo in one study in which no benefit was identified.⁶⁰ By contrast, IV immunoglobulins (IVIg) have been found to be as effective as oral GC in patients with active GO. Studies have found the response rate to be between 62% (defined by an index of extraocular muscle area, proptosis, diplopia, and intraocular pressure) and 76% (assessed by a composite severity score).^{61,62} The individual features that improved included soft tissue changes, diplopia, visual acuity, and proptosis. A low rate of side effects was seen, none of them serious. In these studies, IVIg were

administered on 2 consecutive days every 3 weeks for 6 cycles in the former study, and daily for 5 days, repeated every 3 weeks for 3 cycles and then 1 dose every 3 weeks for an 9 additional cycles in the latter. Somatostatin analogues have been studied in 4 placebo-controlled trials which, in aggregate, demonstrated no clinically significant benefit and significant gastrointestinal side effects.^{63–66}

Rituximab is an anti-CD20 chimeric monoclonal antibody that induces transient B-cell depletion, blocks early B-cell activation and differentiation, and inhibits cytokine secretion, antigen presentation, and T-cell activation.⁶⁷ This agent has been identified in case series to have a potentially beneficial effect on GD and GO.^{68–71} In these case series with a total of 17 patients, rituximab treatment was associated with a decrease in the CAS of 3 to 4 points on average. However, as no randomized control trial of rituximab treatment in GO has yet been completed, its true efficacy is unknown. Given its side-effect profile (potential for infections, worsening hypertension, serum sickness, and so forth) and high cost, use of this agent in GO is currently best limited to centers performing randomized controlled trials.

Most randomized trials of orbital radiotherapy (OR) in GO have studied patients with moderate to severe disease and have shown a positive impact on ocular dysmotility, without improvement in disease progression.^{72–76} The exception is a single trial using a somewhat different patient population, which failed to identify any clinically meaningful difference between OR and sham OR on the contralateral orbit.⁷⁷ Several studies addressed radiation dose and treatment duration to minimize exposure and side effects. One trial randomized patients to either 1 Gy/wk, 1 Gy/d, or 2 Gy/d, for a total dose of 20 Gy, and found 1 Gy/wk to be best tolerated and most effective in terms of regression in subjective signs and improvement in eye motility.⁷⁵ Another study found the lower total dose of 2.4 Gy to be as effective as higher doses.⁷⁸ A study of OR in patients with mild GO concluded that in these patients motility was improved, but that the treatment did not affect soft tissue swelling, proptosis, or QOL.⁷⁴ At present, several centers are using low cumulative-dose OR (<10 Gy) in selected active mild and moderate to severe GO, especially when significant diplopia or restricted motility is present. Several studies of OR used in conjunction with oral GC therapy have demonstrated the combination to be superior to oral GC used alone in expediting resolution of the active inflammatory phase of the disease.^{76,79} A study of OR in which the therapy was used in conjunction with either oral GC or IVGC found IVGC to be better tolerated and somewhat more effective than oral GC in this regimen.⁸⁰ Whether IVGC therapy benefits from the addition of OR was examined in a nonrandomized study that suggested lack of additional benefit.⁸¹ However, this finding has to be considered provisional until randomized clinical trials of IVGC with or without OR have been completed. The side-effect profile of OR includes retinopathy in 1% to 2% overall, with higher risk in patients with diabetes mellitus in whom the therapy is contraindicated owing to the lower threshold for radiation retinopathy in such patients.^{82,83}

A caveat to the therapeutic trials discussed here is that although investigators studied various parameters or indices (proptosis, diplopia score, soft tissue features, QOL, CAS, and in many cases a composite score) to ascertain benefit, none is uniformly agreed to consistently represent “improvement” in GO. However, in summary it may be said that approximately 40% to 80% of GO patients treated with immunomodulatory therapy experience benefit, that patients with inactive disease are not likely to respond, and that IVGC therapy appears to be the most effective of the treatment options that have been well studied to date. Risks and benefits of these treatments should be carefully discussed with the patient who is best fully involved in the therapeutic decision-making process.

