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Graves’ orbitopathy: a multidisciplinary approach

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ABSTRACT

Orbitopathy is the main extra thyroidal manifestation of Graves’ disease. It is a very challenging condition, which requires a cooperation between many specialists (endocrinologists, ophthalmologists, radiologists, radiotherapeutic, orbital surgeons) for an optimal clinical management. An accurate diagnostic assessment is required, in order to plan an adequate treatment of Graves’ orbitopathy. Medical therapy, radiotherapy or surgery may be necessary to control the disease. In this review, the authors analyze the various therapeutic strategies, as well the more recent therapies based on pharmacologic immunomodulation.


KEY WORDS: Graves ophthalmopathy; Hyperthyroidism; Graves disease.

Graves’ orbitopathy (GO), also known as thyroid eye disease or thyroid orbitopathy, is an extrathyroidal manifestation of Graves’ disease (GD).

GO occurs in 25-50% of patients with GD, although the literature reports show that subtle ocular abnormalities can be observed in the majority of patients with GD.1

The factors predisposing to the development of orbitopathy are unknown, with the exception of smoking (which may also worsen the course of the disease) and of radioiodine used for the treatment of autoimmune hyperthyroidism; other predisposing factors are elevated titers of thyrotropin receptor antibodies (TRAb), a high clinical activity score (CAS) and the duration of symptoms of hyperthyroidism.2,3

GO is an autoimmune inflammatory disease, which shares pathogenetic mechanisms with thyroid disorder.

Briefly, the trigger mechanism of the autoimmune/inflammatory process is the binding of thyroid stimulating antibodies to TSH receptors, which are highly expressed by orbital fibrocytes and fibroblasts, similarly to thyroid cells; the binding activates insulin-like growth factor I receptor (IGF-IR) which, in turn, induces the synthesis of highly hydrophilic glycosaminoglycans by fibrocytes, contributing to orbital remodeling, along with the differentiation of fibroblasts into myofibroblasts and adipocytes; in addition, activation of T-lymphocytes leads to inflammatory cascade mediated by cytokines release. These processes account for the inflammatory symptoms which are the first manifestations of GO, while in the advanced phases a fibrosis occurs, mainly mediated by transforming growth factor-β and IL-17 activation, which is responsible for permanent remodeling of the orbit.4

The inflammatory/autoimmune process involves all the orbital structures: eyelids, soft tissues and extraocular muscles; the increase in orbital fat and in muscle volume due to inflammation may raise infraorbital pressure and push forward the globe, leading to exophthalmos, which is a typical sign of GO. The fibrosis of extraocular muscles may impair their motility, with consequent diplopia.4

Clinical presentation may be highly variable, depending on the extent and on the combination of the involvement of each structure.
The signs and symptoms at presentation include any combination of proptosis, lid retraction, pain, tearing, orbital movement impairment, with or without diplopia, eyelid swelling and erythema, conjunctival redness, chemosis, oedema and redness of the caruncle, grittiness, photophobia, visual impairment, corneal ulceration and rarely blindness due to optical nerve neuropathy. The clinical course of GO was well described by Rundle in 1945, who highlighted that, after an initial phase characterized by inflammatory symptoms, a stabilization phase follows, without further deterioration; in more advanced phases, inflammatory symptoms gradually disappear and permanent abnormalities in both function and appearance remain.

To describe the course of the disease, two terms are generally used: “activity” describes the inflammatory symptoms of the initial phase, while “severity” refers to the degree of functional or cosmetic abnormalities at any stage of orbitopathy. The assessment of these parameters is a useful guidance for the clinical management of GO, since anti-inflammatory or immunomodulating therapies are more effective in the initial phase, when there is an active inflammatory process, while rehabilitative surgical procedures should be only undertaken when the disease has reached an inactive phase and spontaneous improvement is unlikely.

Assessment of thyroid status
In most cases, the onset of GO is concomitant to that of hyperthyroidism; however, orbital disease may occur before the onset or during the course of hyperthyroidism. In some cases, orbitopathy appears also some time after the cure of hyperthyroidism, in particular, when the patient has been treated by radioactive iodine, which is an established risk factor for the development of GO.

What is more, GO may occur in patients with Hashimoto thyroiditis, irrespective of thyroid function. For these reasons, thyroid function must always be evaluated when GO is suspected; moreover, the determination of TRAb is mandatory in every patient, both for diagnostic and prognostic purposes.

Assessment of Graves’ orbitopathy
Although in most cases GO present with mild symptoms, requiring a wait and see approach or minimal interventions only, the clinical management of more severe GO is often difficult and requires a skilled team of specialists, including endocrinologists, ophthalmologists, radiologists, radiotherapeutics and orbital surgeons. Furthermore, clinicians have to keep in mind that mild forms may worsen in a rather short time, and that a precocious treatment leads to a better outcome; therefore, it is recommended that primary-care physicians, general practitioners, general internists and specialists refer patients with GO to combined thyroid-eye clinics or centers where specialists are available.

