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Review

Novel Approaches to the Management of Graves' Ophthalmopathy

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ABSTRACT

Severe Graves' ophthalmopathy constitutes a complex therapeutic challenge and treatment outcome often is not satisfactory. Established methods of treatment include high-dose glucocorticoids, orbital radiotherapy and orbital decompression. Recently, the use of intravenous glucocorticoids has been shown to provide more favorable results than oral glucocorticoids. Novel treatments under investigation include somatostatin analogues, intravenous immunoglobulins and antioxidants. Low-dose immunosuppressive drugs (namely cyclosporine and, possibly, methotrexate) might be useful as an adjunct to established methods, particularly in view of a glucocorticoid-sparing action. Because cytokines play an important role in the pathogenesis of the disease, cytokine antagonists, which are currently evaluated in rheumatoid arthritis and other autoimmune conditions, might constitute in the future a valuable tool for the management of eye disease. Prevention of Graves' ophthalmopathy would be desirable, but so far it is limited to secondary prevention (arrest of progression of subclinical disease to clinical disease) and tertiary prevention (avoidance of deterioration or complications of clinical disease): among preventive measures smoking withdrawal is probably the most important one. Primary prevention (in the absence of disease) is only speculative, but oral tolerance induction or vaccination with the offending antigen(s) might prove beneficial for prevention of Graves' ophthalmopathy in genetically susceptible individuals.

Key-Words: Graves' ophthalmopathy, cytokines, cytokine antagonists, somatostatin analogues, methotrexate, oral tolerance, pentoxifylline

INTRODUCTION

Graves' ophthalmopathy (GO) is the complex of ocular signs and symptoms often present in Graves' disease; similar eye involvement can, however, less frequently be observed in patients with Hashimoto's thyroiditis or in subjects with no apparent thyroid abnormalities (so-called Euthyroid Graves' Disease)[1]. In most cases, ocular involment is nonsevere, but 3-5% of cases have severe and progressive ocular manifestations[1]. It is noteworthy that the quality of life of affected individuals is markedly impaired not only in severe ophthalmopathy but also in nonsevere eye disease[2].

Severe GO represents a complex therapeutic problem and, despite any effort, approximately one third of

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patients are dissatisfied with the therapeutic outcome at the end of follow-up[3]. This is because currently available methods of treatment frequently result in a partial or absent response of the ophthalmopathy. The unfavorable outcome can partly be explained by selection of patients because longstanding and inactive GO is unlikely to show relevant and substantial changes in response to whatever medical treatment, while results are more likely to be favorable in recent-onset and active eye disease[1].

Available treatments for GO are listed in Table 1. They have recently been extensively reviewed[1,4]. The aim of the present article is to analyze novel treatments (or novel modalities of established treatments) currently under investigation as well as therapeutic and preventive perspectives for this disease.

INTRAVENOUS GLUCOCORTICOIDS

Glucocorticoids have been used for decades and still represent a milestone in GO management due to their nonspecific anti-inflammatory and immunosuppressive actions[4,5]. In a recent survey of the European Thyroid Association they were indicated as the first-line treatment, alone or in combination with orbital radiotherapy, by the majority of respondents[6]. They have been administered via systemic (mainly oral until 15 years ago) or local (subconjunctival or retrobulbar) routes[7]. Oral glucocorticoids provide overall favorable responses in slightly more than 60% of patients, whereas the local route is associated with beneficial effects only in about 40% of cases[1]. They are mostly effective in patients with severe and active florid eye disease. Soft tissue inflammatory changes, recent-onset extraocular muscle involvement, and optic neuropathy are the most responsive expressions of the disease, while proptosis and longstanding extraocular muscle involvement associated with fibrotic changes are poorly influenced by treatment. The major drawbacks of glucocorticoid treatment are the

Table 1. Methods of medical treatment for Graves' ophthalmopathy.

	Comment
High-dose glucocorticoids	
Oral	Effective on severe and active GO
Intravenous	Effective on severe and active GO; better tolerated than oral steroids
Local	Low effectiveness
Retrobulbar	
Subconjunctival	
Orbital radiotherapy	Effective on severe and active GO; more effective if associated with glucocorticoids
Somatostatin analogues	Effective on severe and active GO; limited number of treated patients; high cost
Octreotide	
Lanreotide	
Intravenous immunoglobulins	Limited number of treated patients; high cost; risks related to plasma-derived products
Immunosuppressive drugs	
Azathioprine	Poorly effective
Cyclophosphamide	Poorly effective
Chlorambucil	Poorly effective
Ciamexone	Poorly effective
Cyclosporine	Limited effectiveness as a single-agent; possible use in association with glucocorticoids (glucocorticoid-sparing effect)
Antioxidants	
Allopurinol and Nicotinamide	Only one pilot (nonrandomized) study
Cytokine antagonists	
IL-1 antagonists	Studies in vitro for GO; used in vivo in other autoimmune disorders; preliminary study on pentoxifylline
TNF-a antagonists	Used in vivo in other autoimmune disorders; preliminary study on pentoxifylline
Total thyroid ablation	Only few uncontrolled and nonrandomized studies of GO

need for continuative administration of high doses of the drug, the long duration of treatment, the frequent relapses of the ophthalmopathy after drug withdrawal and the frequent and potentially dangerous adverse effects and complications[7].

