Graves' Orbitopathy: Imperfect Treatments for a Rare Disease

Luigi Bartalena

Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy

Key Words

Graves' orbitopathy · Graves' disease · Glucocorticoids · Orbital radiotherapy · Rituximab · Orbital decompression · Smoking · Radioiodine

Abstract

Graves' orbitopathy (GO) is the most frequent and invalidating extrathyroidal expression of Graves' disease. Its incidence and prevalence are, however, low. About three quarters of Graves' patients have no GO at diagnosis, and moderate-to-severe and severe forms represent no more than 5–6% of cases. Progression to severe forms occurs rarely, but it may be caused by risk factors, the most important being smoking and poor control of thyroid dysfunction. Lot of progress has been recently achieved in the understanding of GO pathogenesis, while the disease remains a therapeutic challenge and dilemma. Common treatments for moderate-to-severe and active forms of GO (glucocorticoids and orbital radiotherapy) frequently provide incomplete responses and may be followed by relapse or progression of GO. After the disease has been inactivated by medical treatment, many patients need rehabilitative surgery for residual manifestations (orbital decompression for exophthalmos, squint surgery for extraocular muscle dysfunction, eyelid surgery for eyelid malposition). Novel pharmacological treatments are on the horizon and might target pathogenetic mechanisms of the disease better than glucocorticoids. Clinical evidence concerning their efficacy and safety is presently lacking.

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Introduction

Management of Graves' orbitopathy (GO), the most important extrathyroidal expression of Graves' disease, remains a major challenge and dilemma [1]. Available therapies are largely imperfect, and a large proportion of patients are in the end unhappy with the treatment outcome [2]. After medical treatment, many patients require some kind of rehabilitative surgery (orbital decompression, squint surgery, eyelid surgery) to correct residual manifestations. The reasons for this unfavorable outcome of medical treatment include: (i) a still incomplete understanding of the pathogenesis of GO, which prevents the use of targeted therapies; (ii) the low incidence and prevalence of GO, which makes it difficult to validate new and old treatments in large and well-designed randomized clinical trials (RCTs); (iii) the persisting difficulties (outside specialized centers) in assessing the activity and severity of GO, which may either delay a prompt management of active GO or lead to the use of immunosuppressive treatments (i.e. glucocorticoids) in inactive GO when their efficacy is inevitably low or absent (table 1).

The aim of this paper is to analyze these different aspects, to provide an overview of the currently available treatments, and to briefly introduce novel treatments on the horizon.

ETA Aldo Pinchera Prize Lecture presented at the 37th Annual Meeting of the European Thyroid Association in Leiden on September 7–11, 2013.

Table 1. Causes of the incomplete effectiveness of available therapies for moderate-to-severe and active GO

Fact	Consequence
Incomplete understanding of the pathogenesis of GO	Therapies do not specifically target the pathogenetic mechanisms of GO
Low incidence and prevalence of GO	Old and new therapies are difficult to validate in randomized clinical trials with large series of patients
Persisting difficulties in diagnosis and early assessment of GO activity and severity in clinical practice	Referral to specialized centers/thyroid-eye clinics and prompt institution of treatment are frequently delayed

Pathogenesis

Recent years have witnessed interesting progress in unraveling the pathogenetic mechanisms leading to development of GO [3, 4]. Autoimmune reactions ongoing in the orbit of GO patients are probably (although not certainly) triggered by recognition of the TSH receptor (TSHR), ultimately responsible for hyperthyroidism due to Graves' disease, presented to autoreactive T-lymphocytes infiltrating the orbit by antigen-presenting cells, including B lymphocytes and macrophages [5]. TSHR is expressed on orbital fibroblasts and adipocytes after differentiation from preadipocytes [5]. Other cell surface antigens, i.e. the insulin-like growth factor-1 (IGF-1) receptor (IGF-1R), may also be involved in the initiation or maintenance of orbital autoimmunity [6]. IGF-1R is expressed on orbital fibroblasts, T lymphocytes, B lymphocytes, and fibrocytes [6]. Interaction and crosstalk of TSHR and IGF-1R (defined as 'partners in crime' [6]) with each other and with signaling molecules are likely required for the full development of orbital autoimmunity [7]. The colocalization of TSHR and IGF1R may support the view that the two receptors form physical and functional complexes [8]. The abnormal expression of IGF-1R is not specific to GO, since it is observed in other autoimmune disorders, e.g. rheumatoid arthritis [6]. Accordingly, autoimmunity to the TSHR might trigger GO, but autoimmunity to IGF-1R might play a relevant role in maintaining ongoing reactions [9].

After recognition of the autoantigen(s), a number of reactions occur leading to proliferation of orbital fibroblasts, differentiation of preadipocytes into adipocytes, production of autoantibodies, secretion of cytokines, infiltration of extraocular muscles, increased synthesis and

secretion of glycosaminoglycans [3, 4]. The expansion of the fibroadipose tissue and the infiltration (with an increased volume) of extraocular muscles in a rigid anatomic site like the orbit make clinical manifestations of GO (exophthalmos, extraocular muscle dysfunction, congestion of periorbital soft tissues, possible compression of the optic nerve) easily understandable [10].

In summary, although considerable progress has been made in unveiling the pathogenic basis of the orbital disease, much remains to be achieved. In addition, such a complex array of reactions makes it difficult to envision which step in the cascade of events should be addressed by novel therapies to interrupt the process or make it remit. B lymphocytes, T lymphocytes, and cytokines might be possible targets but, for the time being, it seems premature to anticipate the development of specific therapeutic agents in the near future (see Perspectives).

Incidence, Prevalence, and Natural Course

Graves' disease is the most common form of hyperthyroidism in iodine-replete areas [11]. In a prospective descriptive study from Sweden, the total incidence of Graves' disease was 21.4 cases/100,000/year, which is much higher than that of toxic multinodular goiter (4.3 cases/100,000/year) or toxic adenoma (1.8 cases/100,000/year) [12]. In a study from Olmsted County, Minnesota, USA, the age-adjusted incidence of GO of any degree was 16 cases/100,000/year in women and 2.9 cases/100,000/year in men [13]. The incidence of moderate-to-severe GO is much lower: in a Danish study the incidence rate was 16.1 cases/million/year (26.7 in women and 5.4 in men) [14].

An admittedly approximate calculation of GO prevalence in the general population was between 0.1 and 0.3% [15]. Restricting the calculation to Graves' patients, in a recent large study of patients with newly diagnosed and recent onset Graves' disease seen at a single center, the majority (255/346, 73.7%) had no ocular involvement, 70 (20.2%) had mild and inactive GO, 5 (5.8%) had moderate-to-severe and active GO, and 1 (0.3%) had sight-threatening GO (dysthyroid optic neuropathy) [16]. Several years ago, a questionnaire-based survey among European specialists suggested a declining prevalence of GO, possibly related to a decrease in smoking habits [17]. As recently reviewed [18], it is hard to ascertain whether the prevalence of GO has truly decreased with time, mainly because of poor definition and grading of GO in old studies. The recent study by Tanda et al. [16], the first

Fig. 1. Modifiable and nonmodifiable risk factors contributing to the occurrence/progression of GO. Ab = Autoantibody.

to use standardized evaluation criteria developed by the European Group on Graves' Orbitopathy (EUGOGO) [19], clearly indicates that most patients have no ocular involvement at diagnosis.

