

MEDICAL MANAGEMENT OF EXTRATHYROIDAL MANIFESTATION OF GRAVES DISEASE

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ABSTRACT

Objective: To review preventive measures and the current medical management of extrathyroidal manifestation of Graves disease and to provide an overview of potential immune therapies.

Methods: A literature review of investigative trials of treatments for Graves disease and its extrathyroidal manifestations.

Results: Given new knowledge of the stages of the autoimmune cascade responsible for the development of these extrathyroidal manifestations, the possibility has been raised of performing randomized trials of agents shown to provide benefits in other immune conditions. Two randomized trials on the efficacy of rituximab in moderate-to-severe Graves ophthalmopathy have reported conflicting results.

Conclusion: Additional studies of rituximab and other agents are needed before they become routinely used in treating Graves disease. Meanwhile, the standard medical therapy for moderate-to-severe ophthalmopathy is intravenous (IV) or oral corticosteroids and, for dermopathy, local corticosteroid application with occlusive dressing. Because major adverse effects such as life-threatening

hepatic failure can occur with very high doses of IV prednisolone, the cumulative total dose should not exceed 8 g. (Endocr Pract. 2014;20:1333-1344)

Abbreviations:

IGF-1R = insulin-like growth factor 1 receptor; **IL** = interleukin; **IV** = intravenous; **RAI** = radioactive iodine; **TSHR** = thyrotropin receptor

INTRODUCTION

In Graves disease, hyperthyroidism develops because of the stimulating action of thyrotropin receptor (TSHR) antibodies (1). The systemic immune process of the disease leads to extrathyroidal manifestations (2). Among patients who have such manifestations, 90% to 95% have concomitant or previous history of hyperthyroidism, and 5% to 10% are euthyroid or hypothyroid and may have never had hyperthyroidism (2-4).

Known extrathyroidal manifestations include ophthalmopathy (Fig. 1) (5), dermopathy (6) (Fig. 2), and acropachy (7) (Fig. 3). The pathogenesis of these manifestations is complex. The existing knowledge suggests that the interaction of TSHR antibodies with TSHRs expressed in fibroblasts in retroorbital and dermal tissues initiates an immune cascade. Fibroblast proliferation and excessive glycosaminoglycan production ensue (1,3,8). A role for insulin-like growth factor 1 receptor (IGF-1R) antibodies was recently postulated in this process (1,3).

In the present review, we discuss preventive measures and current medical management of extrathyroidal manifestations, with an overview of potential immune therapies on the horizon.

Epidemiology of Extrathyroidal Manifestations in Graves Disease

In a population-based study in the midwestern United States, the incidence of Graves ophthalmopathy per year was 16.0 per 100,000 population for females and 2.9 per

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100,000 population for males (4). Among patients who had ophthalmopathy, 4% had dermopathy. In severe cases of ophthalmopathy, 13% have dermopathy (2), and 20% of patients with dermopathy have acropachy, mainly in the form of digital clubbing (9). Hyperthyroidism is usually

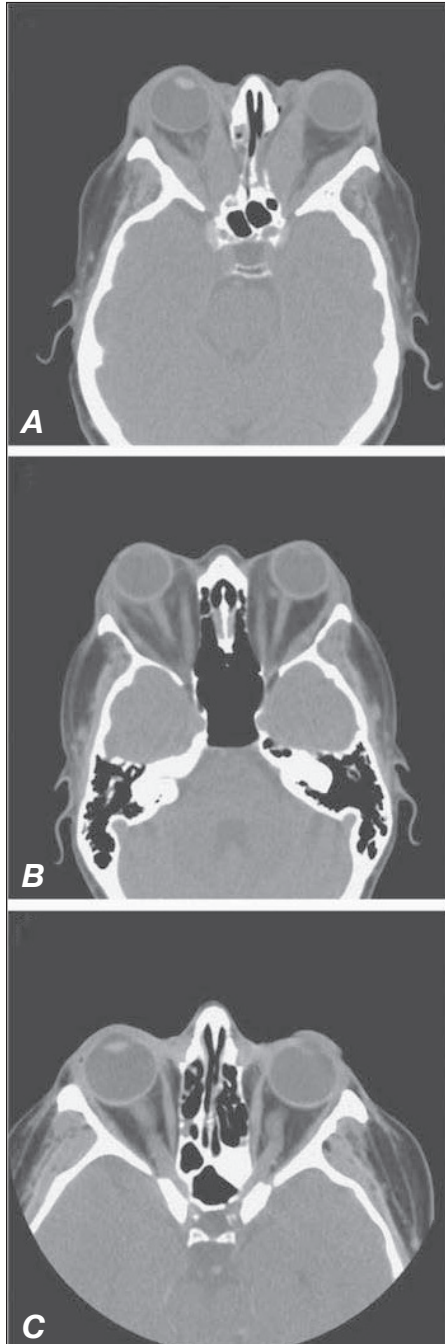


Fig. 1. Computed tomography scans of patients with Graves ophthalmopathy and a healthy patient. *A*, Proptosis in Graves ophthalmopathy. The extraocular muscles show generalized enlargement. *B*, Marked proptosis with asymmetrical extraocular muscle involvement. *C*, Normal orbit, included for comparison. Adapted from Bahn (5), used with permission.