Glucocorticoids do not constitute a novel treatment for GO. What is relatively new is the intravenous (iv) route of administration. Glucocorticoids, admistered as iv pulse therapy, repeated several times, have been used for the treatment of other autoimmune disorders, and have been employed for GO since 1987 (see 1 for review). An overall analysis of reported results indicates that favorable responses can be achieved in slightly less than 80% of cases[1]. However, interpretation of results is complicated by the lack of control groups (namely, oral glucocorticoids), by the heterogeneity of doses and protocols and by the virtually constant administration of oral glucocorticoids or immunosuppressive agents in the interpulse period ([1]. We recently reported the results of the first randomized prospective study directly comparing the effects of oral and iv glucocorticoids[8]. Patients were treated by orbital radiotherapy combined with either oral prednisone (100 mg/day, initial dose, to be gradually tapered and withdrawn over a 5-month period) or iv methylprednisolone (15 mg/kg bodyweight for 4 cycles followed by 7.5 mg/kg bodyweight for 4 cycles; each cycle consisting of two infusions on alternate days at 2-week intervals). No maintenance oral glucocorticoid treatment was given in the interpulse period. Each group included 41 patients whose baseline clinical and laboratory features did not differ. Both treatment modalities were effective, but the proportion of favorable responses was higher in the iv group (88% vs 63% in the oral group, $p<0.005$)[8]. Likewise, both treatments were associated with a significant reduction in the Clinical Activity Score (CAS), but CAS decrease after treatment was greater with the iv route ($p<0.005$; Figure 1)[8]. This study also showed that the iv route was better tolerated than the oral route because side effects occurred in 56% of iv-treated patients and 83% of orally-treated patients (Table 2). In particular, cushingoid features, present in the large majority of orally-treated patients, were apparent in only a few patients treated by iv glucocorticoids (Table 2). It must be mentioned that one case of fatal acute liver failure was reported in a patient given high doses of iv glucocorticoids for GO[9]. We have observed a few cases of liver toxicity when the cumulative dose of steroids was higher than 10 grams; accordingly, we now use a lower cumulative dose of iv methylprednisolone (8 grams rather than 12-14 grams) and are satisfied with the lower liver toxicity of this regimen.

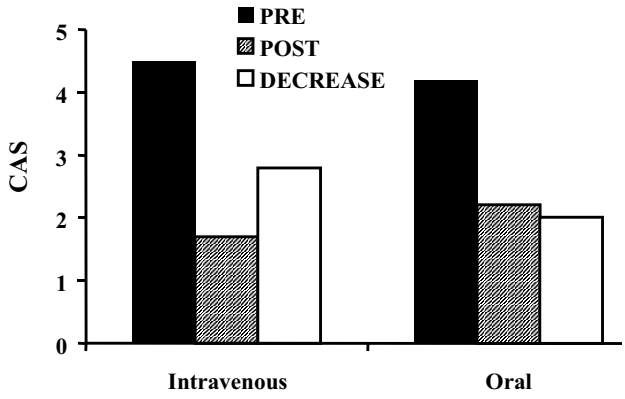

Figure 1. Changes in the Clinical Activity Score (CAS) following treatment of severe Graves' ophthalmopathy with either intravenous or oral high-dose glucocorticoids. Derived from Marcocci C et al.[8].

Table 2. Side effects of intravenous and oral glucocorticoids in 82 patients with severe Graves' ophthalmopathy.

	Intravenous n = 41	Oral n = 41
Gastritis	4 (10%)	4 (10%)
Urinary tract infections	8 (20%)	8 (20%)
Depression	1 (2.5%)	2 (5%)
Hepatitis	1 (2.5%)	0
Glucose intolerance	9 (22%)	8 (21%)
Blood hypertension	1 (2.5%)	2 (5%)
Cushingoid features	5 (12%)	35 (85%)
Total side effects*	23	60

*Some patients had more than one side effect or complication. Derived from Marcocci C et al.[8].

In summary, high-dose iv glucocorticoids appear to be more effective and better tolerated than oral glucocorticoids or locally-administered glucocorticoids (Figure 2). The rapidity of action of iv glucocorticoids make them a valuable and suitable treatment for very severe and active ophthalmopathy (so-called "malignant exophthalmos"), when an immediate surgical approach (orbital decompression) is generally advised: in these cases, a short-term (2-3 weeks) course of iv glucocorticoids can be carried out. In the absence of relevant beneficial effects, the patient will be submitted to surgery, but, if a response does occur (and this often is dramatic), medical treatment with iv steroids (possibly associated with orbital radiotherapy) can be continued.

SOMATOSTATIN ANALOGUES

The idea to use somatostatin analogues (SMSa) (oc-

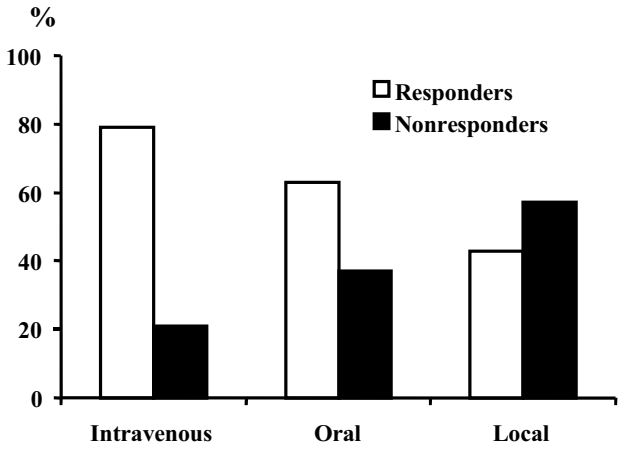

Figure 2. Overall effects of intravenous, oral or locally-administered glucocorticoids. Compiled from the literature.

treotide and lanreotide) for the management of severe and active GO derives from the observation that SMS receptors can be visualized in vivo in the orbital tissue of GO patients by ^{111}In-DTPA-D-Phe-octreotide scintigraphy (octreoscan)[10]. Octreoscan positivity is higher in Graves' patients with than in those without ophthalmopathy[11]; in patients with active than in those with inactive GO[11-13]; in patients with recent-onset than in those with longstanding eye disease[12]. Octreoscan positivity correlates with other indicators of activity of the ophthalmopathy, such as high CAS[10] or T2-relaxation time of the extraocular muscles at magnetic resonance imaging[14]. Thus, a positive octreoscan is an indicator of GO activity[15] and may predict a subsequent favorable response not only to SMSa therapy but also to high-dose glucocorticoids and/or orbital radiotherapy[11,16-18]. Limitations to a wide-scale use of octreoscan in making a therapeutic decision for GO patients include: high demand of this technique in terms of accuracy needed for prediction, high cost, a not negligible radiation burden and relative lack of specificity (i.e., the number of false positives in other inflammatory or noninflammatory orbital disorders)[15].