Ophthalmological evaluation
Patients with suspected GO should undergo an accurate clinical evaluation, with the aim of identifying symptoms and signs to define the stage of the disease (based on the activity and severity assessment), which is the prerequisite for planning a therapeutic strategy, as stated above. The activity and the severity of the disease are generally assessed by scores known by the acronyms CAS (clinical activity score), made by seven items for initial evaluation which can be integrated with three other items for the assessment during the follow-up (Table I), and NOSPECS which mainly measures the severity (Table II).

An atlas, available at the EUGOGO website, provides a useful guide for the assessment of each parameter. The guidelines of the EUGOGO (European Group On Graves’ Orbitopathy of the European Thyroid Association) set the criteria for defining the activity (a CAS≥3/7 at baseline is indicative of active GO) (Figure 1) and the severity of the disease, which is divided into mild, moderate-to-severe and sight-threatening or highly severe (Table III). Patients should be asked about the time of onset of symptoms and any previous therapies, as well as the presence of symptoms such as spontaneous orbital pain, gaze evoked pain, excessive watering, grittiness, blurred vision and diplopia, the last of which can be classified according to the Bahn and Gorman Scale (Figure 2) (Table IV).

Initial clinical assessment includes the search for signs

<table>
<thead>
<tr>
<th>Table I.—Clinical activity score (CAS) of Graves’ orbitopathy.</th>
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</thead>
<tbody>
<tr>
<td>CAS</td>
</tr>
<tr>
<td>1. Spontaneous retrobulbar pain</td>
</tr>
<tr>
<td>2. Pain on attempted upward or downward hazy</td>
</tr>
<tr>
<td>3. Redness of eyelids</td>
</tr>
<tr>
<td>4. Redness of conjunctiva</td>
</tr>
<tr>
<td>5. Swelling of caruncle or plica</td>
</tr>
<tr>
<td>6. Swelling of eyelids</td>
</tr>
<tr>
<td>7. Swelling of conjunctiva (chemosis)</td>
</tr>
</tbody>
</table>

According to EUGOGO criteria, GO is defined as active if CAS is ≥3, as inactive if CAS is <3.
of soft tissue inflammation, exophthalmometry, measurement of palpebral retraction, examination with the slit lamp and measurement of intraocular pressure.

Ocular motility is assessed by prism cover test, Hess screen, measurement of monocular ductions and the field of binocular single vision.\textsuperscript{13}

A serious clinical picture is that of optic neuropathy (or dysthyroid optic neuropathy [DON]), a sight-threatening condition, which in most cases is due to the compression of the optic nerve by enlarged muscles at the apex of the orbit. In some cases, exophthalmos may be slight or absent and the compression of the nerve is due to the increase in infraorbital pressure. In other cases, a severe proptosis is present, and a stretching of the nerve, rather than its compression, is responsible for nerve damage. A restriction of motility is present in almost all patients (Figure 3).\textsuperscript{14}

Male gender, older age, diabetes and smoking are considered to be risk factors for the development of DON, but every patient with active GO may develop DON.

<table>
<thead>
<tr>
<th>Class</th>
<th>Grade</th>
<th>Suggestions for grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No physical signs or symptoms</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Only signs</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Soft tissue involvement</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Marked</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Proptosis</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>3 or 4 mm over upper normal</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>5 to 7 mm increase</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>8 mm increase</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Extraocular muscles involvement</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Limitation of motion at extremes of gaze</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Evident restriction of motion</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Fixation of a globe or globes</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Corneal involvement</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Stippling of cornea</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Clouding, necrosis, and perforation</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>Sight loss (due to optic nerve involvement)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Disc pallor or choking, or visual field defect, vision 20/20-20/60</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>The same but vision 20/70-20/200</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Blindness, vision &lt;20/200</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class</th>
<th>Grade</th>
<th>Suggestions for grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild</td>
<td>Patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually 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, no or intermittent diplopia and corneal exposure responsive to lubricants.</td>
</tr>
<tr>
<td>II</td>
<td>Moderate to severe</td>
<td>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). They usually have two or more of the following: lid retraction ≥2 mm, moderate or severe soft-tissue involvement, or exophthalmos ≥3 mm above normal for race and gender, inconstant or constant diplopia.</td>
</tr>
<tr>
<td>III</td>
<td>Sight-threatening (very severe)</td>
<td>Patients with DON and/or corneal breakdown.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Intermittent diplopia, present only when patient fatigued</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Inconstant diplopia, present only on lateral or upward gaze</td>
</tr>
<tr>
<td>III</td>
<td>Constant diplopia, present in primary gaze but correctable with prisms</td>
</tr>
<tr>
<td>IV</td>
<td>Constant diplopia, not correctable with prisms</td>
</tr>
</tbody>
</table>

Figure 1.—Active GO.

Figure 2.—Severe involvement of left inferior rectus. Inflammation is almost absent.
Ultrasound

Diagnostic ultrasound in eye diseases is performed using high frequencies probe (8 MHz). Ultrasound diagnosis of GO is based on the following points: no mass lesion, enlarged orbital tissues with a heterogeneous reflectivity, thickening of the bellies of at least two extraocular muscles, enlarged subarachnoid space of the optic nerve in case of dysthyroid optic neuropathy and thickened periorbital tissue. Despite in the active phase of the disease the internal reflectivity of extraocular eye muscles is low due to inflammatory infiltration whilst it is irregularly high in fibrotic end-stage disease, the reliability of orbital ultrasound in the assessment of the activity of the disease is rather low, due to the interobserver variability. The main advantages of orbital ultrasound are the absence of invasivity, its low cost and the lack of ionizing radiation, with a relatively short examination time. The disadvantages are that US scan is highly dependent on the skill of the operator and that the quality of information on the posterior orbit, as well as on the bony orbital walls, is poor.

