Thieme

Teprotumumab: The Dawn of Therapies in Moderate-to-Severe Thyroid-Associated Ophthalmopathy

Authors
Yizhi Ding, Shaoqin Yang, Hua Gao

Affiliations
Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital, Tianjin, China

Key words
thyroid eye disease, proptosis, treatment, insulin-like growth factor I receptor, monoclonal antibody, teprotumumab

received 15.11.2020
accepted after revision 31.01.2021

Bibliography
Horm Metab Res 2021; 53: 211–218
DOI 10.1055/a-1386-4512
ISSN 0940-6689

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence
Hua Gao
Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital
Tianjin
China
Tel.: +86 18703176611
huagao0706@vip.sina.com

ABSTRACT

Thyroid-associated ophthalmopathy (TAO) is a potentially sight-threatening ocular disease. About 3–5 % of patients with TAO have severe disease with intense pain, inflammation, and sight-threatening corneal ulceration or compressive optic neuropathy. The current treatments of TAO are often suboptimal, mainly because the existing therapies do not target the pathogenesis of the disease. TAO mechanism is unclear. Ocular fibrocytes express relatively high levels of the functional TSH receptor (TSHR), and many indirect evidences support its participation. Over expression of insulin-like growth factor-1 receptor (IGF-IR) in fibroblasts, leading to inappropriate expression of inflammatory factors, production of hyaluronic acid and cell activation in orbital fibroblasts are also possible mechanisms. IGF-1R and TSHR form a physical and functional signaling complex. Inhibition of IGF-IR activity leads to the attenuation of signaling initiated at either receptor. Teprotumumab (TMB) is a human immunoglobulin G1 monoclonal antibody, binding to IGF-IR. Recently two TMB clinical trials had been implemented in TAO patients, indicating dramatic reductions in disease activity and severity, which approved its use for the treatment of TAO in the US. This review summarizes the treatments of TAO, focusing on the pathogenesis of IGF-1R in TAO and its application prospects.

Introduction

Thyroid-associated ophthalmopathy (TAO aka Graves' ophthalmopathy/orbitopathy or thyroid eye disease TED) represents the ocular manifestation of thyroid autoimmunity, most commonly occurring in Graves' disease (GD) [1, 2]. TAO is often related to hyperthyroidism, but it is still not clear how hyperthyroidism influences TAO. It can also occur in other autoimmune thyroid diseases, including hypothyroidism, normal thyroid function, and Hashimoto's thyroiditis [3, 4]. TAO often appears within 18 months following a GD diagnosis [5]. TAO is characterized by inflammation in the retrobulbar tissues, increased adipogenesis, and accumulation of extraocular intramuscular glycosaminoglycans (GAGs) leading to expansion and remodeling of orbital contents [6]. Common symptoms may include eye pain, excessive lacrimation, photophobia, blurry vision, and diplopia. TAO can cause eyelid withdrawal, exophthalmos, chemical reactions, periorbital edema, and changes in eye movement. Severe TAO can cause exposure keratopathy, diplopia, and compressive optic neuropathy, even loss of vision. Modifiable risk factors for the development or progression of TAO include smoking, radioactive iodine (RAI), and uncontrolled hypothyroidism or hyperthyroidism [7]. The ideal TAO treatment is based on the pathogenic mechanism, which can rapidly reduce inflammation, improve exophthalmos and diplopia, reduce the need for surgical intervention, and restore the quality of life of patients [3]. Immune cross-reaction of thyroid and orbital antigens is a possible mechanism of Graves' ophthalmopathy, in which co-expression of thyroid stimulating hormone receptor (TSHR) and insulin growth factor-1 receptor (IGF-1R) on orbital fibroblasts plays a key

role [8]. In vitro studies of orbital fibroblasts and fibrocytes show that IGF-IR-inhibitory antibodies can attenuate the actions of IGF-I, thyrotropin, thyroid-stimulating immunoglobulins, and immunoglobulins isolated from patients with Graves' disease [9, 10].

Treatments for TAO

Glucocorticoid

Glucocorticoid has been the main treatment for Graves' ophthalmopathy. European Group on Graves' orbitopathy (EUGOGO) currently recommend IV-GCs as a first-line treatment for active moderate to severe GO [11]. A meta-analysis of randomized clinical trials clearly demonstrates that intravenous methylprednisolone shock therapy (IVMP) has higher efficacy and fewer side effects than oral prednisone [12]. At the same cumulative dose, the weekly dose of GCs seems to be better than the daily dose, and they found a significantly greater response rate for the weekly protocol vs the daily protocol at the 12th week (76.92 vs. 41.03 %; p = 0.0025) [13]. Compared with the 12-week protocol, the 4-week alternative with the same cumulative dose of 4.5 g was less effective (41 vs. 77 %) and had more side effects [13]. For moderate-to-severe TAO, EUGOGO recommends 500 mg GCs once weekly for 6 weeks and 250 mg once weekly for 6 weeks (cumulative dose 4.5 g) [14]. Although glucocorticoids are usually used to treat TAO, there are currently not enough placebo-controlled trials to prove their efficacy. Generally, glucocorticoids can control orbital inflammation, reduce edema, improve soft tissue lesions (redness and swelling of the eyelids and conjunctiva), and eye muscle movement, but they are less effective in reducing exophthalmos and diplopia. In the maximum randomized controlled trial (RCT) using three different cumulative doses of IV-GCs (2.25 g, 4.98 g, 7.47 g methylprednisolone), the average reduction in exophthalmos was less than 1 mm even with the highest dose [15]. However, this RCT did not take into account the natural course of TAO, and there was no placebo control. Approximately 10–20 % of clinically active and severe TAO patients may not respond to glucocorticoids and/or relapse after withdrawal [15]. Potential side effects and contraindications of glucocorticoids remain an important consideration, and dose-dependent effects make it difficult to balance increased clinical efficacy with higher doses and greater risk of side effects [15, 16]. In addition to the common side effects of glucocorticoids, such as Cushing syndrome, hyperglycemia, hypertension, osteoporosis and so on, there are also cases of IVMP related to acute and serious hepatic injury, even leading to fatal hepatic failure, recommended that the cumulative dose of IVMP should not exceed 8 g [17].