With this background, it is not surprising that several, although small, studies have investigated the effects of SMSa on GO (see refs. 5 and 19 for review). The mechanism of action of these drugs remains to be fully elucidated, but they might exert beneficial effects by modulating the immunologic and metabolic activities of orbital cells (fibroblasts, adipocytes, myocytes), which contribute to perpetuation of immune and inflammatory reactions ongoing in the orbit of affected individuals[5]. The use of SMSa in GO patients was first reported by Chang et al.[20] in an uncontrolled study of 6 patients treated with 0.1 mg subcutaneous octreotide three times daily for 3 months: treatment was associated with an improvement in soft tissue inflammatory changes and extraocular muscle impairment. In addition, there was a decrease in urinary glycosaminoglycan excretion after only one week of treatment[21]. In a nonrandomized study, Krassas et al.[11] observed favorable responses to octreotide (0.1 mg three times daily for 3 months) in 7 of 12 patients (58%) with active ophthalmopathy. These beneficial effects were achieved in patients who had positive octreoscans prior to treatment[11]. In a similar uncontrolled study (octreotide, 0.1 mg three times daily for 8 weeks) Khoo et al.[22] reported an improvement of eye disease in 6 of 8 patients (75%). Comparison between the effects of either octreotide (0.2 mg three times daily for 3 months) or prednisone was made by Kung et al.[23] who observed, in an open randomized study, that octreotide treatment was associated with an improvement in ocular conditions in 5 of 8 patients (62%; 1 complete response and 4 partial responses); however, in this study the effectiveness of octreotide was not as high as that of prednisone. Ozata et al.[24] observed a clinical response (most evident on soft tissue involvement) in 5 of 10 patients (50%) treated with the above doses of octreotide: this was associated with a decrease in serum intercellular adhesion molecule-1 (ICAM-1) levels, suggesting a reduced endothelial and fibroblast activation. Another nonrandomized study reported positive results with octreotide therapy in 7 of 9 patients (78%)[25]. A major limitation of octreotide is its short half-life, which requires multiple daily injections. To overcome this problem, the use of the long-acting analogue, lanreotide, was proposed. Krassas et al.[16] found that lanreotide (40 mg every other week for 3 months) was effective in all 5 patients (100%); a subsequent nonrandomized study from the same group[26] showed a favorable outcome in all 10 patients with no differences between the subgroups treated with octreotide or lanreotide. Finally, in a recent report by Krassas et al.[27], mainly devoted to the study of serum cytokine and adhesion molecule concentrations during SMSa therapy. Responders to treatment were 9 of 15 enrolled patients (60%).

In summary, the available data indicate favorable effects of SMSa in slightly more than 70% of patients (Table 3). Side effects of this treatment are very limited. These promising results must, however, be weighed against the following considerations: i) The number of patients so far treated is too small (Table 3); ii) Most published studies are nonrandomized or uncontrolled; iii) A selection bias was probably applied in some stud-

Table 3. Overall effects of somatostatin analogue (SMSa) on Graves' ophthalmopathy.

Author	Year	SMSa	Patients	Responders	
			(n)	(n)	(%)
Chang	1992	Octreotide	6	6	100
Krassas	1995	Octreotide	11	7	58
Khoo	1995	Octreotide	8	6	75
Kung	1996	Octreotide	8	5	62
Ozata	1996	Octreotide	10	5	50
Uysal	1999	Octreotide	9	7	78
Krassas	1999	Octreotide	5	5	100
Krassas	2001	Octreotide	6	3	50
Krassas	1997	Lanreotide	5	5	100
Krassas	1999	Lanreotide	5	5	100
Krassas	2001	Lanreotide	9	6	67
Total			82	60	76

ies! because positivity of pretherapy octreoscans was a prerequisite for enrollment of patients. Should the activity of the ophthalmopathy have been considered a prerequisite to enroll patients in previous studies, overall results of high-dose glucocorticoid treatment or orbital radiotherapy would probably be much better than those reported in the literature (see 1 for review). Accordingly, large, multicenter, prospective and randomized studies are needed to draw definite conclusions on SMsa effectiveness. In addition, comparison with established methods of treatment for GO (namely, high-dose glucocorticoids or orbital radiotherapy) should also be made to assess, in comparable series of patients, the relative effectiveness and tolerability of the different treatments. Finally, the high cost of these drugs must be taken into account before including them among the established treatments for GO.

INTRAVENOUS IMMUNOGLOBULINS

Human iv immunoglobulins (IvIg) have been used with a variable degree of success in several inflammatory/autoimmune disorders, such as thrombocytopenic purpura, membranous glomerulonephritis, myasthenia gravis, polymyositis, Guillain-Barre syndrome, vasculitis and Kawasaki's disease[28]. Recently, IvIg have also been used in systemic lupus erythematosus, with favorable, although frequently transient, responses in 75-85% of cases[29]. Their mechanism of action is not fully understood but immunoglobulins might act by blocking idiotypic epitopes through anti-idiotypic antibodies, by down-regulating immunocompetent cells through suppression of Fcg receptors, by modulating or suppressing cytokine secretion or by solubilizing immune complexes[1]. Whether all the above targets are relevant for GO remains to be unequivocally demonstrated.