THYROIDECTOMY AND THYROID ABLATION

Interest in the potential benefit of eliminating the thyroid as a source of pathogenic antigen has increased as autoantibodies directed against the thyrotropin receptor have become more clearly implicated in the pathogenesis of GO.^{1,7} A retrospective study of patients who were treated with IVGC and surgery compared those who underwent near-total thyroidectomy with patients receiving total thyroidectomy plus RAI for thyroid remnant ablation. Using a composite outcome (proptosis, CAS, eyelid fissure, diplopia) at 9 months following surgery, results showed a higher proportion of patients in the latter group with improved GO.⁸⁴ By contrast, another study comparing GO outcome in patients with moderate disease undergoing either subtotal (2 g thyroid remnant) or total thyroidectomy found no difference between groups and a higher surgical complication rate in the latter.⁸⁵ Recent guidelines recommend against RAI therapy for the management of hyperthyroidism in patients with moderate to severe active GO, extrapolating from its known deleterious impact on mild active disease.⁴³ Because no study to date has compared the therapeutic alternatives for hyperthyroidism therapy in these patients regarding GO progression, the choice between thyroidectomy and antithyroid medication is best based on clinical factors including degree of thyrotoxicosis, goiter size, comorbidities, and the preference of the patient. Given the paucity of evidence that thyroidectomy or thyroid remnant ablation in euthyroid GO patients is of value, neither practice is recommended.

THERAPY FOR SIGHT-THREATENING GO

Corneal ulceration, globe subluxation, and DON are sight-threatening disorders that require emergent therapy. DON is multifactorial in etiology, and generally occurs when the optic nerve is compressed by enlarged extraocular muscles at the orbital apex.⁸⁶ Response to therapy is not well studied because of the rarity of this condition (3%–5% of GO patients) and the lack of a uniformly accepted definition.⁸⁷ Therapy for DON consists of IVGC, orbital decompression surgery, or both modalities.⁸⁸ A direct comparison between the 2 modalities showed that 83% of patients needed additional therapy with IVGC following decompressive surgery, whereas only 56% of patients needed further therapy for DON (decompression surgery or OR) following IVGC therapy.⁸⁹ Although both approaches suffered from a significant failure rate, DON ultimately resolved in all cases as patients failing one approach responded to the other. Mainly based on these data showing overall excellent results, the EUGOGO consensus statement advises starting with IVGC therapy and observing the response over a 2- to 3-week period.¹⁷ A commonly followed regimen is the administration of 1.0 g methylprednisolone for 3 consecutive days, repeated 1 week later.⁹⁰ If no improvement is seen or deterioration is noted, patients should be referred promptly for orbital decompression surgery. Surgery may be indicated as first-line therapy if the corneal exposure from proptosis is significant, if congestive features are prominent, or if side effects of steroids are to be avoided. Sight-threatening corneal breakdown or ulceration typically results from one or a combination of the following: excessive proptosis, excessive eyelid retraction, incomplete blinks, or incomplete eyelid closure. Initial treatment includes the frequent use of topical lubricants, intensive topical antibiotics where appropriate, moisture chambers, and surgical procedures to temporarily cover the globe until healing has taken place. Occasionally orbital decompression, eyelid surgery or even corneal grafting is required.¹⁷

REHABILITATIVE TREATMENT

After the eye disease has been inactive for 3 to 6 months, a patient may be evaluated for rehabilitative surgery, which can have a positive impact on both ocular function and QOL. Intervening earlier before a stable baseline is reached may increase the likelihood that

additional surgery will be needed in future. The surgical sequence is generally orbital decompression (if needed), followed by extraocular muscle surgery (if needed), with eyelid procedures (if needed) performed last. Thus, changes induced by one intervention can be addressed in a subsequent step. Indications for orbital decompression include excessive proptosis, orbital congestion, corneal exposure, side effects of steroids, deep orbital pain, and enhanced cosmesis. Patients with DON, or those who have shown intolerance or insufficient response to immunosuppressive therapy or who have debilitating retrobulbar or periorbital pain, may also benefit from this surgery. Decompressive surgery involves removal of one or more orbital walls, retrobulbar fat, or both, to expand the retrobulbar space, decrease orbital pressure, and allow the globe to recede. The extent of the surgery generally depends on the degree and distribution of extraocular muscle involvement; the improvement in proptosis is directly related to the number of orbital walls removed.^{91,92} Following decompression surgery, preexisting diplopia may worsen or new diplopia develop in 10% to 50% of patients.^{93,94} If diplopia is mild, the use of prisms inserted in the eyeglass lens may suffice. The goal of extraocular muscle surgery (strabismus surgery) is single vision in primary gaze and the reading position; diplopia with deviant gaze may persist after surgery. Multiple surgeries over an extended period are sometimes needed to address limited extraocular muscle mobility. Eyelid surgery is generally performed to address symptomatic eyelid retraction or asymmetric lid position, its functional role being to ensure adequate corneal coverage. Upper lid retraction is relieved by weakening (recessing) the levator and/or Müller muscles. Lower lid retraction may be treated by recessing the lower lid retractors or, more typically, by inserting a spacer of some material, usually cartilage or a hard palate graft. Additional reconstructive procedures that may be performed include lateral tarsorrhaphy or blepharoplasty to remove excessive eyelid skin and eyelid fat. Removal of skin should be done with caution, as eyelid closure may be impaired if too much skin is removed.