noted first, ophthalmopathy next, and dermopathy later (10). The development of dermopathy requires a longer and more severe immune process (6). Tobacco use is a major risk factor (Box) for extrathyroidal manifestation development and severity (11,12). It is likely that if the number of smokers is reduced in a population, the incidence of these manifestations will also be reduced. It has been shown that decreased smoking, a greater awareness of ophthalmopathy, and improved diagnosis and management of Graves hyperthyroidism modify the course of ophthalmopathy and contribute to a lower prevalence of ophthalmopathy (13-15).

Preventing the Development and Worsening of Extrathyroidal Manifestations

Tobacco Cessation

An analysis of 15 published studies indicated that a causal relationship exists between tobacco use and both the development and severity of Graves ophthalmopathy (16). An investigation of 178 patients with thyroid dermopathy showed that 75% were smokers (6,9). Among the patients with acropachy, 81% of females and 75% of males were smokers (9). Some studies have reported increased adipogenesis in orbital fibroblast cultures exposed to cigarette smoke extract (11). Despite this evidence, the exact mechanism of tobacco is not clear. The strength of observational studies for this association suggests that patients with or at risk for Graves disease who use tobacco products should enter a rigorous tobacco cessation program.



Fig. 2. Bilateral symmetrical thyroid dermopathy (pretibial myxedema).



Fig. 3. Hand radiograph of a patient with thyroid acropachy. Notably, the proximal phalanges are involved in the periosteal reaction and clubbing.

Box Factors Predictive of Worsening of Graves Ophthalmopathy and Dermopathy
Tobacco use
Increased serum T ₃ level
High serum level of TSI or TSHR antibody
Presence of thyroid dermopathy
Failure to rapidly control hyperthyroidism
RAI therapy without concomitant corticosteroids, particularly for smokers
Longer duration of hypothyroidism before therapy and after RAI therapy
Progressive activity of ophthalmopathy
Large goiter
Male sex and older age?
Abbreviations: RAI = radioactive iodine; TSHR = thyrotropin receptor; TSI = thyroid-stimulating immunoglobulin; T ₃ = triiodothyronine.

Effect of Stress on Immune Processes

Potential effects of stress hormones on T cells, thereby causing an immune imbalance, may be a possibility in subjects with Graves disease (17). Although the clinical evidence is largely anecdotal, it is likely that the psychological and emotional burden of extrathyroidal manifestations are major factors affecting patient quality of life. Appropriate supportive management of these issues is important when treating subjects with Graves disease (18).

Optimal Management of Thyroid Dysfunction

The experience of most thyroidologists and the findings of some observational studies suggest that uncontrolled hyper- and hypothyroidism may have adverse effects on extrathyroidal manifestations of Graves disease (19-21). A recent study suggested that thyroid dysfunction has a stronger adverse effect on the exacerbation of existing ophthalmopathy than therapy type (22). Thus, experts recommend that hyperthyroidism be managed expeditiously and treatment-related hypothyroidism be resolved as quickly as possible (20).

Effects of Type of Hyperthyroidism Treatment

Radioactive Iodine Therapy

Therapy with radioactive iodine (RAI) may be associated with a 15% increased risk of worsening ophthalmopathy, though only one-third of the 15% increased risk is persistent (23). In randomized studies, this worsening did not occur with antithyroid therapy alone or in patients who took a 3-month course of oral prednisone after RAI therapy (24).

Recent studies indicate that a 6-week course of corticosteroid given with RAI therapy may be protective for

eye disease (25). One investigation suggested that 10% of patients will develop ophthalmopathy after RAI therapy (26). In that study, oral glucocorticoid therapy did not prevent activation of ophthalmopathy, but 9 patients who received intravenous (IV) glucocorticoid did not experience ophthalmopathy activation or worsening. These studies have led to a reluctance of endocrinologists to use RAI ablative therapy in patients with Graves disease who have evidence of ophthalmopathy (27). Guidelines published by the American Thyroid Association and American Association of Clinical Endocrinologists recommend that concomitant corticosteroid therapy be considered for patients with mildly active ophthalmopathy without other risk factors who select RAI therapy (28). Patients who have similar eye disease, are smokers, or have other risk factors for ophthalmopathy should definitely receive concurrent corticosteroids with RAI therapy, and patients with active, moderate-to-severe sight-threatening ophthalmopathy should receive methimazole or undergo surgery (28). For inactive ophthalmopathy, the guidelines specify that RAI therapy without concurrent corticosteroids, methimazole, or thyroidectomy is equally acceptable.