The first nonrandomized study on the use of IvIg for GO was published 10 years ago by Antonelli et al.[30] who treated 7 patients with high-dose IvIg alone (400 mg/kg/day for 5 consecutive days; the cycle was repeated five times at 3-week intervals) and 7 patients with IvIg associated with orbital radiotherapy; the results were compared with a so-called "historical" group of patients previously treated with high-dose glucocorticoids and orbital radiotherapy. They found that IvIg, either alone or combined with orbital radiotherapy, caused an improvement in the ocular conditions which did not substantially differ from that observed with the "historical" group[30]. The same authors subsequently reported the results of another prospective, nonrandomized study in which the percentage of responders to IvIg (76%) was similar to the percentage of responders to systemic glucocorticoids[31]. In the only randomized study, Kahaly et al.[32] reported a similar percentage of successful outcome (slightly more than 60%) in patients treated with either systemic glucocorticoids or IvIg. On the other hand, Seppel et al.[33] failed to show any beneficial effect of this treatment in 10 GO patients.

This treatment has not gained wide popularity among thyroidologists and no further reports on its use for GO have been published in the last 5 years. As a matter of fact, in a recent survey of the European Thyroid Association only 2% of respondents suggested its use for this disease[6]. The reasons for this reluctancy can be summarized as follows: i) Results so far published refer to small

series of patients and all studies but one are nonrandomized; ii) Treatment is very expensive; iii) There is concern as to the possibility of disease transmission using plasma-derived products. For example, an outbreak of hepatitis C was associated with IvIg treatment in the United States in the period October 1993-June 1994[34].

Bearing these important limitations in mind, we do not believe that, in spite of enthusiastic reports, available data presently justify the choice of IvIg, at least as a first-line therapeutic approach, for GO. Carefully conducted, prospective, randomized and controlled studies of large series of patients are required to support or disprove our current attitude.

IMMUNOSUPPRESSIVE DRUGS

The use of immunosuppressive drugs other than steroids was proposed on the basis of the autoimmune nature of GO[1]. However, results obtained with several immunosuppressants or immunomodulators, like azathioprine, cyclophosphamide, chlorambucil and ciamexone, have generally been discouraging[35]. Results with cyclosporine as a single agent were rather conflicting but mostly nonsatisfactory[1]. However, even though poorly effective as a single agent, cyclosporine might have a role, according to Prummel et al.[36], in association with glucocorticoids, in patients who do not respond to glucocorticoids alone. While its use in transplanted patients or in severe autoimmune disorders is obviously worthwhile (and may be inevitable), the potential toxicity of cyclosporine must seriously be taken into account before using it for a disease such as GO. Thus, GO management with immunosuppressive agents other than glucocorticoids is not very popular. As a matter of fact, cyclosporine or azathioprine were indicated as a suitable therapeutic option by only 6% and 2% of respondents, respectively, to the recent European Thyroid Association survey[6].

Another immunosuppressive agent which is currently being evaluated in GO patients is methotrexate. This drug, together with its metabolites, inhibits several enzymes in the folic acid metabolic pathway[37]. When used at high doses, it has cytotoxic and antiproliferative actions attributed to the inhibition of dihydrofolate reductase activity leading to inhibition of DNA, RNA and protein synthesis[37]. Chronic, low-dose treatment with methotrexate causes an accumulation of adenosine, a lymphotoxic and anti-inflammatory autocoid[38]. Methotrexate also affects cytokine synthesis and secretion since it increases interleukin (IL)-2 production and decreases soluble IL-2 receptor, IL-6, IL-8 and leucotriene B4 production[38]. In addition, methotrexate impairs neutrophil chemotaxis[38]. Low-dose methotrexate is useful for the management of nonneoplastic disorders, such as rheumatoid arthritis[39], psoriasis[40], sarcoidosis[41], asthma[42] and Crohn's disease[38]. Particularly interesting in all the above conditions is the glucocorticoid-sparing effect of methotrexate since in several series, patients were weaned from or required lower doses of glucocorticoids following the addition of methotrexate.

Thus, methotrexate is by no means a novel drug. However, it has not systematically been evaluated in GO management. Indeed, the only available report on the use of methotrexate for this disease is a study of its role in noninfectious orbital inflammatory disorders: among the 14 patients reported, three were affected with GO[43]. All three patients, treated with a maximum of 20-25 mg/day for long periods of time (25-36 months), had an improvement in their ocular conditions, with particular effect on soft tissue changes, extraocular muscle involvement and, in one case, visual acuity[43]. In addition to this report, Heufelder communicated preliminary (and as yet unpublished in a final form) favorable results in a few patients treated with methotrexate for refractory ophthalmopathy[44]. Thus, data must be considered anecdotical. Nevertheless, methotrexate, the use of which was indicated by 1% of respondents to the European Thyroid Association survey[6], probably deserves a more careful evaluation in controlled and randomized prospective studies. We are rather skeptical about its true effectiveness and the possibility that treatment outcomes may substantially differ from those reported with other immunosuppressive drugs. Our current view, based on what was reported in other disorders, such as rheumatoid arthritis, asthma and sarcoidosis, is that methotrexate should not be used as a first-line treatment, but might, at low doses, have a role as a second-line therapeutic approach, in association with disease-modifying treatments in patients with persistently active and recalcitrant ophthalmopathy, with the aim of reducing the dose of glucocorticoids necessary to control the clinical picture. As for other medical treatments, methotrexate should probably be used early in the course of the ophthalmopathy when the disease is florid and active. Finally, when proposing methotrexate as a therapeutic tool for GO, its possible side effects, albeit usually reversible and responsive to dose reductions, should carefully be considered in a cost/benefit assessment. The latter include gastrointestinal disturbances, an increased risk of opportunistic infections, bone marrow depression, interstitial pneumonitis and liver toxicity[42]. Conception and pregnancy

should be avoided for at least 6 months after drug withdrawal because of its teratogenic effect[42]. Folate represents a useful antidote to methotrexate toxicity, without affecting its effectiveness.