SUMMARY

Optimum care of the patient with GO is achieved through teamwork between the endocrinologist and ophthalmologist, with input from ancillary specialists as needed. If no sight-threatening complications of the disease are initially identified, an accurate determination of disease activity and severity narrows the available treatment options to those most likely to benefit the patient (Fig. 2). Smoking and possible dysthyroidism constitute important modifiable risk factors for disease progression that should be addressed on diagnosis. Of importance is early assessment of the impact of disease on patients' QOL, and their priorities and expectations regarding management. Once this information has been gathered, careful discussion between patients and physicians can define the initial management plan, which includes the timing of the next visit and general parameters for a future change in course.

REFERENCES

1. Bahn RS. Graves' ophthalmopathy. *N Engl J Med*. 2010; 362:726–738. [PubMed: 20181974]
2. Khoo DH, Eng PH, Ho SC, et al. Graves' ophthalmopathy in the absence of elevated free thyroxine and triiodothyronine levels: prevalence, natural history, and thyrotropin receptor antibody levels. *Thyroid*. 2000; 10:1093–1100. [PubMed: 11201855]
3. Wiersinga WM, Smit T, van der Gaag R, et al. Temporal relationship between onset of Graves' ophthalmopathy and onset of thyroidal Graves' disease. *J Endocrinol Invest*. 1988; 11:615–619. [PubMed: 2907524]
4. Rundle FF, Wilson CW. Development and course of exophthalmos and ophthalmoplegia in Graves' disease with special reference to the effect of thyroidectomy. *Clin Sci*. 1945; 5:177–194. [PubMed: 21011937]