Thyroidectomy

Theoretically, total thyroid ablation with either surgery or RAI treatment should have beneficial long-term effects on thyroid autoimmunity because ablation eliminates the antigen source. Hence, it should also be beneficial for extrathyroidal manifestations. One randomized study comparing thyroidectomy with thyroidectomy plus an ablative RAI dose (i.e., total ablation) showed that although total thyroid ablation allows the best possible outcome and an improvement of ophthalmopathy within a shorter period,

the final eye status was not different in long-term follow-up than for thyroidectomy alone (29). A more recent trial of moderate-to-severe ophthalmopathy compared randomized thyroidectomy versus thyroidectomy followed by recombinant human thyrotropin-stimulated iodohippurate sodium iodide 131 ablation (30). The investigators reported better results with the addition of RAI than with thyroidectomy alone. It is unclear whether high-dose RAI ablation alone, which is more practical, would achieve the same results. If RAI treatment is used in cases with moderate-to-severe extrathyroidal manifestations, the practice at my institution is to administer a high ablative dose of RAI with concurrent corticosteroid therapy. Other experts also recommend a similar approach (31,32).

Do Antithyroid Medications

Have Immunosuppressive Action?

Remission of Graves disease is 50% after 18 months of antithyroid therapy, whereas the rate of spontaneous remission or remission with β -blockers is much lower. The debate has been whether this disparity results from adverse effects of thyrotoxicosis on the immune system or the immunosuppressive action of antithyroid drugs (33). Evidence from in vitro and in vivo studies suggests that these medications may have immunosuppressive actions. Thionamide drugs may interfere with immunoglobulin production (34). Methimazole may reduce major histocompatibility complex class I gene expression and inhibit interferon- γ -induced expression of the major histocompatibility complex class II gene in thyroid epithelial cells (35). However, if the immunosuppressive action of these medications is indeed significant, then a dose-response correlation should occur, and a better outcome would result from the block-and-replace method in hyperthyroidism management. This plan has not been shown to be helpful in the immune process of Graves disease when block-and-replacement treatment was compared with carbimazole dose adjustment in a controlled prospective study (36). Although evidence is not conclusive for clinically significant immunosuppressive actions of antithyroid medications, both the immunosuppressive effect of antithyroid medications and the normalization of thyroid function have beneficial effects regarding the prevention and worsening of extrathyroidal manifestations in Graves disease.

Selenium Replacement

Selenium is considered as an antioxidant that possibly affects improvement of autoimmune thyroid disease and reductions in thyroperoxidase antibodies (37). The European Group on Graves Orbitopathy recently reported on the effects of selenium supplementation at 100 mcg twice daily for 6 months and a 6-month follow-up (38). This multicenter randomized, double-blind, placebo-controlled trial included 159 patients with mild Graves

orbitopathy. Compared with placebo, selenium resulted in a significantly higher improvement rate in quality of life and a significantly lower rate and frequency in eye disease progression. Although the clinical activity score improved in all groups, the improvement rates at 6 and 12 months were significantly higher in the selenium-treated group. Because no adverse effects from this therapy were noted, it is reasonable to use selenium as an adjunctive therapy in ophthalmopathy and perhaps as a preventive measure in all patients with Graves disease (39).

Preventive Management Specific to Thyroid Dermopathy

The effects of trauma and local factors such as lower extremity dependency are important in dermatopathy. Dermopathy develops in unusual areas exposed to trauma and in scar tissues and is likely to be aggravated by obesity that worsens the lower extremity dependency (40). Weight loss should be recommended for individuals at risk for dermatopathy who have a high body mass index (7). In addition, patients at risk for dermatopathy should generally avoid unnecessary surgical trauma to a lower extremity (7).

Medical Management

Most patients with ophthalmopathy (74%) do not require specific therapies; supportive measures for the eyes are usually adequate (41). For some patients with moderate-to-severe disease, multiple medical and surgical treatments may be required at different stages. The treatments should be applied in the appropriate sequence. Medical therapy should only be used in the active phase of the disease, and surgical rehabilitative therapies such as orbital decompression and eye muscle surgery should be administered in the inactive phase (42,43). For those who require specific treatments, immunosuppressive therapies (systemic corticosteroids) and surgical rehabilitation may be needed (41).