Computed tomography

Due to different X-ray absorption, CT allow to distinguish the different density of tissues: as a matter of fact, fat and water, which have low densities, appear black in contrast...
signal enhancement of the extraocular muscles or the eyelid, which may be seen in the stage of acute inflammation. In GO the standardized MR-imaging protocol includes coronal fast spin echo T1-w and T2-w RM sequences in transverse and coronal planes, with 3 mm slice thickness.\textsuperscript{19, 20} Diffusion sequences and normalized-apparent diffusion coefficient could be quantitative parameters of thyroid-orbitalopathy activity and severity, since they correlate with clinical scores. DWI can identify clinically silent inflammation of deep orbital structures and can detect subclinical modifications during follow-up. Therefore, such quantitative MRI parameters may be of fundamental importance for treatment choices and for monitoring the orbital part of disease;\textsuperscript{21} furthermore, they are less influenced by the operator than clinical scores (Figure 3, 4, 5, 6).

MRI is superior to CT in evaluating soft tissues and in differentiating imaging features of active and stable disease. MRI may be preferable in cases where there are overlapping orbital disease processes and imaging features.

In all stages, on T1-weighted imaging, isointense enhancement of the enlarged extraocular muscles is observed. Contrast administration may demonstrate decreased or delayed muscle enhancement compared with normal, due to impaired microcirculation secondary to venous stasis or infraorbital mass effect. MRI T1-weighted imaging can also be used to detect fatty degeneration in the muscle body. Increased signal intensity on T2-weighted imaging with fat saturation is an expression of elevated water content, a finding indicative of active inflammation and oedema.\textsuperscript{21}

This has been associated with active disease and may be a positive predictor of response to immunosuppression or radiation therapy.\textsuperscript{22}

The diminished signal in chronic and stable stage disease is a landmark of low water content, fat infiltration and fibrotic degeneration.

Diffusion-tensor imaging (DTI) is a MRI technique which may help to detect early signs of disease activity in the optic nerve that could reflect risk of DON.\textsuperscript{22}

Differential diagnosis

Nonspecific orbital inflammation

Nonspecific orbital inflammation may present with clinical picture and radiographic features similar to GO. The differential diagnosis in based on the radiological aspect of the muscles: indeed, in GO the enlargement spares the anterior tendon insertion, while in nonspecific orbital inflammation involves the tendon too and the lesions are mostly unilateral.\textsuperscript{23}
Specific orbital inflammation

Inflammation of orbital muscles and of the lacrimal glands may occur in systemic inflammatory/autoimmune systemic diseases, such as lupus erythematosus sarcoidosis, and may be difficult to differentiate on imaging. The systemic clinical manifestations may help in the differential diagnosis.23

Vascular

Arteriovenous malformations and carotid cavernous fistulas may cause an enlargement of the extraocular muscles due to an increase in orbital venous pressure; unilateral uniform muscle enlargement associated with congestion of the ophthalmic vein may be an indicator of a vascular process.18

Neoplasia

Lymphoma is the most common primary orbital tumor, which mainly affect the superior muscles.

The lacrimal gland is typically affected, but isolated muscle enlargement can also be observed.

Neoplasms may invade extraocular muscles or compress their venous drainage causing secondary muscle enlargement. Carcinoid and cutaneous melanoma are the tumors which most frequently spread to the orbit, but metastasis may come from breast, renal, thyroid, or other gastrointestinal cancers.18, 19

Treatment of Graves’ orbitopathy

Smoking

All patients who smoke should be strongly encouraged to stop smoking, irrespective of the severity of the disease.24

Indeed, it is well established that smokers have more severe GO than non-smokers and that they have a higher probability of progression of the disease to more severe stages as well as of its appearance after radioiodine treatment; furthermore, smoking hampers the efficacy of immunosuppressive therapies, and its cessation is associated with a more favorable outcome of GO.25

What is more, patients with Graves’ hyperthyroidism have a higher risk of developing GO: therefore, all patients with GD should abstain from smoking.12

Control of thyroid dysfunction

Any abnormality of thyroid function may have a negative impact on the clinical course of Graves’ orbitopathy and should be promptly corrected.12, 26-28

In hypothyroid patients, a substitutive therapy with LT4 should be started (or the dosage should be adjusted in those who are already in therapy but with abnormal TSH), with the aim of rapidly normalizing TSH levels.

In the minority of patients with autoimmune thyroiditis and normal function, circulating fT4 and TSH should periodically be assessed, in order to find an early dysfunction.