5. Perros P, Crombie AL, Kendall-Taylor P. Natural history of thyroid associated ophthalmopathy. *Clin Endocrinol*. 1995; 42:45–50.
6. Bahn RS. Pathophysiology of Graves' ophthalmopathy: the cycle of disease. *J Clin Endocrinol Metab*. 2003; 88:1939–1946. [PubMed: 12727937]
7. Wiersinga WM. Autoimmunity in Graves' ophthalmopathy: the result of an unfortunate marriage between TSH receptors and IGF-1 receptors? *J Clin Endocrinol Metab*. 2011; 96:2386–2394. [PubMed: 21677036]
8. van Zeijl CJ, Fliers E, van Koppen CJ, et al. Thyrotropin receptor-stimulating Graves' disease immunoglobulins induce hyaluronan synthesis by differentiated orbital fibroblasts from patients with Graves' ophthalmopathy not only via cyclic adenosine monophosphate signaling pathways. *Thyroid*. 2011; 21:169–176. [PubMed: 20954819]
9. Kumar S, Nadeem S, Stan MN, et al. A stimulatory TSH receptor antibody enhances adipogenesis via phosphoinositide 3-kinase activation in orbital preadipocytes from patients with Graves' ophthalmopathy. *J Mol Endocrinol*. 2011; 46:155–163. [PubMed: 21321093]
10. Rapoport B, Alsabeh R, Aftergood D, et al. Elephantiasic pretibial myxedema: insight into and a hypothesis regarding the pathogenesis of the extrathyroidal manifestations of Graves' disease. *Thyroid*. 2000; 10:685–692. [PubMed: 11014313]
11. Stan MN, Bahn RS. Risk factors for development or deterioration of Graves' ophthalmopathy. *Thyroid*. 2010; 20:777–783. [PubMed: 20578901]
12. Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol*. 1977; 7:481–493.
13. Wiersinga WM, Bartalena L. Epidemiology and prevention of Graves' ophthalmopathy. *Thyroid*. 2002; 12:855–860. [PubMed: 12487767]
14. Enzmann DR, Donaldson SS, Kriss JP. Appearance of Graves' disease on orbital computed tomography. *J Comput Assist Tomogr*. 1979; 3:815–819. [PubMed: 583152]
15. Bartley GB. The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. *Trans Am Ophthalmol Soc*. 1994; 92:477–588. [PubMed: 7886878]
16. Fatourehchi V. Pretibial myxedema: pathophysiology and treatment options. *Am J Clin Dermatol*. 2005; 6:295–309. [PubMed: 16252929]
17. Bartalena L, Baldeschi L, Dickinson AJ, et al. Consensus statement of the European Group on Graves' Orbitopathy (EUGOGO) on management of Graves' orbitopathy. *Thyroid*. 2008; 18:333–346. [PubMed: 18341379]
18. Mourits MP, Prummel MF, Wiersinga WM, et al. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. *Clin Endocrinol*. 1997; 47:9–14.
19. Wiersinga WM, Perros P, Kahaly GJ, et al. Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers. *Eur J Endocrinol*. 2006; 155:387–389. [PubMed: 16914591]
20. Yeatts RP. Quality of life in patients with Graves ophthalmopathy. *Trans Am Ophthalmol Soc*. 2005; 103:368–411. [PubMed: 17057811]
21. Terwee CB, Gerding MN, Dekker FW, et al. Development of a disease specific quality of life questionnaire for patients with Graves' ophthalmopathy: the GO-QOL. *Br J Ophthalmol*. 1998; 82:773–779. [PubMed: 9924370]
22. Terwee CB, Dekker FW, Mourits MP, et al. Interpretation and validity of changes in scores on the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) after different treatments. *Clin Endocrinol*. 2001; 54:391–398.
23. Jacobson EM, Tomer Y. The CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 gene quintet and its contribution to thyroid autoimmunity: back to the future. *J Autoimmun*. 2007; 28:85–98. [PubMed: 17369021]
24. Tsai CC, Kau HC, Kao SC, et al. Exophthalmos of patients with Graves' disease in Chinese of Taiwan. *Eye*. 2006; 20:569–573. [PubMed: 15905866]
25. Burch HB, Wartofsky L. Graves' ophthalmopathy: current concepts regarding pathogenesis and management. *Endocr Rev*. 1993; 14:747–793. [PubMed: 8119236]

26. Davies TF, Kandler DL. Mechanisms of human autoimmune thyroid disease. *Monogr Pathol.* 1993; (35):103–117. [PubMed: 8502247]
27. Prummel MF, Wiersinga WM, Mourits MP, et al. Effect of abnormal thyroid function on the severity of Graves' ophthalmopathy. *Arch Intern Med.* 1990; 150:1098–1101. [PubMed: 1691908]
28. Tallstedt L, Lundell G, Blomgren H, et al. Does early administration of thyroxine reduce the development of Graves' ophthalmopathy after radioiodine treatment? *Eur J Endocrinol.* 1994; 130:494–497. [PubMed: 8180678]
29. Kung AW, Yau CC, Cheng A. The incidence of ophthalmopathy after radioiodine therapy for Graves' disease: prognostic factors and the role of methimazole. *J Clin Endocrinol Metab.* 1994; 79:542–546. [PubMed: 7913934]
30. Baujat B, Krastinova D, Bach CA, et al. Orbital morphology in exophthalmos and exorbitism. *Plast Reconstr Surg.* 2006; 117:542–550. [discussion: 551–2]. [PubMed: 16462337]
31. Tallstedt L, Lundell G, Torring O, et al. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group [see comment]. *N Engl J Med.* 1992; 326:1733–1738. [PubMed: 1489388]
32. Traisk F, Tallstedt L, Abraham-Nordling M, et al. Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131. *J Clin Endocrinol Metab.* 2009; 94:3700–3707. [PubMed: 19723755]
33. Pfeilschifter J, Ziegler R. Smoking and endocrine ophthalmopathy: impact of smoking severity and current vs lifetime cigarette consumption. *Clin Endocrinol.* 1996; 45:477–481.
34. Krassas GE, Segni M, Wiersinga WM. Childhood Graves' ophthalmopathy: results of a European questionnaire study. *Eur J Endocrinol.* 2005; 153:515–520. [PubMed: 16189172]
35. Eckstein AK, Plicht M, Lax H, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. *J Clin Endocrinol Metab.* 2006; 91:3464–3470. [PubMed: 16835285]
36. Gerding MN, van der Meer JW, Broenink M, et al. Association of thyrotrophin receptor antibodies with the clinical features of Graves' ophthalmopathy. *Clin Endocrinol.* 2000; 52:267–271.
37. Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med.* 1998; 338:73–78. [PubMed: 9420337]
38. Perros P, Kendall-Taylor P, Neoh C, et al. A prospective study of the effects of radioiodine therapy for hyperthyroidism in patients with minimally active graves' ophthalmopathy. *J Clin Endocrinol Metab.* 2005; 90:5321–5323. [PubMed: 15985483]
39. Eckstein A, Quadbeck B, Mueller G, et al. Impact of smoking on the response to treatment of thyroid associated ophthalmopathy. *Br J Ophthalmol.* 2003; 87:773–776. [PubMed: 12770979]
40. Bartalena L, Marcocci C, Tanda ML, et al. Cigarette smoking and treatment outcomes in Graves ophthalmopathy. *Ann Intern Med.* 1998; 129:632–635. [PubMed: 9786811]
41. Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. *JAMA.* 1993; 269:479–482. [PubMed: 8419666]
42. Bartalena L, Marcocci C, Bogazzi F, et al. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. *N Engl J Med.* 1989; 321:1349–1352. [PubMed: 2811943]
43. Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid.* 2011; 20:593–646.
44. Baldeschi L, Wakelkamp IM, Lindeboom R, et al. Early versus late orbital decompression in Graves' orbitopathy: a retrospective study in 125 patients. *Ophthalmology.* 2006; 113:874–878. [PubMed: 16530839]
45. Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract.* 2011; 17:456–520. [PubMed: 21700562]
46. Lai A, Sassi L, Compri E, et al. Lower dose prednisone prevents radioiodine-associated exacerbation of initially mild or absent graves' orbitopathy: a retrospective cohort study. *J Clin Endocrinol Metab.* 2010; 95:1333–1337. [PubMed: 20061414]