Systemic Corticosteroid Therapy

The standard therapy for Graves ophthalmopathy is systemic corticosteroids. Oral prednisone (60 mg/day) is superior to cyclosporine (7.5 mg/kg), but a combination of cyclosporine and corticosteroids is superior to corticosteroids alone (44). European studies have demonstrated the superiority and improved safety profile of IV pulse therapy over oral corticosteroid therapy (40%) (45-47). Investigators have suggested that the response rate is 80% with a 12-week course of high-dose IV glucocorticoid pulses (31). However, major adverse effects such as fatal hepatic failure can occur. Comorbid conditions should be excluded before IV corticosteroid therapy is initiated, and the total prednisolone dose should not exceed 8 g (45-47).

Active ophthalmopathy for most patients responds to IV prednisolone as early as 6 to 8 weeks; for patients

whose ophthalmopathy does not respond, therapy should be switched to other treatments alone or in combination with corticosteroids (47).

Orbital Radiotherapy

A Mayo Clinic study of sham radiotherapy, with the other eye as the control and a crossover analysis, did not find a benefit following orbital radiotherapy in subjects with mild-to-moderate Graves ophthalmopathy (48). A 3-year long-term follow-up with no control group concluded that orbital radiotherapy was neither effective nor innocuous and did not seem to be indicated for mild-to-moderate ophthalmopathy (49). Another randomized double-blind trial of sham radiotherapy (44 patients with mild ophthalmopathy in each group) demonstrated improvement in eye motility but no benefit in quality of life or prevention of worsening ophthalmopathy (50).

A 2012 Cochran Database systematic review of 5 randomized trials including a total of 244 participants did not allow a reliable meta-analysis (51). However, the reviewers concluded that orbital radiotherapy was more effective than sham radiotherapy for managing mild-to-moderate ophthalmopathy and that radiotherapy plus corticosteroids was more effective than corticosteroids alone. In addition, a 2008 position paper published by the American Academy of Ophthalmology concluded that extraocular motility may improve with orbital radiotherapy, but proptosis, lid retraction, and soft tissue changes do not improve (52). The investigators considered that radiation-induced retinopathy (53), although rare even in nondiabetic patients, is a risk of this therapy (53). Thus, the benefits and specific indications of orbital radiation continue to be controversial.

Somatostatin Analogs

Reports of uncontrolled studies had suggested possible benefit from octreotide therapy in ophthalmopathy (54) and dermopathy (55). A double-blind placebo-controlled trial of 9 months with 30-mg long-acting octreotide treatment every 4 weeks versus placebo in 53 euthyroid patients with active ophthalmopathy showed significant soft tissue reductions in both groups regarding inflammation and clinical activity scores (56). No therapeutic effect of octreotide was noted other than what could be related to the natural course of mildly severe ophthalmopathy. Another prospective double-blind placebo-controlled study of 35 similar patients showed greater improvement of clinical activity scores in the treated group (57); however, because of some differences in baseline values and overrepresentations of higher clinical activity score in the treated group, no firm benefit of octreotide was shown except for a significant improvement in lid retraction.

In conclusion, octreotide therapy does not appear promising in the management of ophthalmopathy or dermopathy associated with Graves disease.

IV Immunoglobulin

In a study comparing IV immunoglobulin at a dosage of 1 g/kg given 2 days per week for 3 weeks versus prednisone in a 20-week therapy for Graves ophthalmopathy, the investigators noted equal results for immunoglobulin and prednisone (58). All 7 patients with ophthalmopathy and pretibial myxedema treated with high-dose immunoglobulins reported improvement of dermopathy (59). In contrast, a study of 10 patients with ophthalmopathy noted no benefit (60). It does not appear that this therapy is indicated for extrathyroidal manifestations.

Apheresis

Combined plasmapheresis and rituximab treatment was reported to be beneficial in a single case of severe dermopathy with elephantiasis (61). In a randomized trial of 20 patients with severe ophthalmopathy who received IV glucocorticoids, multiple sessions of apheresis were performed in 10 patients. Improvement occurred sooner and was more pronounced in the apheresis group (62). No change in proptosis or eye muscle involvement was noted. The long-term results were not clear; therefore, its benefits continue to be questionable.

New Suggested Immune Therapies

Several agents have been evaluated in pilot studies with promising results. Few other agents have shown potential benefits according to *in vitro* studies. Various agents that block the immune cascade also merit future studies (Fig. 4).