As to hyperthyroidism, its therapy is still a challenge, since no treatment modality has been clearly demonstrated to be superior to another; therefore, antithyroid drugs (ATD), radioiodine (RAI) and surgery may be all considered, according to the general rules for the treatment for Graves’ hyperthyroidism as well as to the stage of GO.26, 29

The effects of the various modalities of treatment of Graves’ hyperthyroidism have been recently reviewed in a Consensus document of the Italian Society of Endocrinology.27

Antithyroid drugs

Thionamides (methimazole, carbimazole and propylthiouracil) are the first-line treatment for Graves’ hyperthyroidism in most countries, due to their efficacy and good tolerability; however, a definitive cure of hyperthyroidism is achieved in no more than 50-60% of the patients. The advantage of thionamide is their ability to rapidly restore euthyroidism, which is beneficial for the course of GO (rather than the pharmacologic properties of ATDs per se).28, 30

In particular, this is advantageous in patients with severe GO, in whom a very rapid control of hyperthyroidism is advised.12, 27 During ATD therapy, thyroid function should be monitored at 6–8-week intervals, in order to prevent fluctuations in thyroid function, which may be detrimental for GO.28 The association of L-thyroxine to ATD (the

Figure 6.—Enlargement of the ophthalmic vein.
so-called “block and replace” regimen) has been proposed to prevent hypothyroidism, but its promising results were not subsequently confirmed, and this protocol is no longer used, except in few selected cases. The concentrations of TRAb should be periodically determined; indeed, their progressive fall is believed to be a favorable prognostic factor for GO, while the persistence of elevated levels may be a reason to continue pharmacologic therapy, or to choose alternative treatments aiming to obtain a definitive resolution of thyroid dysfunction, as specially required in patients with large goiters, severe hyperthyroidism or repeated fluctuations of thyroid function.

### Radioiodine

Radioiodine is an effective and safe therapeutic tool for Graves’ hyperthyroidism; in the majority of patients hypothyroidism develops almost invariably within 1 year from I\textsuperscript{131} administration. Few controlled studies were addressed to evaluate the effects of RAI in patients with GO, but there is a general agreement that RAI treatment is associated with a higher risk of progression of GO, which is ascribed to immune stimulation due to the release of thyroid autoantigens. The progression is more likely to occur in active smokers; in addition, in patients treated with RAI also the severity of hyperthyroidism, the persistence of untreated post-RAI hypothyroidism and, perhaps, high titers of TRAb are considered risk factors for progression of GO. In such patients, a steroid prophylaxis has been demonstrated to prevent the progression of pre-existing GO, or its new onset in those without previous orbital involvement. Low doses of prednisone (2 mg/kg body weight) are generally prescribed, starting the day after I\textsuperscript{131} administration, and gradually tapered over 6 weeks until withdrawal. Steroid prophylaxis is generally not required in patients with absent or inactive GO, or absence of risk factors of progression/development of orbitopathy. Short duration of hyperthyroidism is also an indication to steroid prophylaxis.

### Surgery

Total or near-total thyroidectomy is an effective therapy for Graves’ disease, leading to a rapid resolution of the symptoms of thyroid hyperfunction; in a recent metaanalysis it was shown to be superior to radioiodine as definitive treatment of hyperthyroidism, being able to obtain also a more rapid fall in TRAB concentrations.

Regarding the effects of thyroidectomy on GO, a randomized clinical trial showed that the rate of de novo occurrence or progression of GO among patients submitted to subtotal thyroidectomy or ATD treatment was similar, but significantly lower than that observed after RAI treatment.

Apart the general indications in autoimmune hyperthyroidism, surgery is the preferred treatment in patients with an active GO in whom a rapid and definitive resolution of thyroid dysfunction is advised in order to improve orbitopathy, or in those who have risk factors for a worsening of GO after radioiodine, such as smoking or elevated TRAb titers.

### Total thyroid ablation

Total thyroid ablation (TTA) is a procedure which aims to eliminate thyroid antigens, which are similar to those expressed in orbital tissue, and are the target of the autoimmune process leading to orbitopathy. TTA is obtained by combining total thyroidectomy and, subsequently, radioiodine. Two retrospective studies reported a beneficial effect of such therapeutic strategy. A randomized clinical trial, addressed to compare the effects of TTA to thyroidectomy alone in moderate to severe orbitopathy, showed an earlier improvement of GO a lesser need as well for further therapies for GO in patients who underwent TTA. However, in the long-term follow-up, the outcome was not different in the two groups of patients.

Although no sufficient evidence is available to support the systematic use of TTA in clinical practice, such modality of therapy may be considered in patients in whom a rapid inactivation of GO is advised.

### Topical treatments

Patients with active GO very often show inflammation of the ocular surface; moreover, palpebral retraction, proptosis and lagophthalmos induce exposure of the cornea, leading to dryness of the ocular surface which, besides causing symptoms such as grittiness, increases the risk of corneal ulceration. Furthermore, lacrimal glands are involved in the autoimmune process with alteration of their secretory function, increasing osmolarity of the tears, which contributes to subjective ocular trouble and, sometimes, to visual disturbances due to the abnormality of ocular film.