47. Uddin JM, Davies PD. Treatment of upper eyelid retraction associated with thyroid eye disease with subconjunctival botulinum toxin injection. *Ophthalmology*. 2002; 109:1183–1187. [PubMed: 12045064]
48. Bouzas EA, Karadimas P, Mastorakos G, et al. Antioxidant agents in the treatment of Graves' ophthalmopathy. *Am J Ophthalmol*. 2000; 129:618–622. [PubMed: 10844053]
49. Marcocci C, Kahaly GJ, Krassas GE, et al. Selenium and the course of mild Graves' orbitopathy. *N Engl J Med*. 2011; 364:1920–1931. [PubMed: 21591944]
50. Zang S, Ponto KA, Kahaly GJ. Clinical review: intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. *J Clin Endocrinol Metab*. 2011; 96:320–332. [PubMed: 21239515]
51. Kahaly GJ, Pitz S, Hommel G, et al. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. *J Clin Endocrinol Metab*. 2005; 90:5234–5240. [PubMed: 15998777]
52. Macchia PE, Bagattini M, Lupoli G, et al. High-dose intravenous corticosteroid therapy for Graves' ophthalmopathy. *J Endocrinol Invest*. 2001; 24:152–158. [PubMed: 11314743]
53. Le Moli R, Baldeschi L, Saeed P, et al. Determinants of liver damage associated with intravenous methylprednisolone pulse therapy in Graves' ophthalmopathy. *Thyroid*. 2007; 17:357–362. [PubMed: 17465867]
54. Marino M, Morabito E, Brunetto MR, et al. Acute and severe liver damage associated with intravenous glucocorticoid pulse therapy in patients with Graves' ophthalmopathy. *Thyroid*. 2004; 14:403–406. [PubMed: 15186621]
55. Marcocci C, Watt T, Altea MA, et al. Fatal and non-fatal adverse events of glucocorticoid therapy for Graves' orbitopathy: a questionnaire survey among members of the European Thyroid Association. *Eur J Endocrinol*. 2012; 166(2):247–253. [PubMed: 22058081]
56. Bahn R. High-dose intravenous glucocorticoid therapy for Graves' ophthalmopathy: where are we now? *Thyroid*. 2012; 22:1–2. [PubMed: 22216984]
57. Ebner R, Devoto MH, Weil D, et al. Treatment of thyroid associated ophthalmopathy with periocular injections of triamcinolone. *Br J Ophthalmol*. 2004; 88:1380–1386. [PubMed: 15489477]
58. Kahaly G, Schrezenmeir J, Krause U, et al. Cyclosporin and prednisone versus prednisone in treatment of Graves' ophthalmopathy: a controlled, randomized and prospective study. *Eur J Clin Invest*. 1986; 16:415–422. [PubMed: 3100309]
59. Prummel MF, Mourits MP, Berghout A, et al. Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. *N Engl J Med*. 1989; 321:1353–1359. [PubMed: 2519530]
60. Perros P, Weightman DR, Crombie AL, et al. Azathioprine in the treatment of thyroid-associated ophthalmopathy. *Acta Endocrinol*. 1990; 122:8–12. [PubMed: 2305608]
61. Kahaly G, Pitz S, Muller-Forell W, et al. Randomized trial of intravenous immunoglobulins versus prednisolone in Graves' ophthalmopathy. *Clin Exp Immunol*. 1996; 106:197–202. [PubMed: 8918563]
62. Baschieri L, Antonelli A, Nardi S, et al. Intravenous immunoglobulin versus corticosteroid in treatment of Graves' ophthalmopathy. *Thyroid*. 1997; 7:579–585. [PubMed: 9292946]
63. Dickinson AJ, Vaidya B, Miller M, et al. Double-blind, placebo-controlled trial of octreotide long-acting repeatable (LAR) in thyroid-associated ophthalmopathy. *J Clin Endocrinol Metab*. 2004; 89:5910–5915. [PubMed: 15579735]
64. Wemeau JL, Caron P, Beckers A, et al. Octreotide (long-acting release formulation) treatment in patients with Graves' orbitopathy: clinical results of a four-month, randomized, placebo-controlled, double-blind study. *J Clin Endocrinol Metab*. 2005; 90:841–848. [PubMed: 15562016]
65. Chang TC, Liao SL. Slow-release lanreotide in Graves' ophthalmopathy: a double-blind randomized, placebo-controlled clinical trial. *J Endocrinol Invest*. 2006; 29:413–422. [PubMed: 16794364]
66. Stan MN, Garrity JA, Bradley EA, et al. Randomized, double-blind, placebo-controlled trial of long-acting release octreotide for treatment of Graves' ophthalmopathy. *J Clin Endocrinol Metab*. 2006; 91:4817–4824. [PubMed: 16984988]