Rituximab

Rituximab is a chimeric monoclonal antibody that targets CD20, depleting B cells and blocking the activation and differentiation of circulating B lymphocytes. The end results are decreased cytokine secretion, antigen presentation, and T-cell activation. It has been used effectively for treatment of many autoimmune conditions.

Preliminary uncontrolled studies have shown benefits of rituximab in Graves ophthalmopathy. Rituximab therapy after IV glucocorticoid treatment showed improvement in all 9 patients included in 1 study at 16 months (63). One of these patients had dermopathy that also improved. In that study, TSHR antibodies were reduced in all patients, but another investigation did not find a reduction in TSHR antibody levels (64). A recent literature review concluded that the current evidence is insufficient to support rituximab use in ophthalmopathy and emphasized a need for randomized studies investigating rituximab versus placebo or corticosteroids in patients with active ophthalmopathy (65).

Salvi et al (66) recently reviewed the literature and concluded that although controlled trials are needed before proposing rituximab as a novel therapeutic tool in Graves

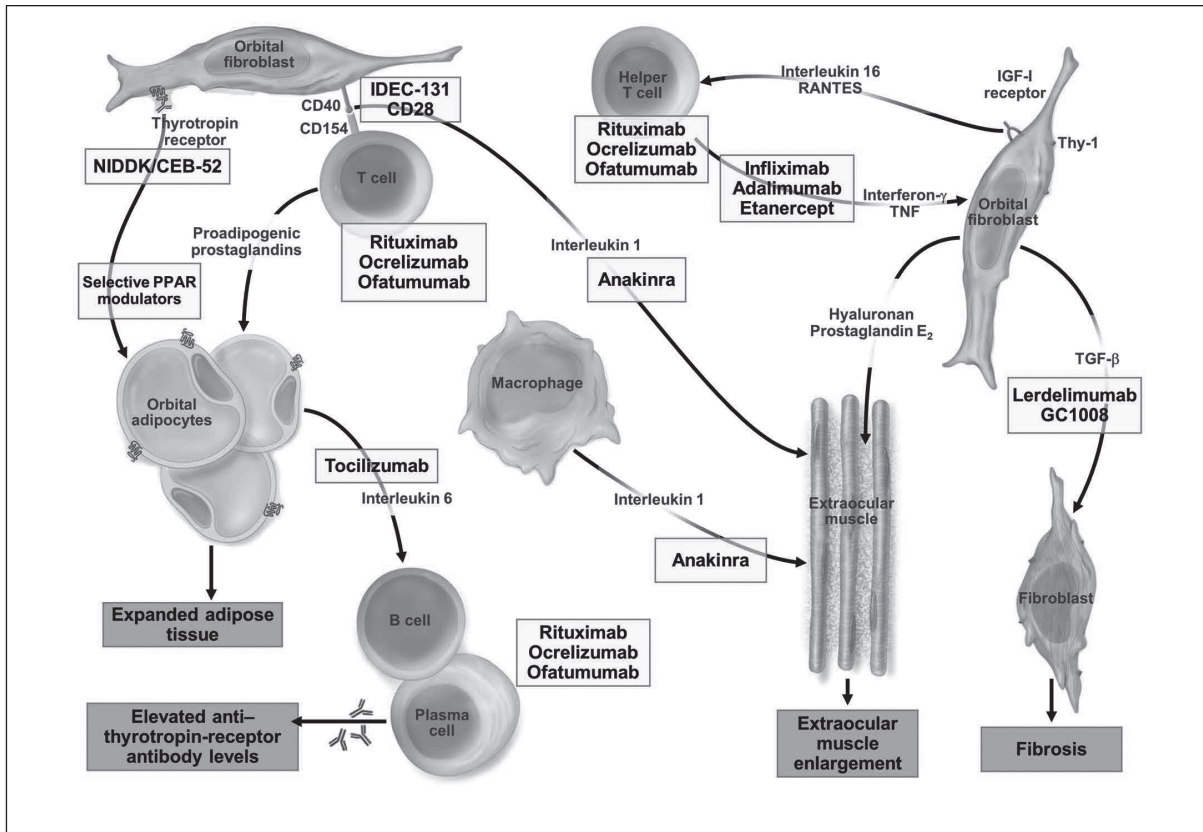


Fig. 4. Model of interactions between orbital fibroblasts and the autoimmune process leading to tissue changes in Graves ophthalmopathy. Potential therapeutic candidates (shown) should be assessed in randomized studies to determine their abilities to ameliorate the extrathyroidal manifestations of Graves disease. *IGF-1* = insulin-like growth factor 1; *PPAR* = peroxisome proliferator-activated receptor; *TGF-β* = transforming growth factor β; *TNF* = tumor necrosis factor. Adapted from Bahn (5), used with permission.

orbitopathy, the available information of 43 patients suggests that rituximab significantly improves the activity and severity of ophthalmopathy. Controlled studies should also provide guidance on whether rituximab should be used in all active cases or only in those unresponsive to other therapies. The data reported on rituximab therapy in ophthalmopathy suggest that B-cell depletion may be pursued shortly after diagnosis, not only as a therapeutic option when standard immunosuppression has failed. Without evidence from confirmatory randomized studies and because of the natural course of ophthalmopathy and the uncontrolled nature of the current reports, no definite recommendations can be made.