Because the onset of GO may not infrequently follow the onset of hyperthyroidism, it is of interest to ascertain what the natural course of GO is. Information on this issue is limited. In a prospective study of 59 patients seen at a tertiary referral center for GO, 38 (64%) improved, 13 (22%) had no significant variations, and 8 (14%) worsened [20]. In a Swiss study of 53 patients with untreated GO, 25 (47%) improved with time, 26 (49%) had stable involvement, and 2 (4%) progressed to more severe forms [21]. In our recent study [16], progression to moderate-to-severe GO occurred in 6 of 237 patients (2.5%) during an 18-month follow-up.

In summary, it seems that in the general population the incidence of GO is low and the incidence of moderate-to-severe forms is extremely low, although it is difficult to judge whether it has been decreasing over time. Among patients with Graves' disease, the prevalence of GO of any degree is about 25%, but moderate-to-severe forms are rare in nontertiary referral centers. Progression to severe forms occurs rarely over time. These epidemiologic data have an inevitable impact on the management of GO because it is extremely difficult to enroll a sufficient number of patients with moderate-to-severe GO in trials evaluating the therapeutic effects of novel or old drugs.

Prevention

Several risk factors may influence the course of GO (fig. 1). Some of them, such as genetics, age, and gender, cannot be modified. Others are modifiable, implying that

the course of GO can to some extent be affected by preventive measures [22]. Modifiable risk factors for the occurrence/progression of GO include smoking, thyroid dysfunction, radioiodine treatment for hyperthyroidism, and high TSHR antibody levels [22].

Smoking increases the risk for Graves' patients to develop GO and severe forms of the disease [23, 24]. The prevalence of smokers is higher among Graves' patients with GO than among those without GO [25]. Smokers have a lower and delayed response to immunosuppressive therapies for GO [26, 27]. Smoking is associated with an increased risk of GO occurrence/progression after radioiodine treatment for GO [28, 29]. In a retrospective study, smoking cessation was associated with a decreased risk of developing exophthalmos and diplopia [30]. Passive smoking might also have detrimental effects on GO, at least in children [31]. The effect of smoking seems to be dose dependent [30]. The mechanisms underpinning these undue effects of smoking are not fully understood. They might include smoking-induced hypoxia and/or increased production of oxygen-free radicals in the orbital space [22].

Both hyperthyroidism and hypothyroidism are risk factors for GO, possibly in relation with TSHR activation by TSHR antibody and TSH, respectively [22]. Restoration of euthyroidism with thionamides causes improvement of ocular conditions [32]. GO may occur during a period of uncontrolled hypothyroidism [33, 34].

While thyroidectomy and antithyroid drugs are believed to not be GO-modifying treatments [35, 36], radioiodine treatment can cause occurrence/progression of GO in about 15–20% of cases [28, 29, 37, 38], although this phenomenon is permanent only in about 5% of cases [28]. This detrimental effect is in most cases prevented by concomitant short-term treatment with low doses of oral

glucocorticoids (steroid prophylaxis) [28, 39, 40]. In view of the above considerations and in the absence of well-designed (and extremely difficult to perform) RCTs, selection of the optimal thyroid treatment (antithyroid drugs, radioiodine, thyroidectomy, thyroidectomy followed by radioiodine treatment) in patients with GO is still a matter of argument and more an expert opinion than an evidence-based choice [36]. It seems unlikely that the final word on this issue will be said in the years to come.

High levels of TSHR antibodies have been associated with an increased odds ratio of GO [41]. A correlation between GO activity and TSHR antibody levels was reported in a Dutch study [42], while a German study concluded that TSHR antibody levels are an independent risk factor for GO helpful to identify patients who are prone to develop severe GO [43]. There is no way to directly decrease TSHR antibody levels, but antithyroid drug treatment and thyroidectomy are associated with a decline in TSHR antibody concentration, whereas radioiodine treatment is followed by an increase in TSHR concentration persisting for a long period of time [44].

A recent RCT carried out by EUGOGO showed that selenium should be included among preventive tools. In fact, a 6-month course of selenium was associated not only with significant improvement of preexisting mild GO compared to placebo but also with a significant reduction in the risk of progression of GO even after the treatment was stopped [45].

In summary, the course of GO can be partially affected by preventive measures [46, 47]. The latter, as summarized in the EUGOGO consensus statement [48], include: (i) smoking withdrawal; (ii) prompt correction of thyroid dysfunction and stable maintenance of euthyroidism; (iii) steroid prophylaxis after radioiodine treatment, to be used in most patients, particularly if risk factors for radioiodine-associated progression of GO are present, and (iv) selenium treatment for 6 months in patients with mild GO. The optimal treatment for hyperthyroidism in patients with GO remains a matter of controversy.

Assessment

GO undergoes an initial phase of florid inflammation (active disease) followed by a phase of stabilization (plateau phase) and a final phase of remission (burned-out or inactive disease) [49]. Concomitantly with these three phases, clinical manifestations of the disease appear and

progress, stabilize, and then remit. However, complete recovery of normal ocular appearance and/or function rarely occurs spontaneously, except in mild forms of GO. Two aspects of the disease are, therefore, essential to define: activity and severity. The former is important to decide whether medical or surgical treatment is appropriate in a given patient. Medical treatment, usually with high-dose glucocorticoids, is effective only in active GO, while inactive GO should rather be treated with surgical procedures, as required [48]. Severity is also important to decide whether it is worth running the risks of high-dose glucocorticoids or it is preferable to limit the therapeutic intervention to local measures and preventive measures (see above).