67. El Fassi D, Banga JP, Gilbert JA, et al. Treatment of Graves' disease with rituximab specifically reduces the production of thyroid stimulating autoantibodies. *Clin Immunol.* 2009; 130:252–258. [PubMed: 18964302]
68. Salvi M, Vannucchi G, Campi I, et al. Efficacy of rituximab treatment for thyroid-associated ophthalmopathy as a result of intraorbital B-cell depletion in one patient unresponsive to steroid immunosuppression. *Eur J Endocrinol.* 2006; 154:511–517. [PubMed: 16556712]
69. El Fassi D, Nielsen CH, Hasselbalch HC, et al. Treatment-resistant severe, active Graves' ophthalmopathy successfully treated with B lymphocyte depletion. *Thyroid.* 2006; 16:709–710. [PubMed: 16889501]
70. Khanna D, Chong KK, Afifiyan NF, et al. Rituximab treatment of patients with severe, corticosteroid-resistant thyroid-associated ophthalmopathy. *Ophthalmology.* 2010; 117:133–139. e132. [PubMed: 19818507]
71. Heemstra KA, Toes RE, Sepers J, et al. Rituximab in relapsing Graves' disease, a phase II study. *Eur J Endocrinol.* 2008; 159:609–615. [PubMed: 18628345]
72. Bradley EA, Gower EW, Bradley DJ, et al. Orbital radiation for Graves ophthalmopathy: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2008; 115:398–409. [PubMed: 18082885]
73. Prummel MF, Mourits MP, Blank L, et al. Randomized double-blind trial of prednisone versus radiotherapy in Graves' ophthalmopathy. *Lancet.* 1993; 342:949–954. [PubMed: 8105213]
74. Prummel MF, Terwee CB, Gerding MN, et al. A randomized controlled trial of orbital radiotherapy versus sham irradiation in patients with mild Graves' ophthalmopathy. *J Clin Endocrinol Metab.* 2004; 89:15–20. [PubMed: 14715820]
75. Kahaly GJ, Rosler HP, Pitz S, et al. Low- versus high-dose radiotherapy for Graves' ophthalmopathy: a randomized, single blind trial [see comment]. *J Clin Endocrinol Metab.* 2000; 85:102–108. [PubMed: 10634372]
76. Marcocci C, Bartalena L, Bogazzi F, et al. Orbital radiotherapy combined with high dose systemic glucocorticoids for Graves' ophthalmopathy is more effective than radiotherapy alone: results of a prospective randomized study. *J Endocrinol Invest.* 1991; 14:853–860. [PubMed: 1802923]
77. Gorman CA, Garrity JA, Fatourechi V, et al. A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for Graves' ophthalmopathy [see comment]. *Ophthalmology.* 2001; 108:1523–1534. [erratum appears in *Ophthalmology* 2004; 111(7)1306]. [PubMed: 11535445]
78. Gerling J, Kommerell G, Henne K, et al. Retrobulbar irradiation for thyroid-associated orbitopathy: double-blind comparison between 2.4 and 16 Gy. *Int J Radiat Oncol Biol Phys.* 2003; 55:182–189. [PubMed: 12504052]
79. Bartalena L, Marcocci C, Chiovato L, et al. Orbital cobalt irradiation combined with systemic corticosteroids for Graves' ophthalmopathy: comparison with systemic corticosteroids alone. *J Clin Endocrinol Metab.* 1983; 56:1139–1144. [PubMed: 6341388]
80. Marcocci C, Bartalena L, Tanda ML, et al. Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: results of a prospective, single-blind, randomized study. *J Clin Endocrinol Metab.* 2001; 86:3562–3567. [PubMed: 11502779]
81. Ohtsuka K, Sato A, Kawaguchi S, et al. Effect of steroid pulse therapy with and without orbital radiotherapy on Graves' ophthalmopathy. *Am J Ophthalmol.* 2003; 135:285–290. [PubMed: 12614743]
82. Marcocci C, Bartalena L, Rocchi R, et al. Long-term safety of orbital radiotherapy for Graves' ophthalmopathy. *J Clin Endocrinol Metab.* 2003; 88:3561–3566. [PubMed: 12915636]
83. Wakelkamp IM, Tan H, Saeed P, et al. Orbital irradiation for Graves' ophthalmopathy: is it safe? A long-term follow-up study. *Ophthalmology.* 2004; 111:1557–1562. [PubMed: 15288988]
84. Menconi F, Marino M, Pinchera A, et al. Effects of total thyroid ablation versus near-total thyroidectomy alone on mild to moderate Graves' orbitopathy treated with intravenous glucocorticoids. *J Clin Endocrinol Metab.* 2007; 92:1653–1658. [PubMed: 17299076]