Two randomized studies were reported at the 83rd Annual Meeting of the American Thyroid Association in 2013; however, the results were conflicting. In a Mayo Clinic study, 25 patients with moderately severe active ophthalmopathy who were not opting for corticosteroid therapy and did not require orbital decompression were randomly assigned to placebo ($n = 12$) or rituximab ($n = 13$) (67). In each group, ophthalmopathy improved in 50% of patients. The need for decompression within 12 months

of drug infusion was more common in the rituximab group. Although the adverse effects of rituximab were substantial, no infection occurred. This study concluded that for patients with active, moderately severe, progressive ophthalmopathy of 1-year duration, rituximab does not offer a therapeutic benefit and is not indicated. Whether patients with shorter-duration ophthalmopathy might benefit from this treatment is unknown.

In the second randomized study presented at the 2013 American Thyroid Association meeting, Salvi (68) reported impressive positive results of rituximab therapy in Graves ophthalmopathy from an Italian study. The patients were randomly assigned to IV methylprednisone ($n = 16$) or rituximab ($n = 16$). In both groups, 6 patients had received previous corticosteroid therapy. The patients initially received 1,000 mg of rituximab in 2 doses, but the dose was decreased to 500 mg after 2 adverse reactions. After 12 weeks of treatment, no difference was found in the 2 groups, but after 24 weeks, 93% of patients in the rituximab group had experienced improvement in their ophthalmopathy versus 69% of patients in the corticosteroid group.

The designs of these 2 randomized studies differ. In the Mayo Clinic study, the control group received placebo (67); in the Italian study, the control group received IV corticosteroid (68). The rituximab dose was less in the Italian study, and 6 patients in each arm had prior corticosteroid therapy. The duration of ophthalmopathy was shorter in the Italian subjects, but more were smokers and had more severe disease. In addition, patients were at different disease stages in the 2 studies. Given these conflicting results, the evidence is insufficient to support routine use of rituximab in patients with ophthalmopathy and dermopathy at this time. Additional randomized studies are needed to compare rituximab with placebo and standard corticosteroid therapy before recommending evidence-based guidelines on the efficacy and safety of rituximab for extrathyroidal manifestations of Graves disease (65).

Etanercept

Etanercept, an antitumor necrosis factor drug, was used in a pilot study to treat 10 patients with recent onset, mildly-to-moderately severe ophthalmopathy (69). All patients were treated with 25-mg subcutaneous etanercept injections twice weekly. Six patients (60%) reported moderate to marked improvement. However, despite a potential for benefit, no results of randomized studies of etanercept are available to recommend it at this point.

Small-Molecule TSHR Antagonists

Hyaluronan production is a fibroblast function activated through TSHR signaling and is important in the pathogenesis of Graves ophthalmopathy and dermopathy. Thus, TSHR antagonists may prove effective in its treatment or prevention (70). Recently, monoclonal antibodies and small-molecule ligand TSHR antagonists have been developed (1).

Low-molecular-weight thyrotropin analogs called small molecules are compounds with agonist and antagonist actions on TSHR. Rapid advances in this field in the coming years will lead to clinical trials of small molecules related to TSHR for Graves disease management (71). For example, NCGC00229600 is a recently developed drug-like small-molecule inverse agonist of TSHR that binds to TSHR and blocks basal and stimulated signal transduction. In a culture of fibroblasts from a patient with Graves ophthalmopathy, the compound inhibited basal cyclic adenosine monophosphate and hyaluronan production in a dose-dependent manner (70). The authors of this *in vitro* study suggested that small-molecule TSHR antagonists may prove effective in the treatment or prevention of Graves ophthalmopathy in the future. These molecules have been shown to inhibit TSHR antibody-induced orbital fibroblast functions involved in the pathogenesis of Graves ophthalmopathy (70,72).

In another study, another novel low-molecular-weight TSHR antagonist, Org-274179-0, was shown to inhibit

cyclic adenosine monophosphate production induced by recombinant human thyrotropin and Graves TSHR antibodies in cultured and differentiated orbital fibroblasts from patients with Graves ophthalmopathy (73). These findings suggest that druglike TSHR antagonists may have a role in the treatment of Graves ophthalmopathy (74).