Almost all patients with active disease should use artificial tears to protect the ocular surface and to prevent dryness of the cornea. The drops of such preparations should be applied several times per day, whilst a gel or ointment is preferred for use at nighttime in order to ensure a long-lasting effect.
Treatment of mild GO

In most cases, mild forms of GO show a progressive improvement along with the control of thyroid dysfunction, giving up smoking and local therapies; therefore, a “wait and see” strategy is sufficient. Since the orbital inflammatory process is characterized by an excessive production of oxygen free radicals, substances endowed with antioxidant activity have been proposed for treating mild forms of GO. Selenium, the antioxidant activity of which has been demonstrated in experimental studies, was used in a randomized, double blind, placebo-controlled study in patients with mild GO.

Patients who received sodium selenite (200 mg/day, corresponding to 93.6 mg of elemental selenium) showed a significant improvement in QoL and in overall ocular involvement at six months, compared to the placebo group, lasting until 12 months after selenium withdrawal; it is worth noting that the rate of progression of GO to more severe forms was significantly lower in the selenium group than in the placebo group.

Based on these observations, a 6-month course of selenium (commercially available as seleniomethionine) is recommended by EUGOGO guidelines in patients with mild GO, in particular in recent onset cases.

Treatment of moderate-to-severe GO

Systemic glucocorticoids

High doses of glucocorticoids (GCs) are the first-line treatment for moderate-to-severe GO. GCs exert an anti-inflammatory effect through a rapid suppression of the activity of proinflammatory cytokines (IL-β, IL-6, IL-8).

Many studies have demonstrated that i.v. GCs are more effective and better tolerated than oral steroids; GCs are effective on soft-tissue inflammation and on extraocular muscles motility, while the improvement in proptosis is generally poor.

As to the dosage, the most common schedule is a 12-week course of i.v. methylprednisolone (0.5 g as a single dose per week for six consecutive weeks, followed by 0.25 as a single dose for 6 consecutive weeks). Higher doses can be used for treating more severe cases. It is recommended that single i.v. dose of methylprednisolone should not exceed 0.75 g, and the cumulative dose should be less than 8.0 g.

The above protocol is believed to combine the best efficacy with a reasonable risk of side effects, on the basis of a large EUGOGO multicenter randomized trial which compared three different cumulative doses of methylprednisolone (7.47, 4.98 and 2.25 g). The CAS improved to a similar extent with the three doses, but the overall ophthalmic improvement occurred more frequently in the group which received the highest dosage (52% vs. 35% and 28% with the three doses, respectively); however, in the high dose group adverse events were slightly more frequent.

Before starting the therapy, liver function, viral markers of hepatitis and blood glucose must be assessed, and liver ultrasound should be performed. Liver function, glucose and blood pressure are monitored during treatment every 4 weeks.

A careful clinical evaluation of the patients must be carried out to ascertain the presence of cardiovascular, liver diseases or poorly controlled diabetes, which could be a contraindication to steroid therapy; depressive disorders may be worsened by glucocorticoids and caution is warranted in deciding to start therapy in patients with depression.

Vitamin D supplementation is recommended, especially in postmenopausal women and in elderly patients (if osteoporosis is already diagnosed, bisphosphonates may be prescribed), as well as proton pump inhibitors in patients at risk of peptic ulcer.

The most serious adverse event of GCs is dose-dependent liver damage; in the case of a slight increase in liver enzymes, the therapy can be continued, by reducing the doses of methylprednisolone and with a close monitoring of liver enzymes. Otherwise, interruption of the therapy may be required. Few cases of fatal hepatitis are reported.

Local steroids

Although less effective than systemic steroids, the injection of steroids in the orbit has been compared with both placebo or oral corticosteroids. After four inferolateral weekly injections of 20 mg of triamcinolone acetate, at six months the treatment group showed a significant improvement in the area of binocular single vision associated with a reduction in the volume of extraocular muscle vs. the placebo group.

A study aimed at comparing the effect of infraorbital to oral steroids (prednisone 60-100 mg) reported a similar reduction in inflammatory signs, with less side effects in patients receiving infraorbital triamcinolone.

Local orbital injections may be considered in selected patients in whom systemic corticosteroids are contraindicated, providing other systemic second-line therapies have been ruled out.
Second-line therapies

Rituximab

Rituximab (RTX) is a chimeric murine/human monoclonal antibody that binds specifically to CD 20 membrane antigen of mature pre-B and B lymphocytes, inducing a depletion of B-cells and a reduction of cytokine production. It is approved for blood malignancies and for other autoimmune diseases such as rheumatoid arthritis.

After an initial report by Salvi et al. of its potential efficacy in GO unresponsive to GCs, a randomized trial was carried out by the same group, in which RTX, (0.5 to 1 g) as a single administration, was compared to methylprednisolone in moderate-to-severe orbitopathy. RTX was able to inactivate the disease in a significantly larger number of patients than methylprednisolone (100% vs. 69% respectively); furthermore, the reactivation of the disease occurred in 31% of the patients treated with corticosteroids, while it was never seen in those who received RTX.

Conflicting results were reported in another study, in which the outcome in patients treated with RTX (two 1 g i.v. infusions two weeks apart) did not differ from that observed in the placebo group: however, it is worth noting that in this study the duration of the disease was longer than in the study of Salvi et al. This could account for the poor outcome; as a matter of fact, the response to immunomodulatory/anti-inflammatory therapies is as good as the treatment is precocious.