85. Jarhult J, Rudberg C, Larsson E, et al. Graves' disease with moderate-severe endocrine ophthalmopathy-long term results of a prospective, randomized study of total or subtotal thyroid resection. *Thyroid*. 2005; 15:1157–1164. [PubMed: 16279849]
86. Feldon SE, Muramatsu S, Weiner JM. Clinical classification of Graves' ophthalmopathy. Identification of risk factors for optic neuropathy. *Arch Ophthalmol*. 1984; 102:1469–1472. [PubMed: 6548373]
87. Wiersinga WM, Prummel MF. Graves' ophthalmopathy: a rational approach to treatment. *Trends Endocrinol Metab*. 2002; 13:280–287. [PubMed: 12163229]
88. Soares-Welch CV, Fatourehchi V, Bartley GB, et al. Optic neuropathy of Graves disease: results of transantral orbital decompression and long-term follow-up in 215 patients. *Am J Ophthalmol*. 2003; 136:433–441. [PubMed: 12967795]
89. Wakelkamp IM, Baldeschi L, Saeed P, et al. Surgical or medical decompression as a first-line treatment of optic neuropathy in Graves' ophthalmopathy? A randomized controlled trial. *Clin Endocrinol*. 2005; 63:323–328.
90. Wiersinga WM. Management of Graves' ophthalmopathy. *Nat Clin Pract Endocrinol Metab*. 2007; 3:396–404. [PubMed: 17452966]
91. Baldeschi L, MacAndie K, Hintschich C, et al. The removal of the deep lateral wall in orbital decompression: its contribution to exophthalmos reduction and influence on consecutive diplopia. *Am J Ophthalmol*. 2005; 140:642–647. [PubMed: 16140250]
92. Cansiz H, Yilmaz S, Karaman E, et al. Three-wall orbital decompression superiority to 2-wall orbital decompression in thyroid-associated ophthalmopathy. *J Oral Maxillofac Surg*. 2006; 64:763–769. [PubMed: 16631482]
93. Mourits MP, Koornneef L, Wiersinga WM, et al. Orbital decompression for Graves' ophthalmopathy by inferomedial, by inferomedial plus lateral, and by coronal approach. *Ophthalmology*. 1990; 97:636–641. [PubMed: 2342809]
94. Boulou PR, Hardy I. Thyroid-associated orbitopathy: a clinicopathologic and therapeutic review. *Curr Opin Ophthalmol*. 2004; 15:389–400. [PubMed: 15625899]