IGF-1R Antagonist

A role has recently been postulated for IGF-1R antibodies in the pathogenesis of extrathyroidal manifestations of Graves disease. Autoimmunity against IGF-1R is not specific for Graves disease but may contribute to ongoing immune reactions, including the Graves immune process (3). This theory raises the possibility that IGF-1R antibodies may be effective in treating Graves ophthalmopathy and dermopathy.

An ongoing clinical trial is investigating a compound named RV001 at Mayo Clinic and several other centers. It binds with high affinity and selectivity to human IGF-1R and prevents its activation. It also inhibits hyaluronic acid synthesis induced by a TSHR stimulatory antibody.

Enalapril

Enalapril has antiproliferative and hyaluronan-suppressing actions in both Graves and control fibroblasts, but no clinical studies are available (75).

Thalidomide

The immunosuppressive drug thalidomide has been used to treat other autoimmune diseases. Recently, it was reported to dose-dependently inhibit the adipogenesis of 3T3-L1 preadipocytes and orbital fibroblasts of patients with Graves ophthalmopathy by downregulating peroxisome proliferator-activated receptor expression. Thalidomide also inhibits expression of TSHR, tumor necrosis factor, and interleukin (IL)-6 (76).

Mycophenolate

Mycophenolate is the most commonly used immunosuppressive therapy for preventing transplant rejection. It has been used for retroperitoneal fibrosis (77) and Riedel thyroiditis (78). It inhibits the *de novo* pathways of guanosine nucleotide synthesis, on which T and B lymphocytes are critically dependent. A European multicenter study of Graves ophthalmopathy is under way comparing combination therapy of corticosteroid and mycophenolate with corticosteroid alone. The response rate will be assessed at 24 and 36 weeks (79).

Management Specific to Thyroid Dermopathy

In most dermopathy cases, patients have severe ophthalmopathy that is usually treated with corticosteroids (7). Thus, systemic immune therapy used for eye disease is effective in preventing or improving dermopathy. In the

future, whatever therapies are shown to improve ophthalmopathy can be used for dermatopathy.

All preventive measures for ophthalmopathy described herein also apply to dermatopathy and acropachy. Some local measures are specific to dermatopathy, such as avoidance of trauma (including surgical), appropriate shoes, support stockings, weight reduction, and reduction of dependency on lower extremities (6,40). In most dermatopathy cases, the application of local corticosteroids under an occlusive dressing is adequate. Midpotency corticosteroids, such as fluocinolone acetonide, or high-potency clobetasol propionate or triamcinolone cream base 0.05% to 0.1% under plastic wrap occlusive dressing can be used for 12 hours per day for 4 to 6 weeks (6,40). Athletic wrap compression stockings with 20 to 40 mm Hg of pressure and, in severe cases, intermittent pump use (as employed for lymphedema), are also helpful. Complete decompressive physiotherapy, manual lymphatic drainage, manual massage, multilayered low-stretch compressive bandaging, and exercise to create a pump under a graduated bandage are also beneficial in severe cases, including elephantiasis forms (80). Surgical excision should be avoided. Intralesional corticosteroid injection with mesodermic needles have been reported, with notable resolution of dermatopathy (81). More studies are needed in larger patient groups before this method is routinely used. Tacrolimus ointment with local clobetasol propionate therapy was reported to be effective in 1 patient (82). For local corticosteroid therapy to be effective, treatment should start early in the disease process; advanced cases, such as elephantiasis, do not respond well (40).

Isolated case reports of systemic immune therapies exclusively for dermatopathy including immunoglobulin IV, plasmapheresis, and rituximab have been reported with variable results. Plasmapheresis plus rituximab was beneficial in a single case of severe dermatopathy with elephantiasis (61).

No specific treatment is available for thyroid acropachy other than therapy for the basic immune process and associated dermatopathy. Occasionally, painful periostitis of acropachy requires pain management or anti-inflammatory agents.

Other Potential Therapies for Future Trials

Multiple other agents have been developed to treat other immune conditions and are potential targeted therapies for extrathyroidal manifestations of Graves disease (Table 1). Given the new understanding of the pathogenesis of extrathyroidal manifestations, inhibitors of factors involved in the immune cascade are candidates for trials. They include inhibitors of IL-1 (gevokizumab) (83), blockers of CD28-mediated costimulatory pathways (abatacept) (84), human anti-B-cell-activating factor monoclonal

antibody (belimumab) (85), tumor necrosis factor inhibitors (infliximab) (86), transforming growth factor β -blocking antibodies (lerdelimumab) (87), IL-6 blockade therapy (tocilizumab) (88), and IL-1 receptor antagonist (anakinra) (89).