Whether tacrolimus, an immunosuppressive drug inhibiting immunophilins, might be beneficial for GO as it proved to be for other autoimmune disorders[45,46], is conjectural.

ANTIOXIDANTS

Thyroid hormones increase the mitochondrial respiration, causing a hypermetabolic state associated with an increased generation of oxygen free radicals: such a metabolic oxidation and a reduced antioxidant capacity may contribute to signs and symptoms of hyperthyroidism[47]. Oxidation also represents an important mechanism in thyroid hormone synthesis, through oxidation of iodide and coupling of iodotyrosines to form iodothyronines[48]. Tissue damage in hyperthyroidism might be related to the increased oxygen free radical generation[48,49]. In a human study, the use of an antioxidant mixture (vitamin E, vitamin C, b-carotene, copper, zinc and manganese) in association with methimazole induced a more rapid decrease in serum thyroid hormone levels and a prompter amelioration of clinical signs and symptoms of thyrotoxicosis than methimazole alone[50].

As far as GO is concerned, oxygen free radicals have been shown in vitro to stimulate proliferation of orbital fibroblasts[51-53] and their expression of 72-kDa heat shock protein[52]. In vitro antioxidant agents, nicotinamide and allopurinol, block superoxide-induced proliferation of orbital fibroblasts[53]; in addition, nicotinamide inhibits cytokine-induced expression of both major histocompatibility antigen class II antigens and sICAM-1 from the same cells[54]. Further to these studies, an in vivo study was carried out in GO patients on the effects of the antioxidant agents, allopurinol (300 mg daily) and nicotinamide (300 mg daily), given for three months[55]. In this prospective, nonrandomized, comparative study, two groups of 11 patients with mild-to-moderately severe ophthalmopathy were given either antioxidants or placebo: improvement of ocular conditions occurred in 9 of 11 (82%) antioxidant-treated patients, but only in 3 of 11 (27%) placebo-treated patients ($p < 0.05$)[55] (Figure 3). Pain (either spontaneous or with eye movements) improved in all patients, diplopia ameliorated in 4 of 7 (57%), proptosis was little affected by treatment; 10 of 11 patients reported satisfaction with treatment outcome in the self-assessment evaluation[55].

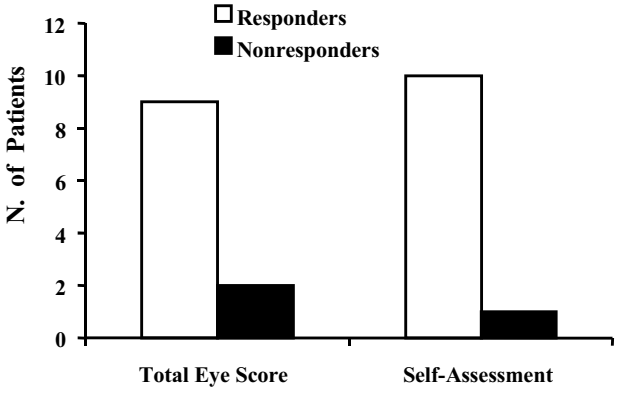

Figure 3. Effects of antioxidants (allopurinol and nicotinamide) on Graves' ophthalmopathy. Responses were evaluated in terms of reduction of the Total Eye Score and of patient's satisfaction at self-assessment evaluation. Derived from Bouzas EA et al.[55].

Because this interesting study is the only one available on the use of antioxidants for GO, it is premature to draw conclusions on their effectiveness and results must be interpreted with caution. Larger, prospective randomized studies are warranted to address this issue. However, the rationale for antioxidant utilization is rather sound, based on in vitro studies, and the side effects of these drugs are very limited. Therefore, in the future the use of antioxidants for GO might be envisioned, at least in light-to-moderate eye disease and as co-adjuvants for more powerful established treatments, like high-dose glucocorticoids.

CYTOKINE ANTAGONISTS

Cytokines play an important role in GO pathogenesis, although they probably are more important for perpetuating the disease than for triggering it[56]. Cytokines exert actions that are relevant for eye disease, such as induction of expression of major histocompatibility class II molecules, heat-shock protein-72 and sICAM-1[57]. In addition, they stimulate orbital fibroblasts to proliferate[58] and to secrete glycosaminoglycans[59].T-cells in the orbital tissue of GO patients have either a Th-1 profile of cytokine production (cell-mediated immunity: IL-2, interferon (IFN-γ, tumor necrosis factor (TNF-α)[60] or a Th-2 pattern (humoral immunity: IL-4, IL-5, IL-10)[61,62], possibly depending upon the stage of the ophthalmopathy (Th-1 in an early stage, Th-2 late in the course of the disease). Based on the above observations, it is evident that blockade of the cascade of events involving cytokines might play an important role in GO management, particularly in the early stage of the disease.

Cytokine blockade can be achieved by different means, i.e., by cytokine receptor antagonists, monoclonal antibodies to cytokines, soluble cytokine receptors, or counterregulatory cytokines[63,64]. Trials with cytokine antagonists have been carried out or are ongoing in some pathophysiological conditions. For example, in the management of rheumatoid arthritis, monoclonal antibodies to human TNF-α[65-67] and soluble IL-1 receptor[68] have been used with variable degree of success[69]. Likewise, clinical trials are ongoing on anti-TNF-α therapies for Crohn's disease, sepsis and myelodisplastic syndromes[70].