Fig. 1.

Immunopathogenesis of Graves ophthalmopathy. Circulating autoantibodies directed against the thyrotropin receptor activate this receptor on orbital fibroblasts; this results in their increased secretion of hyaluronic acid, and the differentiation of a subset into mature adipocytes. In addition, activated T cells infiltrate the orbit, interact with autoreactive B cells, and secrete proinflammatory cytokines. These cellular changes lead to the extraocular muscle enlargement, orbital adipose tissue expansion, and orbital inflammation characteristic of the disease. XRT, radiotherapy.

Fig. 2.
Algorithm for the treatment of Graves ophthalmopathy.

Table 1

Differential diagnosis

Primary Examination Feature	Differential Diagnosis	Symmetry	Prevalence ^a
Proptosis	Primary cancer	Unilateral	Uncommon
	Metastatic cancer	Unilateral	Uncommon
	Orbital meningioma	Unilateral	Common
	Orbital myositis	Uni-/bilateral	Common
	IgG ₄ disease	Uni-/bilateral	Uncommon
	Sarcoidosis	Uni-/bilateral	Rare
	Wegener granulomatosis	Uni-/bilateral	Rare
	Carotid cavernous fistula	Unilateral	Uncommon
	Paranasal sinus mucocoele	Unilateral	Uncommon
Periocular inflammation/congestion/edema	Allergy	Bilateral	Common
	Nephrotic syndrome	Bilateral	Uncommon
	Facial cellulitis	Unilateral	Uncommon
Diplopia	Orbital myositis	Uni-/bilateral	Common
	Myasthenia gravis	Uni-/bilateral	Common
	Contralateral blowout fracture	Unilateral	Uncommon
Lid retraction	Midbrain disease	Unilateral	Uncommon
	Contralateral ptosis	Unilateral	Uncommon
	Sympathomimetic drugs	Bilateral	Common
	Thyrotoxicosis	Bilateral	Common

^aPrevalence within all patients with primary examination feature.

Table 2

GO severity assessment

Degree of Severity	Lid Retraction	Soft Tissue Involvement	Proptosis ^a	Diplopia	Corneal Exposure	Optic Nerve Status
Mild (1 of following)	<2 mm	Mild	<3 mm	Transient ^b or absent	Absent	Normal
Moderate to severe (1 of following)	2 mm	Moderate or severe	3 mm	Inconstant ^b or constant	Mild	Normal
Sight threatening (1 of last 2 categories)	Not contributory	Not contributory	Not contributory	Not contributory	Ulceration	Compromised

^a Proptosis refers to the variation compared with the norm for each race or to the patient's baseline if available.

^b Intermittent diplopia: present when the patient is fatigued; inconstant diplopia: present at extremes of gaze; constant diplopia: present in primary gaze.

Table 3

Risk factors for GO development or deterioration

Risk Factor	Relative Risk	Details	Reference
Genetics	+	Complex genetic basis; similar to Graves disease	23
Ancestry	++	Caucasians > Asians	24
Gender	++	Frequency: women > men Severity: men > women	25,26
Thyroid dysfunction	+++	Both hypo- and hyperthyroidism increase risk	27–29
Mechanical factors	+	Narrower lateral orbital wall angle may affect progression	30
Thyroid hormone levels	+	Both high triiodothyronine and thyroxine levels increase risk (inconsistent results in the literature)	29,31,32
Smoking	++++	Active and passive smoking increases risk	33,34
TSH receptor antibody	++	High titer 5 months after diagnosis predicts worse course of disease	35,36
Radioactive iodine	++	RAI treatment increases risk primarily in smokers and patients with active GO	31,32,37