CONCLUSION

Improved understanding of the pathogenesis of extrathyroidal manifestations has opened the door for trials of new immune therapies; however, uncertainty continues regarding their efficacy and safety. Almost 80% of ophthalmopathy cases resolve with time and require only supportive measures. For moderately severe ophthalmopathy, rapid normalization of thyroid function and systemic corticosteroid therapy remain standard. When RAI therapy is administered, consideration also should be given to concurrent corticosteroid therapy for patients at increased risk for extrathyroidal manifestations.

European studies have documented the superiority of pulse prednisolone therapy to oral corticosteroid therapy. Because major adverse effects such as fatal hepatic failure have been reported with very high doses of intravenous prednisolone, the cumulative total dose should not exceed 8 g. A total dose of 4 to 5 g is usually recommended for most cases. Orbital decompression should be considered for patients with sight-threatening eye disease or for those who do not improve following corticosteroid therapy.

The benefits of orbital radiotherapy are controversial, and this treatment is not used in my institution. Other therapeutic measures such as IV immunoglobulin and apheresis have been reported to have marginal benefits in nonrandomized studies. Cyclosporine may offer an added benefit when combined with corticosteroid therapy.

Biotherapies targeting B cells are promising treatments for Graves ophthalmopathy. Two randomized rituximab trials reported different conclusions; thus, more randomized studies are needed before recommending its use to ameliorate extrathyroidal manifestations of Graves disease. Newer therapies on the horizon will target different levels of the pathogenic process and various stages of immune cascade activation. They include small-molecule ligand antagonists of TSHR, anti-IGF-1R antibodies, and cytokine inhibitors. Large-scale randomized trials of these agents are expected in the near future. For Graves dermatopathy, early local corticosteroid therapy is effective and usually adequate. Systemic therapy solely to treat dermatopathy is rarely needed.

DISCLOSURE

The author has no multiplicity of interest to disclose.

Table 1
Potential Therapeutic Targets in Graves Ophthalmopathy and Dermopathy^a

Target	Current Agents	Description and Potential Benefit
TNF	Infliximab, adalimumab	TNF-specific monoclonal antibodies: reduction in inflammation, leukocyte recruitment, and hyaluronan production
TNF receptor	Etanercept	TNF receptor–IgG Fc fusion molecule: reduction in inflammation, leukocyte recruitment, and hyaluronan production
IL-1 receptor	Anakinra	IL-1 receptor antagonist: reduction in inflammation, leukocyte recruitment, and hyaluronan production
IL-6 receptor	Tocilizumab	IL-6 receptor-specific monoclonal antibody: reduction in inflammation, leukocyte recruitment, and hyaluronan production
TGF- β	Lerdelimumab, GC1008	TGF- β -specific monoclonal antibodies; reduction in fibrosis
Oxygen free radicals	Selenium	Essential trace element: anti-inflammatory activity
CD20	Rituximab, ocrelizumab, ofatumumab	Partially or fully humanized CD20-specific monoclonal antibodies: decreased antigen presentation and T-cell activation, possible modulation of anti-TSHR antibody production
CD3	ChAglyCD3	Fc-mutated CD3-specific monoclonal antibody: induction of tolerance
CD28	Abatacept	CTLA-4-immunoglobulin recombinant protein: modulation of co-stimulatory pathways
CD154	IDEC-131	Humanized CD154-specific monoclonal antibody: modulation of costimulatory pathways
PPAR- γ	Selective PPAR modulators	Novel selective PPAR- γ antagonists: reductions in inflammation and orbital adipogenesis
Somatostatin receptor	SOM230	Synthetic high-affinity somatostatin analog: inhibition of orbital preadipocyte proliferation
TSHR	NIDDK/CEB-52	Low-molecular-weight TSHR antagonist: inhibition of orbital adipogenesis and hyaluronan production
IGF-1 receptor	IGF-1 antagonist (RV001)	High affinity to the IGF-1 receptor: potentially inhibiting hyaluronan production and attenuating immune process
Immunosuppressive	Thalidomide	Inhibitor of adipogenesis: downregulation of PPAR- γ
Immunosuppressive	Mycophenolate	Inhibitor of inosine monophosphate: effectively inhibits on T- and B-lymphocytes

Abbreviations: IGF-1 = insulin-like growth factor 1; IgG = immunoglobulin G; IL = interleukin; PPAR = peroxisome proliferator-activated receptor; TGF = transforming growth factor; TNF = tumor necrosis factor; TSHR = thyrotropin receptor.

^a Adapted from Bahn (5). Used with permission.

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