The recommended dose of rituximab is 0.5 g as single i.v. administration. RTX is generally well tolerated; potential side effects occurring during infusion of the drug (allergic reactions, oedema of the glottis) can be prevented by premedication with antihistaminic and hydrocortisone and by starting with a low infusion rate, followed by a gradual increase.

Cyclosporin

Cyclosporine is a well-known immunosuppressant drug, which affects both humoral and cellular immunity. It has been used as a second-line therapy in patients resistant to steroids or in those showing a relapse after a first course of steroids, in association with oral glucocorticoids. In two randomized trials, the patients treated with the combination showed a better outcome than those treated with each single drug, in terms of both clinical improvement and a less frequent relapse after the discontinuation of therapy.

However, cyclosporine may have side effects, such as an increase in blood pressure and also liver and renal toxicity; furthermore, the high dose of oral prednisone prescribed along with cyclosporine, could be a concern in diabetic patients.

Mycophenolate

Mycophenolate mofetil is an immunosuppressant, which is used in association with glucocorticoids to prevent graft rejection. A Chinese randomized trial compared mycophenolate (500 mg twice a day for 24 weeks) to GCs administered i.v. for 2 weeks and, in a following step, orally for a total period of 24 weeks (prednisone 60 mg/day per 8 weeks, then tapered until the end of the treatment period). At 24 weeks, patients who received mycophenolate showed a greater improvement in CAS, diplopia and proptosis than patients treated with GCs, as well as a reduced risk of relapse.

A perspective study compared the effects of i.v. methylprednisolone alone (cumulative dose of 4.5 g over 12 weeks) with methylprednisolone plus mycophenolate (0.720 g/day for 24 weeks) in active and severe orbitopathy: a composite ophthalmic index (CAS, soft tissue involvement and diplopia) and safety were evaluated. The group of patients treated with this association showed a better outcome than the group which received methylprednisolone alone; side effects occurred in 25% of the former group and in 20% of the latter.

Teprotumumab

Teprotumumab is a monoclonal antibody which is directed against the insulin-like growth factor receptor (IGF-1-R), which is involved in the inflammatory cascade triggered by the binding of TRAb to TSH receptors in orbital tissue. A first double-blind trial showed that at week 24 teprotumumab was able to induce a reduction of 2 points or more in CAS and, what is more, a significant reduction in exophthalmos (2 mm or more) in 69% of patients receiving active treatment versus 20% of those who received placebo (Figure 3). The effect was evident from week 6 after starting the therapy. Teprotumumab was well tolerated; the most common side effect was an increase in blood glucose in diabetic patients, requiring an adjustment in the therapy for diabetes. In a subsequent trial carried out in patients with active thyroid eye disease, teprotumumab resulted in better outcomes with respect to proptosis, clinical activity score, diplopia and quality of life than placebo. At present, the high cost of teprotumumab is the main limitation for use in clinical practice.
Tocilizumab

Tocilizumab is a monoclonal antibody which blocks the receptor of IL-6, a cytokine involved in orbital inflammation.

In a randomized study, tocilizumab (8 mg/kg every 4 weeks for at least 4 cycles) induced a significant reduction in CAS and proptosis and improvement in ocular motility or resolution of diplopia when compared to placebo. The drug was well tolerated in all subjects, but clinical monitoring is recommended due to the risk of infections, which were observed in patients treated for rheumatoid arthritis. Further trials are warranted to confirm the beneficial effects of this monoclonal antibody.

Radiotherapy

Orbital radiotherapy (RT) has been used alone or in combination with oral or intravenous GCs in the treatment of moderate-to-severe GO.

The use of RT in GO is supported by literature data, showing that low doses of RT exert an immunosuppressive effect mainly by reducing the adhesion of leukocytes to the endothelium, by promoting the apoptosis of immune cells involved in the inflammatory process, by increasing the expression of anti-inflammatory cytokines and by decreasing the secretion of pro-inflammatory cytokines, including TNF-α, IL-1β as well as nitric oxide and reactive oxygen species.

There are many reports demonstrating beneficial effects of RT in GO in particular on the motility of extraocular muscles, while other studies showed no significant improvement.

RT was reported to be superior to sham irradiation in mild, as well as in moderate to severe orbitopathy, but Gorman et al. were unable to demonstrate any beneficial therapeutic effect; however, it is worth noting that most patients in the latter study had a longstanding orbitopathy, which is unlikely to respond not only to steroids but also to RT.

A metaanalysis of randomized trials showed that RT improved ocular symptoms in moderate to severe GO. Orbital movements, orbital pain, and tearing show the most robust response ranging from 25.5% to 65.8%. In contrast, vision loss and proptosis are the most refractory symptoms to RT, with improvement rates ranging from 37.1% to 41.5%.

In moderate to severe orbitopathy, combined GCs and radiation therapy may be superior to monotherapy, due to a synergistic effect. Indeed, the combination of oral GCs and orbital RT was more effective than either treatment alone on both soft tissue changes and ocular motility in patients with GO of recent onset. On the contrary, a lack of additional efficacy of RT to oral steroids was reported in a recent randomized controlled trial.