As far as GO is concerned, available information is rather limited[1]. A few years ago Tan et al. showed that both soluble IL-1 receptor antagonist (sIL-1RA), which binds to IL-1 receptor but does not activate it, and sIL-1R produced a dose-dependent inhibition of IL-1-induced glycosaminoglycan production in cultured orbital fibroblasts from GO[71]. IL-1RA was also shown to counteract IL-1 effects on human thyrocytes in culture[72]. Thus, at least in vitro, IL-1 antagonists could inhibit the action of IL-1, a proinflammatory cytokine believed to play a pivotal role in the orbital tissue of patients with ophthalmopathy[73]. Interestingly, the expression of IL-1RA in orbital fibroblasts from both Graves' patients and controls could be inhibited by low-dose UV irradiation, but not by dexamethasone[74]: these findings, while unraveling a new mechanism of action of orbital radiotherapy for GO, underscore the concept that glucocorticoids act not only to counteract proinflammatory cytokines, but also to balance agonist and antagonist mediators, thus preventing hyperactivity of the immune system. In a human study, Hofbauer et al.[75] reported that GO patients who responded to orbital radiotherapy had significantly higher baseline sIL-1RA levels and a greater sIL-1RA increase during treatment than patients who did not respond. The value of measuring baseline sIL-1RA levels was not confirmed by Salvi et al.[76] who found similar levels in patients with ophthalmopathy and controls. In addition, baseline sIL-1RA concentration was not predictive of the subsequent response or lack of response to high-dose glucocorticoids[77].

So far, the only available data on the effects of cytokine antagonists in vivo on GO were reported by Balazs et al. using pentoxifylline[78]. This drug, an analogue of methylxanthine theobromine widely used for peripheral vascular disorders, has complex immunomodulatory effects on cytokine production[79]. Pentoxifylline inhibits proliferation and glycosaminoglycan synthesis of cultured orbital fibroblasts derived from GO patients[80]. In addition, this drug blocks glycosaminoglycan production and HLA-DR expression induced by IL-1, TNF-α and IFN-γ in orbital fibroblasts[81]. Pentoxifylline interferes with the second messenger pathways of a variety of cytokines, including TNF-α, IL-1β and transforming growth factor-β[70]. Based on this premise Balazs et al.[78], in a nonrandomized and uncontrolled study, treated 10 patients with moderately severe GO with pentoxifylline (200 mg daily iv for 10 days, followed by 1800 mg/daily orally for 4 weeks, then reduced to 1200 mg daily until the end of a 3-month treatment). Eight patients (80%) responded favorably in terms of an overall evaluation carried out by assesing variations of the Total Eye Score (Figure 4)[78]. Soft tissue changes and proptosis were most responsive, whereas extraocular muscle involvement response was less impressive[78]. Clearly, the results of this preliminary study must be interpreted with caution and randomized and controlled studies are, also in this case, required to assess more accurately the true effectiveness of pentoxifylline. No other study on the use of IL-1 or TNF-α antagonists is available for GO. Such studies are clearly difficult to perform for several reasons: i) Given the complex network of cytokines, it is difficult to ascertain which cytokine(s) should be blocked; ii) It will not be easy to determine the drug dose (administered systemically) that will reach and be effective on orbital tissue; iii) Long-term safety and cost/benefit evaluations are warranted. Topical soluble TNF-α receptor type I suppresses cytokine gene expression and allogeneic corneal transplant in rats[82]. Whether a similar protocol of locally administered cytokine antagonists might in the future be applied to GO is entirely speculative.

TOTAL THYROID ABLATION

GO is a disorder of autoimmune origin, but its pathogenic mechanisms are not fully understood[1]. A popular

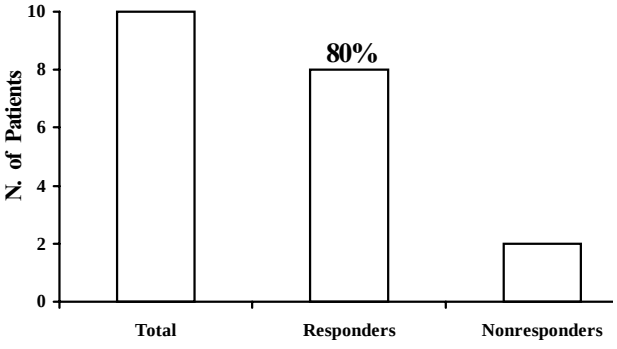

Figure 4. Effects of pentoxifyllline on Graves' ophthalmopathy. Derived from Balazs C et al.[78].

hypothesis links eye disease to the thyroid through the "shared" antigen(s) theory[83]. According to it, the initial event would be represented by the presence of autoreactive T-lymphocytes capable of recognizing and interacting with one or more antigens shared by the thyroid and the orbital tissue[83]. Autoreactive T-lymphocytes would then be recruited in the orbit by systemic and locally produced adhesion molecules and heat-shock proteins; after antigen recognition, a cascade of events would be primed to fibroblast proliferation, preadipocyte-fibroblast differentiation into adipocytes, secretion of glycosaminoglycans and secretion of a complex array of cytokines (responsible for maintenance of the ongoing processes)[1]. The nature of the antigen(s) shared by the thyroid and the orbit is still elusive, but the TSH-receptor is a good candidate[84]. Likewise, the type of orbital cell primarily involved in the reaction is presently undefined but fibroblasts and adipocytes are more likely the culprit than myocytes[84].

If this pathogenic hypothesis is correct, the presence of thyroid tissue bearing the bulk of shared antigen(s) may represent an unfavorable starting point for the development or progression of the ophthalmopathy in subjects who bear the appropriate genetic background and are exposed to environmental risk factors, such as cigarette smoking. While environmental risk factors have been, at least in part, defined, genetic factors remain to be fully elucidated, although they probably play a less relevant role compared to environmental factors[85,86].