Definition of the activity and severity of GO is one of the challenges in GO. After the initial NOSPECS classification used for years, and which still represents a useful mnemonic tool [50], both EUGOGO [19, 48] and North Americans [51, 52] have proposed simple clinical tools for a standardized clinical assessment of patients with GO. It is beyond the scope of this paper to go into the details of GO assessment. Suffice it to say that it is essential that general practitioners take advantage of these documents to distinguish patients who need an urgent referral to specialized centers or thyroid/eye clinics from those who require a routine referral. A simple, though imperfect, tool to assess the activity of GO is the clinical activity score (CAS), based on 7 items basically reflecting inflammation (swelling of the eyelids, redness of the eyelids, redness of the conjunctiva, chemosis, inflammation of the caruncle and/or plica, spontaneous retrobulbar pain, pain on attempted upward or downward gaze) [53]. Giving 1 point to each item, if present, one gets a numerical score ranging from 0 (no activity) to 7 (maximal activity). A CAS $\geq 3/7$ indicates active GO [48]. A high CAS is usually predictive of a good response to glucocorticoid treatment [53]. GO may be mild, moderate to severe, or sight threatening, based on the assessment of various parameters, including soft tissue changes, exophthalmos, extraocular muscle dysfunction and diplopia, corneal involvement, and optic nerve involvement (from subclinical to overt optic neuropathy) [48]. Patients should urgently be referred to specialized centers or thyroid-eye clinics when there is an unexplained decrease in visual acuity, a change in the intensity or quality of color vision, a history of globe subluxation, a corneal opacity, or papilledema [51]. Apart from urgent conditions, it is advised that patients with clinically relevant GO also be promptly referred, because the success of treatment is greater if GO is of recent onset [49]. The

Table 2. Current management of GO

	Management
General measures for all patients with GO	Local treatments (artificial tears, ointments, dark lenses) Smoking withdrawal Stable maintenance of euthyroidism
Mild and active GO	Selenium supplementation for 6 months High-dose glucocorticoids if the quality of life is severely affected
Mild and inactive GO	Rehabilitative surgery as needed or required by the patients for cosmetic/functional reasons
Moderate-to-severe and active GO	First-line: high-dose glucocorticoids, preferably intravenously Second line (particularly for relapsing GO): a second course of high-dose glucocorticoids, possibly associated with orbital radiotherapy; oral glucocorticoids combined with cyclosporine
Moderate-to-severe and inactive GO	Rehabilitative surgery (orbital decompression, squint surgery, eyelid surgery) as needed
Sight-threatening GO (dysthyroid optic neuropathy)	Very high doses of intravenous glucocorticoids Urgent orbital decompression if the response to medical treatment is poor/absent within 2 weeks

reader is referred to the EUGOGO website (www.eugogo.eu) to download relevant documents to score the activity and severity of GO, as well as its impact on the quality of life.

Management

The management of GO depends on its activity and severity [48].

Mild GO

Patients with mild GO usually require anything but local measures (tear drops, ointments) and advice concerning prevention, e.g. refrain from smoking [48]. Careful monitoring of thyroid status is essential to maintain euthyroidism stably [48]. Occasional patients with mild and active GO may require intervention with high-dose glucocorticoids if their quality of life is severely impaired by the disease [48] (table 2).

Established Treatments for Moderate-to-Severe GO and Sight-Threatening GO

Patients with moderate-to-severe and active GO should be treated with high-dose glucocorticoids as first-line therapy (table 2). They exert both anti-inflammatory and immunosuppressive actions [54]. The two main routes for glucocorticoid therapy in use are oral and intravenous. Local (peribulbar, retrobulbar, subconjunctival) injections may be considered under circumstances of absolute contraindications to systemic glucocorticoids [54]. Oral glucocorticoids are given for 5–6 months using a starting dose of 80–100 mg prednisone (or equivalent doses of other steroids) and gradually tapering down the dose until withdrawal [55]. Two RCTs have demonstrated that oral glucocorticoids are less effective than intravenous glucocorticoids [56, 57]. This was confirmed by a meta-analysis [58] and a systematic review [59] of published studies. For these reasons, the intravenous route should be preferred [48] (table 2). A recent questionnaire-based survey among members of the European Thyroid Association showed wide variations in the modality of intravenous glucocorticoid treatment regarding the cumulative dose, the starting dose, the number of infusions, the interpulse period, and the duration of treatment [60]. Intravenous glucocorticoids usually have fewer adverse effects than do oral glucocorticoids [56–59], but severe side effects have been described, including hepatotoxicity and cardiovascular and cerebrovascular events [60, 61]. The risk seems higher using a single dose >0.5 g [62] and a cumulative dose >8.5 g methylprednisolone [63]. Recently EUGOGO published the results of a large, multicenter RCT evaluating the efficacy and safety of 3 different cumulative doses of intravenous methylprednisolone (2.25 g, low dose; 4.98 g, middle dose, and 7.47 g, high dose) given in 12 weekly infusions over a 3-month period [64]. Eight European groups were involved, and it took 5 years to enroll 159 patients into the study. This observation underscores how difficult it is to perform RCTs with adequate statistical power in the field of GO. The EUGOGO study confirmed that intravenous glucocorticoids are an effective treatment. The CAS decreased by at least 2 points in 81% of the high-dose group and in 83% of the middle-dose group, but significantly less (58%) in the low-dose group [64] (table 3). At the end of the treatment, GO was inactive in 60% of high-dose patients, 65% of middle-dose patients, and 45% of low-dose patients [64] (table 3). Quality of life improved in all three groups, but to a greater extent in the high-dose group [64] (table 3). The use of high doses of methylprednisolone was significantly more beneficial for ocular mo-

Table 3. Main results of a randomized clinical trial evaluating 3 different cumulative doses of intravenous methylprednisolone for moderate-to-severe and active GO

Parameter	Low dose (2.25 g MP) (n = 53)	Middle dose (4.98 g MP) (n = 54)	High dose (7.47 g MP) (n = 52)
Overall responders, % of patients	28	35	52
Improvement in the quality of life, % of patients	51	48	67
Decrease in the CAS >2 points, n	58	83	81
Absolute decrease in the CAS (points)	-1.8	-2.3	-2.7
Improvement in eye motility, % of patients	21	26	46
Inactive GO at the end of treatment, % of patients	45	60	65
Relapse of GO after treatment, % of improved patients	21	40	33
Occurrence of DON during or after treatment, n of patients	3	4	3
Major adverse events, n of patients	2	3	5

Derived from Bartalena et al. [64]. DON = Dysthyroid optic neuropathy; MP = methylprednisolone.

Fig. 2. Percent of favorable responses to intravenous glucocorticoids in 3 RCTs. In the study by Marcocci et al. [56] patients were concomitantly treated with orbital radiotherapy; in the study by Kahaly et al. [57] patients were treated with intravenous glucocorticoids as monotherapy. In the study by Bartalena et al. [64] patients were randomized to 3 different cumulative doses, shown here are responses in the group receiving the highest cumulative dose (7.47 g). Patients with dysthyroid optic neuropathy were excluded in the study by Bartalena et al. [64], while they were included in the other two studies.

tility [64]. However, high doses were also associated with a higher adverse event rate [64]. It should be noted that the proportion of responders, as assessed by the overall ophthalmic improvement, was lower than in the two previous RCTs [56, 57] (fig. 2), possibly due to the inclusion of patients with GO of longer duration and lower severity [64]. In addition, in all three groups some patients had relapse or progression of GO, including the occurrence of dysthyroid optic neuropathy [64] (table 3). Thus, some

observations can be made based on this study: (i) intravenous glucocorticoids are an effective treatment, reducing inflammation and improving ocular motility and quality of life, but they are also an imperfect treatment because a relevant proportion of patients do not respond satisfactorily; (ii) selection of patients, based on a well-standardized and rigorous assessment of ocular conditions, is essential to improve the success rate; (iii) strategies to decrease the risk of recurrence or progression of GO at the end of the treatment must be explored; these may include the use of low-dose glucocorticoids in the interpulse period and for a few weeks after intravenous treatment completion, early association of glucocorticoids with other established treatments (e.g. orbital radiotherapy or cyclosporine) or, in the future, novel treatments currently under investigation (rituximab and mycophenolate), and (iv) high doses of methylprednisolone are more effective but also more toxic than lower doses; thus, a cumulative dose of around 5 g should probably be used under most circumstances, reserving higher doses for particularly severe GO.