The association of i.v. GCs and RT was shown to be beneficial on exophthalmos, eyelid aperture, CAS, diplopia and visual acuity, but this was a retrospective study, lacking of a control group. Oeverhaus et al. retrospectively analyzed 148 patients with active, moderate-to-severe GO treated with i.v. GCs versus i.v. GCs in addition to RT. They found that this combined approach was associated with a greater reduction in severity. Similar results were reported in other studies, but most of which have the limitation of being retrospective. Unfortunately, no prospective, randomized trials comparing the effects of RT plus i.v. GCs vs. the effects of the single therapies alone are available.

RT is generally carried out after GCs failure or in patients with predominantly ocular motility impairment/diplopia with scarce inflammatory symptoms.

A still unresolved question is what the best timing for delivering RT is; in most cases it is performed after the end of a complete course of GCs, when no improvement has been recorded.

We retrospectively analyzed a series of 73 patients with moderate-to-severe GO treated with the combination of i.v. GCs and RT, showing a more rapid improvement of inflammatory symptoms in those who received RT halfway through a course of GCs, when compared to the patients who were treated with RT after the completion of the course of steroids. This observation might prompt us to start RT early during steroid therapy, when clinical symptoms do not improve or deteriorate after the first MPN administrations. Prospective randomized studies might throw some light upon this issue.

RT is performed using three-dimensional conformal planning to cover both retrobulbar tissues and extraocular muscles with two opposed fields. According to the available literature, the most commonly used and well-tolerated radiation dose is 20 Gy (ten doses of 2 Gy per each eye), although a good clinical response to total dose of 10 Gy in different fractions has also been reported. An alternative regimen of 1 Gy per week over a 20-week period was shown to be equally effective and better tolerated.

Orbital RT may cause transient exacerbation of the ocular symptoms, which can be controlled by the parallel use of low doses of GCs. The retina, the lens and the lacrimal gland are the eye structures mostly exposed to the side effects of RT. Persistent xerophthalmia is the most common
The recent introduction of mini-invasive techniques has led to an extension of the indications to surgery for Graves’ orbitopathy management for both rehabilitative and cosmetic purposes in cases of disfiguring proptosis. New highly conformed radiation techniques, such as intensity modulated RT (IMRT) and volumetric modulated arc therapy (VMAT), enable more precise and accurate planning of the target volume, reducing the dose to the surrounding healthy tissues, therefore decreasing the risk of the aforementioned side effects.

Wang et al. compared and analyzed the dosimetric data of a dual-partial-arc VMAT and a 7-fixed-field IMRT plans for each of 19 patients enrolled in this study. Homogeneity index (HI) was superior in IMRT plans compared with VMAT (P=0.0014) but there was no significant statistical difference in conformity index (CI) between them (P=0.0673). IMRT plans were advantageous in the protection of the organ at risk, especially for lenses, optic nerves and eyeballs.85

Treatment of sight-threatening GO

Sight-threatening orbitopathy, due to DON and/or to severe corneal exposure or breakdown, is an emergency requiring immediate treatment.86

The first line treatment of DON is i.v. GCs at very high doses (500-1000 mg for 3 consecutive days or on alternate days), which can be repeated after a week.87 Visual acuity is restored at normal or near-normal levels in about 40% of patients, and the GCs can be continued with the protocol recommended for moderate-to-severe cases.12 Should the response be poor or absent, surgical decompression must be performed as soon as possible (see below for surgical approach), to reduce infraorbital pressure and the crowding at the orbital apex.86 Moreover, surgery is the treatment of choice for stretching optic neuropathy, in which the response to steroids is generally poor. Recent onset choroidal folds and globe subluxation also require an urgent surgical approach.12

Surgery

Orbital decompression

Up until recently, orbital decompression was recommended in a few specific clinical situations, such as the presence or an elevated risk of optic neuropathy, severe exposure keratopathy or globe subluxation (Figure 7).

![Figure 7.—Dysthyroid optic neuropathy relapsing after orbital decompression: compression of the optic nerve due to very remarkable enlargement of extrathyroidal muscles.](image)

The recent introduction of mini-invasive techniques has led to an extension of the indications to surgery for Graves’ orbitopathy management for both rehabilitative and cosmetic purposes in cases of disfiguring proptosis.

The currently available surgical techniques include fat removal through a tranpalpebral approach, according to Olivari’s technique88 or removal of lateral wall and/or of the orbital floor,89 and/or of the medial wall by endoscopic trans-nasal approach90 in order to decrease infraorbital pressure.