The concept that total thyroid ablation reduces thyroid autoimmune phenomena is supported by the observation that total thyroidectomy followed by radioiodine therapy is associated with a progressive decrease and disappearance of circulating autoantibodies in initially antibody-positive thyroid cancer patients who are disease-free after treatment[87]. Therefore, also in the case of GO, total antigen deprivation and autoreactive T-lymphocyte depletion might prove beneficial for eye disease[88]. On the other hand, if orbital autoantigens are not crossreactive with the thyroid, removal of thyroid autoantigens (and autoreactive T lymphocytes) would not affect the autoimmune processes involved in the ophthalmopathy[89]. Furthermore, in well established and longstanding ophthalmopathy, autoimmune reactions ongoing in the orbit might have become independent of the presence or absence of residual thyroid tissue. Thyroid ablation has in the past been considered as a tool to also treat associated ophthalmopathy. However, literature data, derived from nonrandomized studies, are controversial: after initial positive reports[90,91] other clinical trials failed to show any relevant influence of this approach for the ophthalmopathy[92]. Indirect evidence for a link between total thyroid ablation and improvement of eye disease comes from a study showing that the risk of GO progression is higher in patients who require more than one dose of radioiodine than in those who become hypothyroid after the first therapeutic dose[93]. Recent nonrandomized and uncontrolled studies on this issue were performed by DeGroot[94,95]. In one study, 15 patients with severe GO were evaluated; they were in most cases hypothyroid under replacement therapy after treatment for hyperthyroidism; residual thyroid tissue was demonstrated, in spite of the hypothyroid state, by a persisting thyroidal radioiodine uptake >1%[95]. When these patients were further treated by radioiodine therapy, 11 of them (73%) showed an amelioration of ocular parameters, whereas the remaining 4 patients were considered as nonresponders[95] (Figure 5). Of course, these results must be interpreted with caution, since DeGroot's studies were neither randomized nor controlled. However, they must prompt the performance of clinical trials addressing this issue, like the prospective, randomized and controlled study presently ongoing in our Institutions.

PREVENTION

GO prevention might theoretically be carried out at different stages. Eye disease schematically goes through three different stages. Stage 1 is the absence of disease, stage 2 is represented by the absence of clinical disease (but the presence of subclinical ocular involvement), stage 3 is when clinical disease (either active or inactive) is present (Table 4). Progression from stage 1 to stage 2 and from stage 2 to stage 3 does not occur in all patients since about 40-45% of Graves' patients apparently have

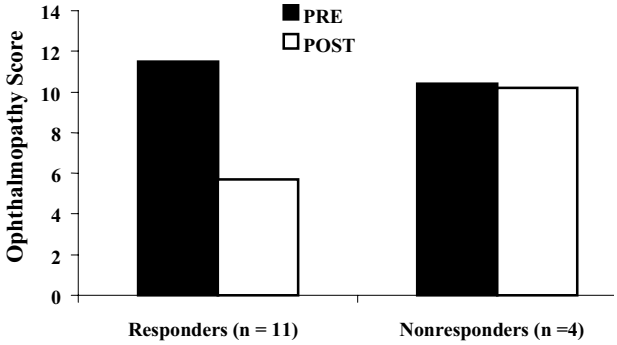

Figure 5. Effects of total thyroid ablation on Graves' ophthalmopathy. Illustrated in the figure are mean changes in the ophthalmopathy score in responders and nonresponders to total thyroid ablation. Derived from DeGroot LJ and Benjasuratwong Y[95].

no ocular involvement, about 50% have sublinical (or mild) ophthalmopathy, and only 3-5% have severe eye disease requiring specific and aggressive treatments[1]. The reason why only a minority of patients develop severe GO is unknown. This disease derives from a complex and not fully understood interplay of endogenous (genetic) and exogenous (environmental) factors[85,86]. At present, preventive intervention can only be carried out on exogenous risk factors. The latter include cigarette smoking[96], thyroid dysfunction, both hyper-[97,98] and hypothyroidism[99] and radioiodine therapy for hyperthyroidism[100-102].

Cigarette smoking is widely used by patients with the ophthalmopathy[103] and is associated with more severe disease[104,105]. Furthermore, smoking reduces the effectiveness of orbital radiotherapy and high-dose glucocorticoids[106]. Interestingly, smoking withdrawal seems to be associated with a decreased risk of occurrence of clinical disease[107]. Accordingly, patients with Graves' disease should be urged to refrain from smoking because this measure may be helpful in preventing the occurrence of subclinical disease (primary prevention), the progression to clinical disease (secondary prevention) and the exacerbation of overt disease (tertiary prevention)[85,86].

Correction of hyperthyroidism or treatment-induced hypothyroidism is also very important for the ophthalmopathy. Restoration of euthyroidism is associated with an amelioration of eye disease[97]. In addition, GO may occur or worsen often after a variable period of hypothyroidism[99]. Thus, a careful control of thyroid function seems essential, at least in terms of secondary and tertiary prevention[7,86]. Whether this should be achieved by thyroid ablation[88] or by a prolonged antithyroid drug treatment[108] remains a matter of controversy.

Radioiodine therapy effects on the ophthalmopathy are controversial, but results of the few randomized studies so far available[103-105] lend support to the concept that this treatment bears a limited but defined risk of causing progression of eye disease, particularly in patients who have associated risk factors, such as preexisting ophthalmopathy, severe hyperthyroidism, high TSH levels, high TSH-receptor antibody levels and cigarette smoking[1] (Table 4). This should not lead to avoidance of radioiodine therapy for Graves' hyperthyroidism because the possible exacerbation of the ophthalmopathy can be prevented by simultaneous administration of middle-dose glucocorticoids[100,102]. Thus, the latter therapeutic measure represents a useful tool, at least in terms of secondary and tertiary GO prevention[86].

It is recommended that earlier diagnosis (and treatment) of hyperthyroidism, as well as earlier diagnosis (and treatment) of the ophthalmopathy, be achieved, but, again, these measures are mostly directed to secondary and tertiary prevention of the disease.