Patients with sight-threatening GO due to dysthyroid optic neuropathy should be treated with high doses of intravenous glucocorticoids as first-line treatment [48]. Various treatment schedules have been used, and there is no proof of the superiority of a given schedule. A commonly used regimen consists of the administration of 1 g of intravenous methylprednisolone for 3 consecutive days, to be repeated on the subsequent week [48]. If, however, there is an absent or poor response, the patient should be submitted within 2 weeks to orbital decompression [48].

Orbital radiotherapy is another established treatment for GO [65]. It is used for its nonspecific anti-inflammatory effects and because of the radiosensitivity of lymphocytes infiltrating the orbital space [66]. Two RCTs showed its efficacy compared to sham irradiation [67, 68], while a third RCT (with limitations in the study design) failed to demonstrate any benefit of orbital radiotherapy versus sham irradiation [69]. Orbital radiotherapy in the two studies with positive results was effective particularly on ocular motility and soft tissue changes, with little effect on exophthalmos [67, 68]. In addition, orbital radiotherapy did not prevent the possible progression of mild GO to more severe forms of orbital disease [68]. In two RCTs, combination of orbital radiotherapy and oral glucocorticoids was more effective than either treatment alone [70, 71]. Whether combination of intravenous glucocorticoids and orbital radiotherapy is associated with a higher response rate compared to intravenous glucocorticoids alone is uncertain [64] and might be worth exploring. Doubts regarding the true efficacy of orbital radiotherapy were raised by a report of the American Academy of Ophthalmology [72] and another recent review [73]. Orbital radiotherapy is certainly not as effective as glucocorticoids. However, in view of its safety and demonstrated effectiveness in some manifestations of the orbitopathy (particularly ocular motility), in my opinion it should still be, for the time being, considered a useful (second-line) treatment to be administered preferably in combination with glucocorticoids. Orbital radiotherapy is contraindicated in patients with concomitant diabetic retinopathy or severe hypertension and should be avoided in patients younger than 35 years of age [48].

A major question is what to do, in terms of nonsurgical treatments, if moderate-to-severe and active GO responds poorly to or relapses after a first course of glucocorticoids (preferably given intravenously) [74]. Evidence is limited, as usual in the field of GO. One possible option, commonly used by me, is a second course of high-dose glucocorticoids associated with orbital radiotherapy; this often leads to inactivation of GO [74]. A second possibility, supported by a Dutch RCT [75], is use of a combination of oral glucocorticoids and cyclosporine. Novel agents, such as rituximab or mycophenolate or other biologicals, might represent a new way of approaching moderate-to-severe GO, even as first-line treatment. However, as mentioned in the following paragraph, for the time being, evidence is missing regarding their effectiveness and safety [74]. Other drugs, such as the somatostatin analogs octreotide and lanreotide, initially surrounded by great hopes based on

the results of small and uncontrolled studies, have been demonstrated to have marginal beneficial effects (if any) in well-designed RCTs [76–79].

Once GO has been inactivated by medical treatment, many patients require rehabilitative surgery for residual ocular manifestations, particularly if these have a negative impact on the quality of life. Surgical procedures may be multiple in some patients, including orbital decompression for exophthalmos (usually poorly responsive to medical treatment), squint surgery for extraocular muscle dysfunction and related diplopia, and eyelid surgery for persisting palpebral malposition. Surgery should be avoided when GO is active (with the exception of urgent orbital decompression in unresponsive dysthyroid optic neuropathy or corneal breakdown); if multiple surgical procedures are needed, orbital decompression should come first, followed by squint surgery and, lastly, by eyelid surgery [80]. A period of 6 months should elapse between one procedure and the following one [80].

Perspectives

From the above discussion it is evident that the current treatments for GO are imperfect and are associated with a high rate of incomplete response. This is mostly related to the fact that the available treatments do not really target pathogenetic mechanisms of GO. Ideally the same drug should intervene in both hyperthyroidism and GO in view of the close link between the two conditions [81]. Given of the important role of TSHR autoantibodies in causing hyperthyroidism due to Graves' disease and, probably, contributing to the pathogenesis of GO, future treatment might be represented by TSHR-blocking antibodies or by small-ligand molecules that might act as allosteric modulators or inhibitors of TSHR signaling [82–84]. In view of the role that IGF-1R also seems to play in the pathogenesis of GO, drugs targeting the IGF-1R might be envisioned as an alternative or complementary targeted therapy for GO. Platelet-derived growth factors (PDGFs) show an increased expression in GO orbital tissues, stimulate proliferation and glycosaminoglycan and cytokine production by orbital fibroblasts [85], and enhance orbital fibroblast response to TSHR autoantibodies [86]. In principle, tyrosine kinase inhibitors, such as imatinib mesylate or AMN107, shown to inhibit PDGF signaling in orbital fibroblasts [87], might prove to be effective in GO. Clathrin is a protein involved in the formation of coated vesicles, through which nutrients, hormones, and liganded receptors are

internalized and transported to intracellular organelles [88]. Clathrin might represent a target of novel therapies, since silencing clathrin expression in GO-derived orbital fibroblasts was associated with decreased proliferation of fibroblasts and related production of glycosaminoglycans and intracellular reactive oxygen species [89]. No data on all of the above agents are presently available apart from in vitro studies [81]. Inhibition of cytokine secretion and action might also be used to treat GO [90]. In a small, open, nonrandomized study, a tumor necrosis factor- α inhibitor, i.e. etanercept, showed more beneficial effects than did placebo [91]. Successful treatment of a single patient with anti-interleukin-6 receptor monoclonal antibody (tocilizumab) was recently reported [92]. A novel somatostatin analog, i.e. pasireotide, which has a wider binding capacity than octreotide or lanreotide for the various somatostatin receptor subtypes, has been shown in vitro to have a greater inhibitory effect on adipogenesis than octreotide [93]. Whether this may translate into a revival of somatostatin analogs as possible therapeutic tools for GO is presently unknown in the absence of clinical trials.