Olivari reported that this approach may lead to a 5 to 7 mm reduction in exophthalmos, in patients with abundant infraorbital fat.88

Removal of the lateral wall allows for a reduction of proptosis from 2 mm to 5 mm, depending on the dimensions of the removed greater sphenoidal wing. Removal of the floor reduces proptosis from 1 mm to 3 mm, due to the necessity of sparing the bone canal of the second branch of the trigeminus (V2).91

Although the presence of the nerve limits the gain obtained by decompression, the maintenance of the bone ensures a support to the inferior rectus muscle, preventing its down displacement. The endoscopic removal of the medial wall frequently associated with osteotomy of the medial half of the floor (infero-medial technique) may induce a 2 to 4 mm reduction of the exophthalmos but implicates the medial displacement of the medial rectus muscle.92

The variability of the reduction of exophthalmos is not only dependent on the amount of the removed bone but also on the extent of the fibrosis involving orbital soft tissues.93
Excluding intra-operative or postoperative hemorrhage, the complications of orbital decompression are closely related to the surgical approach. The more frequent are hypesthesia/dysesthesia of the areas innervated by the second branch (V2) (about 13% of the cases), or of the first branch (V1) of the trigeminus nerve (about 8%). Although uncommon, the most serious complication is rhinoliquorhea due to a lesion of the lamina cribrosa during the transnasal approach, since it entails the risk of meningitis; a permanent visual impairment or corneal lesions (generally transient) are also rare. Sinusitis, palpebral lesions, hypoplasia, are seldom reported.

However, the most common complication is the new onset or worsening of a preexisting diplopia. As a matter of fact, when we have to choose the decompressive technique, we have to take into account the severity of orbitopathy and the presence/absence of diplopia. Some studies demonstrated that the preexisting diplopia in secondary gaze is the most important risk factor for the onset of post-surgical diplopia in primary gaze.94

Also, the surgical technique has relevance, since the removal of an osseous wall causes the displacement of the adjacent muscle: indeed, the presence of restrictive phenomena involving the muscle (the inferior and medial rectus are the most frequently affected by hypertrophy and fibrosis) increases the risk of diplopia. While the displacement of the inferior rectus is avoided by the spared V2 bony canal in the approach to the floor, the displacement of the medial rectus is almost unavoidable when the medial wall is removed. The heterogeneity of the patients included in the study groups and of the difference of surgical techniques used account for the high variability of the reported incidence of post-surgical diplopia.94-96

As a general rule, in patients with compressive optic neuropathy or with severe exposure keratopathy it is mandatory to widen the orbital apex as much as possible, which is obtained by approaching three walls (lateral, inferior and media) in combination with fat removal (if not fibrotic). In such cases, due to the severity of the clinical picture, the risk of onset of diplopia cannot be the primary concern. In patients with a proptosis of less than 25-27 mm, a preoperative assessment of eye motility is mandatory. If diplopia is absent, a three-wall approach may be considered, while if diplopia in secondary gaze is present, the surgical approach should be discussed with the patient to evaluate the risks and benefits of the various approaches.97

In patients with mild proptosis, the removal of one or two walls may be sufficient, and several techniques may be considered; also, the Olivari technique may be effective, in particular in presence of abundant non-fibrotic fat. In patients with minor aesthetic problems the approach may be transconjunctival, limited to the floor.

Orbital decompression may be favorably integrated by eyelid surgery for the correction of retractions which may limit palpebral closure, leading to corneal exposure.

Squint surgery
Squint surgery is performed when the disease is inactive and strabismus has been stable for at least 6 months, due to the stabilized fibrosis of extraocular muscles.

Squint surgery has the aim of restoring single binocular vision in primary gaze. If a decompressive surgical procedure is required, strabismus surgery is generally performed subsequently, since decompression may induce or worsen a pre-existing diplopia.

Strabismus surgery involves recession of the restricted muscles; inferior, medial, and superior rectus are, in order of frequency, the muscles which more often are involved in surgical approach, which may be carried out under topical or general anesthesia.98, 99

Strabismus surgery is generally devoid of significant complications, but the results are not always predictable, and more than one intervention may be seldom necessary to achieve single vision; in this setting, the experience of the surgeon is crucial.

Eyelid surgery
Eyelid surgery is the final step pf the rehabilitative surgery for GO, and has the goal of correcting palpebral retractions, which can be responsible for symptoms as dryness, photophobia, tearing, grittiness and may also induce exposure keratopathy. Moreover, some patients may complain of aesthetic trouble.

Palpebral retraction is due to the combination of sympathetic overactivity, inflammation, thickness of eyelid secondary to fibrosis and restriction of vertical rectus muscles. Surgical approach may be transpalpebral or transconjunctival and implies recession or section of Muller muscle. For the correction of upper lid, no spacer is required, whilst it may be necessary for lower lid. Complications, though rare, are mainly hypo- or hypercorrection and abnormality of palpebral margins.100

Conclusions
Graves’ orbitopathy is the principal extrathyroidal manifestation of Graves’ disease, which may arise with multi-
faceted clinical manifestations, varying from mild forms, requiring a wait and see strategy only, to very severe, sight-threatening conditions, for which an immediate and aggressive therapeutic approach is warranted.

A prompt recognition of GO is the clue for a favorable outcome, especially in moderate to severe forms: as a matter of fact, a precocious anti-inflammatory/immuno-modulating treatment is advised to control the disease in its initial active phase, whilst in late phases rehabilitative surgery may be necessary to correct exophthalmos, strabismus and eyelid defects. Moreover, surgical decompression must be carried out for dysthyroid optical neuropathy unresponsive to high doses of systemic corticosteroids.

Patients with moderate to severe or very severe GO should be referred to Centers where endocrinologists, ophthalmologists, radiologists, radiotherapeutics and orbital surgeons work together for a comprehensive management of this complex clinical condition.

References


GRAVES’ ORBITOPATHY