Can we do something in terms of primary prevention? At the present status of understanding of GO pathogenic mechanisms and immunogenetic basis, the answer is no. However, novel approaches might be on the horizon. Oral tolerization might represent a future possible preventive approach. Immune tolerance can be induced by the oral (or nasal) administration of the offending antigen. This procedure was successfully applied to experimental animal autoimmune disorders: soluble oral type II collagen suppresses or reduces the severity of type II collagen-induced arthritis in mice[109]; oral porcine insulin administration suppresses diabetes in nonobese diabetic (NOD) mice[110]; oral administration of myelin basic protein suppresses experimental autoimmune encephalomyelitis[111]; orally administered acetylcholine receptor suppresses experimental autoimmune myasthenia[112]. Oral tolerization has been attempted in human disorders: oral type II chicken collagen was reported to improve chronic rheumatoid arthritis[113]; orally given myelin basic protein decreased recurrences in patients with multiple sclerosis[114]. It should be noted that these encouraging but preliminary results still await confirmation in larger and randomized studies. Oral administration of human thyroglobulin produces immune tolerance in thyroglobulin-induced experimental autoimmune thyroiditis in mice, with suppression of humoral and cell-mediated immune responses and of thyroid pathologic changes[115]; however, oral administration of human thyroglobulin does not influence the incidence of spontaneous and iodine-induced lymphocytic thyroiditis in the BB/Wor rats[116]. Thy-

Table 4. Staging of Graves' ophthalmopathy.

Stage	Definition	Aim of prevention	Methods
I	Absence of disease	Avoidance of GO occurrence	Immmunologic intervention(?); stop smoking
II	Subclinical disease	Avoidance of progression to overt disease	Early diagnosis and treatment of hyperthyroidism and GO; stop smoking; steroid coverage after ^{131}I-therapy
III	Clinical disease	Avoidance of deterioration and complications	Treatment of GO; stop smoking; total thyroid ablation (?)

Table 5. Risk factors for progression of the ophthalmopathy after radioiodine therapy for Graves' hyperthyroidism.

Preexisting ophthalmopathy
Cigarette smoking
Severe pretherapy hyperthyroidism
Uncorrected postradioiodine hypothyroidism
High TSH-receptor antibody levels

roglobulin of thyroid origin has recently been found in the orbital tissue of GO patients[117]. Should thyroglobulin be one of the antigens involved in the pathogenesis of the ophthalmopathy, oral tolerance induction might prove beneficial for the prevention of eye disease. Oral administration of desiccated porcine thyroid preparations to patients with autoimmune thyroid disorders, while not affecting humoral immunity, was associated with slight changes in cell-mediated reactions to TSH-receptor peptides and thyroid peroxidase[118]. Thus, available data are not unequivocal and need to be further confirmed. However, vaccination with the antigen(s) responsible for the cross-reaction and the orbit (e.g., TSH-receptor peptides, the transgenically expressed extracellular domain of the TSH-receptor, thyroglobulin or other antigens possibly intervening in the mechanism of disease) might produce useful preventive effects in patients who are genetically susceptible to the disease (Table 6). Another possible immune intervention might be represented by the use of specific antigen-presenting dendritic cells (loaded, for example, with TSH-receptor peptides) which do not stimulate Th1 cells but cause a condition of tolerance/anergy. These immunologic interventions imply that we can identify subjects who in the future will develop Graves' disease and ophthalmopathy. This is not possible at the moment. Accordingly, these putative novel approaches are presently theoretical because the mechanism of disease and the antigen(s) primarily involved, as well as the genetic background conferring susceptibility to GO, remain to be fully clarified.

Table 6. Future interventions for Graves' ophthalmopathy.

Cytokine antagonists	Sound rationale from in vitro studies; use in vivo in other autoimmune disorders (e.g., rheumatoid arthritis); only one preliminary study of the effect of pentoxyfilline on GO
Antioxidants	Sound rationale from in vitro studies; only one pilot study of the effects of allopurinol and nicotinamide on GO
Immunologic intervention	Oral tolerization or vaccination with offending antigen(s); preliminary results in other autoimmune disorders
Immunosuppressive drugs	Evaluation of methotrexate: possible use as a second-line drug allowing a glucocorticoid-sparing effect
Total thyroid ablation	Aimed at removal of autoreactive intrathyroidal T-lymphocytes and shared antigen(s) crossreacting with thyroid and orbit; only few nonrandomized and uncontrolled studies available; possibly useful in the early stage of eye disease

CONCLUDING REMARKS

GO represents a complex therapeutic challenge. The outcome of available treatments is often disappointing, and at the end of follow-up many patients are dissatisfied with the results obtained[3]. Once the disease is established, it is difficult to obtain its complete regression. Accordingly, novel treatments capable of intervening on the mechanisms of disease before GO develops or early in its course will be welcome (Table 6). Although the progress in our understanding of GO pathogenesis has been more impressive than that in its management, either novel treatments (SMSa) or novel modalities of established treatments (iv glucocorticoids) have provided encouraging results for overt eye disease. In the field of immunosuppressive drugs, a possible role of low-dose methotrexate is currently being evaluated (at least in mild-to-moderate ophthalmopathy) and the very preliminary results are promising. The possible role of antioxidants deserves to be evaluated. Early intervention in both GO and associated hyperthyroidism is a necessary prerequisite to improve whatever treatment outcome. The most promising novel therapeutic approach is probably represented by cytokine antagonists: these drugs might, indeed, interrupt the vicious cycle of reactions that occur in the orbit, are mediated by cytokine secretion and lead to perpetuation of eye disease. They have been used in other autoimmune disorders (particularly rheumatoid arthritis) with encouraging results: they might also work on GO. The only available report on cytokine antagonists for GO refers to the use of pentoxifylline in a pilot study. Further to the hypothesis that GO may occur in the context of autoimmune reactions to antigen(s) shared by the thyroid and the orbit, total thyroid ablation might be useful to arrest progression of the ophthalmopathy. GO prevention would be desirable rather than treatment of established disease. Presently our possibilities are limited to secondary and tertiary prevention, but in the (near?) future oral tolerance or vaccination with the autoantigen(s) responsible for triggering eye disease

might be feasible and allow primary prevention of the disease.

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