Among potential novel drugs for GO, rituximab has received particular attention in the last few years. Rituximab is a monoclonal antibody targeting the CD20 transmembrane antigen expressed on the surface of pre-B and mature B lymphocytes, but not on stem cells or plasma cells [94]. Its main effect is to deplete CD20-positive B cells. Initially approved for the treatment of non-Hodgkin B-cell lymphoma, it has been used for several autoimmune disorders, including rheumatoid arthritis [95]. In the case of GO, this action would translate in a reduced activity of B cells both as antigen-presenting cells and as autoantibody (against TSHR and/or IGF-1R) producers. An intervention review on the use of rituximab for GO was recently published in the Cochrane Database of Systematic Reviews [96]. Few studies have been published so far, and they have been small and uncontrolled, usually reporting the effect of rituximab in patients with GO resistant to or relapsing after glucocorticoid treatment [97–101]. These reports suggested that rituximab may be an effective agent for the management of moderate-to-severe and active GO. The effects of rituximab on circulating TSHR autoantibody levels (decrease vs. no change) were conflicting. A patient described in a case report showed progression of glucocorticoid-resistant GO after rituximab injections [102]. In addition, two studies suggested a possible beneficial effect of rituximab in Graves' hyperthyroidism [98, 103]. All of these results must be interpreted with caution in view of the experimental de-

sign of the studies. It should, however, be mentioned that 3 RCTs are presently ongoing: one from Italy comparing rituximab with intravenous glucocorticoids, one from the USA comparing rituximab with placebo, and a third one from Sweden comparing rituximab + methotrexate with oral glucocorticoids + methotrexate. It is hoped that results of these studies will provide information and suggestions on whether rituximab can truly represent a novel and effective treatment for GO.

Concluding Remarks (and My Opinion)

GO is a rare disease, particularly in its severe expressions. It remains a therapeutic challenge and a disease with frequent unsatisfactory results, using the currently available treatments. This is partly due to the difficulty to carry out adequately powered RCTs, to the lack of complete understanding of its pathogenesis, and, therefore, to the impossibility of employing targeted therapies. This disease can be devastating in its severe forms, but it profoundly impairs the quality of life also in its milder forms due to its cosmetic and functional consequences [103]. The physician is also frustrated to admit that currently available medical treatments are not as effective as one would wish. To be provocative, I might say that GO is (in many instances) a surgical disease, and the only role of medical treatment is to abate inflammation and inactivate the disease, making it possible to send the patient to the surgeon(s) earlier. In a way, this situation is not different for Graves' hyperthyroidism: medical (pharmacological) treatment is often ineffective and associated with relapses, so that removal of the thyroid by either radioiodine or thyroidectomy is needed. In both instances, hyperthyroidism and orbitopathy, we do not intervene in the pathogenesis. It is hoped that my frustration and pessimism be will relieved in the next few years, before my retirement.

Acknowledgements

This paper is dedicated to my mentor, Prof. Aldo Pinchera (1934–2012). This work was partially supported by grants from the Ministero della Istruzione, Università e Ricerca (MIUR, Rome), and the University of Insubria, Varese, Italy.

Disclosure Statement

I have no conflicts of interest to disclose.

References

- Bartalena L, Tanda ML: Clinical practice – Graves' ophthalmopathy. *N Engl J Med* 2009; 360:994–1001.
- Estcourt S, Hickey J, Perros P, Dayan C, Vaidya B: The patient experience of services for thyroid eye disease in the United Kingdom: results of a nationwide survey. *Eur J Endocrinol* 2009;161:483–487.
- Bahn RS: Mechanisms of Disease – Graves' ophthalmopathy. *N Engl J Med* 2010;362: 726–738.
- Smith TJ: Pathogenesis of Graves' orbitopathy: a 2010 update. *J Endocrinol Invest* 2010; 33:414–421.
- Iyer S, Bahn RS: Immunopathogenesis of Graves' ophthalmopathy: the role of TSH receptor. *Best Pract Res Clin Endocrinol Metab* 2012;26:281–289.
- Smith TJ, Huetwell FGL, Hegedus L, Douglas RS: Role of insulin-like growth factor-1 (IGF-1) pathway in the pathogenesis of Graves' orbitopathy. *Best Pract Res Clin Endocrinol Metab* 2012;26:291–302.
- Smith TJ: Is IGF-1 receptor a target for auto-antibody generation in Graves' disease? *J Clin Endocrinol Metab* 2013;98:515–518.
- Tsui S, Naik V, Hoa N, Hwuang CJ, Afifiyan NF, Hikim Sinha A, Gianoukakis AG, Douglas RS, Smith TJ: Evidence for an association between thyroid-stimulating hormone and insulin like growth factor 1 receptors: a tale of two antigens implicated in Graves' disease. *J Immunol* 2008;181:4397–4405.
- Wiersinga WM: Autoimmunity in Graves' ophthalmopathy: the results of an unfortunate marriage between TSH receptors and IGF-1 receptors? *J Clin Endocrinol Metab* 2011;96:2386–2394.
- Bahn RS: Pathophysiology of Graves' disease: the cycle of disease. *J Clin Endocrinol Metab* 2003;88:1939–1946.
- Brent GA: Clinical practice – Graves' disease. *N Engl J Med* 2008;358:2594–2605.
- Nystrom HF, Jansson S, Berg G: Incidence rate and clinical features of hyperthyroidism in a long-term iodine sufficient area of Sweden (Gothenburg) 2003–2005. *Clin Endocrinol (Oxf)* 2013;78:768–776.
- 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.
- Laurberg P, Berman DC, Bulow Pedersen I, Andersen S, Carlé A: Incidence and clinical presentation of moderate to severe Graves' orbitopathy in a Danish population before and after iodine fortification of salt. *J Clin Endocrinol Metab* 2012;97:2325–2332.
- Lazarus JH: Epidemiology of Graves' orbitopathy (GO) and relationship with thyroid disease. *Best Pract Res Clin Endocrinol Metab* 2012;26:273–279.
- Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, Pariani N, Gallo D, Azolini C, Ferrario M, Bartalena L: Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed Graves' hyperthyroidism seen at a single center. *J Clin Endocrinol Metab* 2013;98:1443–1449.
- Weetman AP, Wiersinga WM: Current management of thyroid-associated ophthalmopathy in Europe: results of an international survey. *Clin Endocrinol (Oxf)* 1998; 49:21–28.
- Piantanida E, Tanda ML, Lai A, Sassi L, Bartalena L: Prevalence and natural history of Graves' orbitopathy in the XXI century. *J Endocrinol Invest* 2013;36:444–449.
- Wiersinga WM, Perros P, Kahaly GJ, Mourits MP, Baldeschi L, Boboridis K, Boschi A, Dickinson AJ, Kendall-Taylor P, Krassas GE, Lane CM, Lazarus JH, Marcocci C, Marinò M, Nardi M, Neoh C, Orgiazzi J, Pinchera A, Pitz S, Prummel MF, Sartini MS, Stahl M, von Arx G: 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.
- Perros P, Kendall-Taylor P: Natural history of thyroid eye disease. *Thyroid* 1998;8:423–425.
- Noth D, Gebauer M, Muller B, Burgi U, Diem P: Graves' ophthalmopathy: natural history and treatment outcomes. *Swiss Med Wkly* 2001;131:603–609.
- Bartalena L: Prevention of Graves' ophthalmopathy. *Best Pract Res Clin Endocrinol Metab* 2012;26:371–379.
- Prummel MF, Wiersinga WM: Smoking and risk of Graves' disease. *JAMA* 1993;269:479–482.
- Wiersinga WM: Smoking and thyroid. *Clin Endocrinol (Oxf)* 2013;79:145–151.
- Bartalena L, Martino E, Marcocci C, Bogazzi F, Panicucci M, Loviselli A, Pinchera A: More on smoking habits and Graves' ophthalmopathy. *J Endocrinol Invest* 1989;12:733–737.
- Bartalena L, Marcocci C, Tanda ML, Manetti L, Dell'Unto E, Bartolomei MP, Nardi M, Martino E, Pinchera A: Cigarette smoking and treatment outcomes in Graves' ophthalmopathy. *Ann Intern Med* 1998;129:632–635.
- Eckstein A, Quadbeck B, Mueller G, Rettenmeier AW, Hoermann R, Mann K, Steuhl P, Esser J: Impact of smoking on the response to treatment of thyroid associated ophthalmopathy. *Br J Ophthalmol* 2003;87:773–776.
- Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, Bruno-Bossio G, Nardi M, Bartolomei MP, Lepri A, Rossi G, Martino E, Pinchera A: Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med* 1998;338:73–78.
- Traisk F, Tallstedt L, Abraham-Nordling M, Andersson T, Berg G, Calissendorff J, Hallengren B, Hedner P, Lantz M, Nystrom E, Ponjavic V, Taube A, Torring O, Wallin G, Asman P, Lundell G, Thyroid Study Group of TT 96: Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131. *J Clin Endocrinol Metab* 2009;94:3700–3707.
- Pfeilschifter J, Ziegler R: Smoking and endocrine ophthalmopathy: impact of smoking severity and current versus lifetime cigarette consumption. *Clin Endocrinol (Oxf)* 1996;45: 477–481.
- Krassas GE, Segni M, Wiersinga WM: Childhood Graves' ophthalmopathy: results of a European questionnaire study. *Eur J Endocrinol* 2005;153:515–520.
- Prummel MF, Wiersinga WM, Mourits MP, Koornneef L, Berghout A, van der Gaag R: Amelioration of eye changes of Graves' ophthalmopathy by achieving euthyroidism. *Acta Endocrinol (Copenh)* 1989;121(suppl 2):185–189.
- Karlsson AF, Westermarck K, Dahlberg PA, Jansson R, Enoksson P: Ophthalmopathy and thyroid stimulation. *Lancet* 1989;2:691, letter.
- Tallstedt L, Lundell G, Blomgren H, Bring J: Does early administration of thyroxine reduce the development of Graves' ophthalmopathy after radioiodine treatment? *Eur J Endocrinol* 1994;130:494–497.
- Marcocci C, Bruno-Bossio G, Manetti L, Tanda ML, Miccoli P, Iacconi P, Bartolomei MP, Nardi M, Pinchera A, Bartalena L: The course of Graves' ophthalmopathy is not influenced by near total thyroidectomy: a case-control study. *Clin Endocrinol (Oxf)* 1999;51:503–508.
- Bartalena L: The dilemma of how to manage Graves' hyperthyroidism in patients with associated orbitopathy. *J Clin Endocrinol Metab* 2011;96:592–599.
- Tallstedt L, Lundell G, Torring O, Wallin G, Ljunggren JG, Blomgren H, Taube A: Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. *N Engl J Med* 1992; 326:1733–1738.
- Acharya SH, Avenell A, Philip S, Burr J, Bevan JS, Abraham P: Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review. *Clin Endocrinol (Oxf)* 2008;69:943–950.
- Bartalena L, Marcocci C, Bogazzi F, Panicucci M, Lepri A, Pinchera A: Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for Graves' hyperthyroidism. *N Engl J Med* 1989;321: 1349–1352.
- Lai A, Sassi L, Compri E, Marino F, Sivelli P, Piantanida E, Tanda ML, Bartalena L: 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.

- 41 Khoo DH, Ho SC, Seah LL, Fong KS, Tai ES, Chee SP, Eng PH, Aw SE, Fong AC: The combination of absent thyroid peroxidase antibodies and high thyroid-stimulating immunoglobulin levels in Graves' disease identifies a group at markedly at markedly increased risk of ophthalmopathy. *Thyroid* 1999;9: 1175–1180.
- 42 Gerding MN, van der Meer JW, Broenink M, Bakker O, Wiersinga WM, Prummel MF: Association of thyrotropin receptor antibodies with the clinical features of Graves' ophthalmopathy. *Clin Endocrinol (Oxf)* 2000;52: 267–271.
- 43 Eckstein AK, Plicht M, Lax H, Neuhauser M, Mann K, Lederbogen S, Eckmann G, Esser J, Morgenthaler NC: 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;91:3460–3470.
- 44 Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Topping O: TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. *Eur J Endocrinol* 2008;158: 69–75.
- 45 Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, Altea MA, Nardi M, Pitz S, Boboridis K, Sivelli P, von Arx G, Mourits MP, Baldeschi L, Bencivelli W, Wiersinga W, European Group on Graves' Orbitopathy: Selenium and the course of mild Graves' orbitopathy. *N Engl J Med* 2011;364:1920–1931.
- 46 Bartalena L, Marcocci C, Pinchera A: Graves' ophthalmopathy: a preventable disease? *Eur J Endocrinol* 2002;146:457–461.
- 47 Wiersinga WM, Bartalena L: Epidemiology and prevention of Graves' ophthalmopathy. *Thyroid* 2002;12:855–860.
- 48 Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marocci C, Mourits M, Perros P, Boboridis K, Boschi A, Currò N, Daumerie C, Kahaly GJ, Krassas GE, Lane CM, Lazarus JH, Marinò M, Nardi M, Neoh C, Orgiazzi J, Pearce S, Pinchera A, Pitz S, Salvi M, Sivelli P, Stahl M, von Arx G, Wiersinga WM: Consensus statement of the European Group on Graves' Orbitopathy (EUGOGO) on management of GO. *Eur J Endocrinol* 2008;158:273–285.
- 49 Wiersinga WM, Prummel MF: Graves' ophthalmopathy: a rational approach to treatment. *Trends Endocrinol Metab* 2002;13:280–287.
- 50 Werner SC: Classification of the eye changes of Graves' disease. *Am J Ophthalmol* 1969;68: 646–648.
- 51 Dolman PJ, Rootman J: VISA classification for Graves orbitopathy. *Ophthal Plastic Reconstr Surg* 2006;22:319–324.
- 52 Dolman PJ: Evaluating Graves' orbitopathy. *Best Pract Res Clin Endocrinol Metab* 2012; 26:229–248.
- 53 Mourits MP, Prummel MF, Wiersinga WM, Koornneef L: Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. *Clin Endocrinol (Oxf)* 1997;47:9–14.
- 54 Bartalena L, Marcocci C, Tanda ML, Piantanida E, Lai A, Marinò M, Pinchera A: An update on medical management of Graves' ophthalmopathy. *J Endocrinol Invest* 2005;28: 469–478.
- 55 Bartalena L, Pinchera A, Marcocci C: Management of Graves' ophthalmopathy: reality and perspectives. *Endocr Rev* 2000;21:168–199.
- 56 Marcocci C, Bartalena L, Tanda ML, Manetti L, Dell'Unto E, Rocchi R, Barbesino G, Mazzi B, Bartolomei MP, Lepri P, Cartei F, Nardi M, Pinchera A: 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.
- 57 Kahaly GJ, Pitz S, Hommel G, Dittmar M: Randomized, single-blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. *J Clin Endocrinol Metab* 2005; 90:5234–5240.
- 58 Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, Ezrachi D, Shimon I, Leibovici L: Treatment modalities for Graves' ophthalmopathy: systematic review and metaanalysis. *J Clin Endocrinol Metab* 2009;94:2708–2716.
- 59 Zang S, Ponto KA, Kahaly GJ: Intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. *J Clin Endocrinol Metab* 2011;96:320–332.
- 60 Marcocci C, Watt T, Altea MA, Krogh Rasmussen A, Feldt-Rasmussen U, Orgiazzi J, Bartalena L, European Group on Graves' Orbitopathy (EUGOGO): 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;166:247–253.
- 61 Marinò M, Morabito E, Brunetto MR, Bartalena L, Pinchera A, Marcocci C: Acute and severe liver damage associated with intravenous glucocorticoid pulse therapy in patients with Graves' ophthalmopathy. *Thyroid* 2004; 14:403–406.
- 62 Zang S, Ponto KA, Pitz S, Kahaly GJ: Dose of intravenous steroids and therapy outcome in Graves' orbitopathy. *J Endocrinol Invest* 2011;34:876–880.
- 63 Le Moli R, Baldeschi L, Saeed P, Regensburg N, Mourits MP, Wiersinga WM: Determinants of liver damage associated with intravenous methylprednisolone pulse therapy in Graves' ophthalmopathy. *Thyroid* 2007;17: 357–362.
- 64 Bartalena L, Krassas GE, Wiersinga W, Marocci C, Salvi M, Daumerie C, Bournaud C, Stahl M, Sassi L, Veronesi G, Azzolini C, Boboridis KG, Mourits MP, Soeters MR, Baldeschi L, Nardi M, Currò N, Boschi A, Bernard M, von Arx G, European Group on Graves' Orbitopathy: Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. *J Clin Endocrinol Metab* 2012;97:4454–4463.
- 65 Tanda ML, Bartalena L: Efficacy and safety of orbital radiotherapy for Graves' orbitopathy. *J Clin Endocrinol Metab* 2012;97:3857–3865.
- 66 Bartalena L, Marcocci C, Tanda ML, Rocchi R, Mazzi B, Barbesino G, Pinchera A: Orbital radiotherapy for Graves' ophthalmopathy. *Thyroid* 2002;12:245–250.
- 67 Mourits MP, Loes van Kempen-Hartenveld M, Begona Garcia Garcia M, Koppeshaar HPF, Tick L, Terwee CB: Radiotherapy for Graves' orbitopathy: randomized placebo-controlled study. *Lancet* 2000;355:1505–1509.
- 68 Prummel MF, Terwee CB, Gerding MN, Baldeschi L, Mourits MP, Blank L, Dekker FW, Wiersinga WM: A randomized controlled trial of orbital radiotherapy versus sham irradiation in patients with mild Graves' ophthalmopathy. *J Clin Endocrinol Metab* 2004;89: 15–20.
- 69 Gorman CA, Garrity JA, Fatourehchi V, Bahn RS, Petersen IA, Stafford SL, Earle JD, Forbes GS, Kline RW, Bergstrahl EJ, Offord KP, Rademacher DM, Stanley NM, Bartley GB: A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for Graves' ophthalmopathy. *Ophthalmology* 2001;108:1523–1534.
- 70 Bartalena L, Marcocci C, Chiovato L, Laddaga M, Lepri G, Andreani D, Cavallacci G, Baschieri L, Pinchera A: Orbital cobalt irradiation combined with systemic corticosteroids for Graves' ophthalmopathy: comparison with systemic corticosteroids alone. *J Clin Endocrinol Metab* 1983;56:1139–1144.
- 71 Marcocci C, Bartalena L, Bogazzi F, Bruno-Bossio G, Lepri A: 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.
- 72 Bradley EA, Gower EW, Bradley DJ, Meyer DR, Cahill KV, Custer PL, Holck DE, Woog JJ: Orbital radiation for Graves ophthalmopathy: a report by the American Academy of Ophthalmology. *Ophthalmology* 2008;115: 398–409.
- 73 Dolman PJ, Rath S: Orbital radiotherapy for thyroid eye disease. *Curr Opin Ophthalmol* 2012;23:427–432.
- 74 Bartalena L: What to do for moderate-to-severe and active Graves' orbitopathy if glucocorticoids fail? *Clin Endocrinol (Oxf)* 2010; 73:149–152.
- 75 Prummel MF, Mourits MP, Blank L, Berghout A, Krennig EP, van der Gaag R, Koornneef L, Wiersinga WM: Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. *N Engl J Med* 1989;321: 1353–1359.

- 76 Dickinson AJ, Vaidya B, Miller M, Coulthard A, Perros P, Baister E, Andrews CD, Hesse L, Heverhagen JT, Heufelder AE, Kendall-Taylor P: Double-blind, placebo-controlled trial of octreotide long-acting repeatable (LAR) in thyroid-associated ophthalmopathy. *J Clin Endocrinol Metab* 2004;89:5910–5915.
- 77 Wemeau JL, Caron P, Beckers A, Rohmer V, Orgiazzi J, Borson-Chazot E, Nocuadie M, Perimemis P, Bisot-Locard S, Bourdeix J, Dejager S: 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.
- 78 Stan MN, Garrity JA, Bradley EA, Woog JJ, Bahn MM, Brennan MD, Bryant SC, Achenbach SJ, Bahn RS: Randomized, double-blind, placebo-controlled trial of long-acting release octreotide for treatment of Graves ophthalmopathy. *J Clin Endocrinol Metab* 2006;91:4817–4824.
- 79 Chang T-C, Liao SL: Slow-release lanreotide in Graves' ophthalmopathy: a double-blind randomized, placebo-controlled clinical trial. *J Endocrinol Invest* 2006;29:413–422.
- 80 Eckstein A, Schittkowski M, Esser J: Surgical treatment of Graves' ophthalmopathy. *Best Pract Res Clin Endocrinol Metab* 2012;26:339–358.
- 81 Bahn RS: Emerging pharmacotherapy for treatment of Graves' disease. *Expert Rev Pharmacol* 2012;5:605–607.
- 82 Neumann S, Pope A, Geras-Raaka E, Bahn RS, Gershengorn MC: A drug-like antagonist inhibits thyrotropin receptor-mediated stimulation of cAMP production in Graves' orbital fibroblasts. *Thyroid* 2012;22:839–843.
- 83 Van Zeijl CJ, van Koppen CJ, Surovtseva OV, de Gooyer ME, Plate R, Conti P, Karstens WJ, Timmers M, Saeed P, Wiersinga WM, Miltenburg AN, Fliers E, Boelen A: Complete inhibition of rhTSH-, Graves' disease IgG-, and M22-induced cAMP production in differentiated orbital fibroblasts by a low-molecular-weight TSHR antagonists. *J Clin Endocrinol Metab* 2012;97:E781–E785.
- 84 Turcu AF, Kumar S, Neumann S, Coenen M, Iyer S, Chiriboga P, Gershengorn MC, Bahn RS: A small molecule antagonist inhibits thyrotropin receptor antibody-induced orbital fibroblasts functions involved in the pathogenesis of Graves ophthalmopathy. *J Clin Endocrinol Metab* 2013;98:2153–2159.
- 85 van Steensel L, Hooijkaas H, van Meurs M, Paridaens D, van den Bosch WA, Kuijpers RW, Dingjan GM, van Daele PL, van Hagen PM, Drexhage HA, Dik WA: Orbit-infiltrating mast cells, monocytes and macrophages produce PDGF isoforms that orchestrate orbital fibroblast activation in Graves' ophthalmopathy. *J Clin Endocrinol Metab* 2012;97:E400–E408.
- 86 van Steensel L, Hooijkaas H, Paridaens D, van den Bosch WA, Kuijpers RWAM, Drexhage HA, van Hagen PM, Dik WA: PDGF enhances orbital fibroblast responses to TSHR stimulating autoantibodies in Graves' ophthalmopathy patients. *J Clin Endocrinol Metab* 2012;97:E944–E953.
- 87 van Steensel L, Paridaens D, Dingjan GM, van Daele PL, van Hagen PM, Kuijpers RW, van den Bosch WA, Drexhage HA, Hooijkaas H, Dik WA: Platelet-derived growth factor-BB: a stimulus for cytokine production by orbital fibroblasts in Graves' ophthalmopathy. *Invest Ophthalmol Vis Sci* 2010;51:1002–1007.
- 88 Moskowitz HS, Yokoyama CT, Ryan TA: Highly cooperative control of endocytosis by clathrin. *Mol Biol Cell* 2005;16:1769–1776.
- 89 Meyer zu Horste M, Stroher E, Berchner-Pfannschmidt U, Schmitz-Spanke S, Pinl M, Gothert JR, Fischer JW, Gulbins E, Eckstein AK: A novel mechanism involved in the pathogenesis of Graves ophthalmopathy (GO): clathrin is a possible targeting molecule for inhibiting local immune response in the orbit. *J Clin Endocrinol Metab* 2011;96:E1727–E1736.
- 90 Bartalena L, Marcocci C, Pinchera A: Cytokine antagonists: new ideas for the management of Graves' ophthalmopathy. *J Clin Endocrinol Metab* 1996;81:446–448.
- 91 Paridaens D, van den Bosch WA, van der Loos TL, Krenning EP, van Hagen PM: The effect of etanercept on Graves' ophthalmopathy: a pilot study. *Eye* 2005;19:1286–1289.
- 92 Butnaru D, Pérex-Moreiras JV, Sanchez-Ramon S: Anti-IL-6R therapy on Graves' ophthalmopathy. *Clin Immunol* 2013;147:120–121, letter.
- 93 Cozma I, Zhang L, Uddin J, Lane C, Rees A, Ludgate M: Modulation of expression of somatostatin receptor subtypes in Graves' orbitopathy orbits: relevance to novel analogs. *Am J Physiol Endocrinol Metab* 2007;293:E1630–E1635.
- 94 Reff ME, Carner C, Chambers KS: Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood* 1994;83:435–445.
- 95 Smolen JS, Keystone EC, Emery P, Breedveld FC, Betteridge M, Burmester GR, Dougados M, Ferraccioli G, Jaeger U, Klareskog L, Kvien TK, Martin-Mola E, Pavelka K, Working Group on the Rituximab Consensus Statement: Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66:143–150.
- 96 Minakaran N, Ezra DG: Rituximab for thyroid-associated ophthalmopathy. *Cochrane Database Syst Rev* 2013;5:CD009226.
- 97 Salvi M, Vannucchi G, Campi I, Currò N, Dazzi D, Simonetta S, Bonara P, Rossi S, Sina C, Guastella C, Ratiglia R, Beck-Peccoz P: Treatment of Graves' disease and associated ophthalmopathy with the anti-CD20 monoclonal antibody rituximab: an open study. *Eur J Endocrinol* 2007;156:33–40.
- 98 El Fassi D, Nielsen CH, Bonnema SJ, Hesselbach HC, Hegedus L: B lymphocyte depletion with the monoclonal antibody rituximab in Graves' disease: a controlled pilot study. *J Clin Endocrinol Metab* 2007;92:1769–1772.
- 99 Silkiss RZ, Reier A, Coleman M, Lauer SA: Rituximab for thyroid eye disease. *Ophthalm Plast Reconstr Surg* 2010;26:310–314.
- 100 Khanna D, Chong KK, Afifyan NF, Hwang CJ, Lee DK, Garneau HC, Goldberg RA, Darwin CH, Smith TJ, Douglas RS: Rituximab treatment of patients with severe, corticosteroid-resistant thyroid-associated ophthalmopathy. *Ophthalmology* 2010;117:133–139.
- 101 Mitchell AL, Gan EH, Morris M, Johnson K, Neoh C, Dickinson AJ, Perros P, Pearce SHS: The effect of B cell depletion therapy on anti-TSH receptor antibodies and clinical outcome in glucocorticoid-refractory Graves' orbitopathy. *Clin Endocrinol (Oxf)* 2013;79:437–442.
- 102 Heemstra KA, Toes RE, Sepers J, Pereira AM, Corssmit EP, Huixinga TW, Romijn JA, Smit JW: Rituximab in relapsing Graves' disease, a phase II study. *Eur J Endocrinol* 2008;159:609–615.
- 103 Wiersinga WM: Quality of life in Graves' ophthalmopathy. *Best Pract Res Clin Endocrinol Metab* 2012;26:359–370.