Orbital radiotherapy

Orbital radiotherapy is a useful therapy, which seems to be effective for ocular dyskinesia, especially in recent cases, but has little effect on exophthalmos and long-term extraocular muscle dysfunction [18]. RCTs from Amsterdam clearly show efficacy on motility [19] and also on soft tissue in less affected patients [20]. Also retrospective in nature but with high patient numbers and uniform inclusion criteria the study from Johnson at al. showed that 16 Gy and 20 Gy are more effective on improvement of motility than lower doses [21]. Another retrospective study revealed that orbital irradiation had a significant additional benefit to iv. steroids on improvement of motility [22]. And even the CIRTED study revealed in the secondary outcomes in the so called ophthalmopathy index (the severity index) that the combined therapy of azathioprin and orbital irradiation reached nearly significance (p = 0.06) while no therapy alone. However this study suffered from to many drop outs [23].

Orbital surgery

Orbital decompression is often used as a secondary treatment if there is a poor response to corticosteroids or the need to avoid corticosteroid complications [24]. Surgery is required in the acute phase of TAO where there is immediate danger to vision (e. g., optic neuropathy). A variety of procedures for surgical decompression include balanced decompression, medial and floor decompression, lateral wall decompression, and orbital fat decompression. Orbital surgery may cause recurrence of ophthalmopathy and may cause or aggravate diplopia [25]. Garrity at al. showed even with the now outdated technology of transanthral decompression that inflammation improved in more than 80 % of the patients due to the reduction of congestion [26]. Even basic science has clearly shown that from a certain point onwards, congestion-related hypoxia plays a significant role in the progression of GO [27]. So, recurrence of ophthalmopathy is rather rare.

Immunotherapy and biotherapy

Antiproliferative agent

Based on these issues, new therapies targeting the pathogenesis of TAO is essential to advance the treatment and improve clinical efficacy. CIRTED trial shows that it is potentially beneficial of combining steroids and azathioprine, but drawing final conclusions is limited by the high number of people who dropped out of the study [23]. Mycophenolate mofetil (MMF) has been shown to have a beneficial therapeutic effect in inflammatory and autoimmune diseases. Post-hoc analysis of MINGO trial suggested that addition of mycophenolate with methylprednisolone improved rate of response to therapy in patients with active and moderate-to-severe TAO and had potential effects in preventing long-term recurrence after steroids discontinuation. But the addition of mycophenolate did not prevent dysthyroid optic neuropathy or improve the severity of proptosis [28].

Etanercept

In several autoimmune diseases, including TAO, TNF-α (Tumor Necrosis Factor-α) has a significant role [29]. Etanercept is a large molecule, a genetically engineered anti-TNF compound consisting of receptors that bind TNF. Binding to TNF-α, it inhibits its function in autoimmune diseases (rheumatoid arthritis, ankylosing spondylitis, psoriasis, etc.) [30]. Paridaens et al. have explored that etanercept may suppress the clinical symptoms in TAO, but that was an uncontrolled study. Further studies are required to investigate the efficacy and safety of this treatment [31].

Tocilizumab

Targeted biotherapy will bring a new hope; rituximab (anti-CD20) and tocilizumab (anti-IL-6) appear to reduce inflammation and improve exophthalmos [32]. IL-6 is a pleiotropic cytokine produced by a wide variety of immune and nonimmune cells, including leu-

kocytes, macrophages ,fibroblasts, and many different tumor cells [33]. Tocilizumab is a humanized anti-IL-6R monoclonal antibody (mAb), approved for the treatment of rheumatoid arthritis (RA) [34] and systemic juvenile idiopathic arthritis [35]. Salvi M et al. observed that in GD patients with active inflammatory TAO, the IL-6 system is activated, and serum sIL-6R concentrations were higher than those in patients with inactive TAO [36]. Several prospective studies manifested that Tocilizumab may significantly improve the clinical features of patients with active TAO refractory to corticosteroids [37, 38].

Rituximab

Rituximab (RTX), is a chimeric monoclonal antibody targeting CD20, a membrane-embedded protein expressed on the surface of B cell [39]. Because RTX depletes CD20 B cells, it has been considered that RTX may be effective for treating TAO. A few studies support that rituximab is conducive to deplete peripheral B-cell, reduce disease activity, permit a decreased administration of systemic steroid and induce long-term remission of TAO. Furthermore low-dose rituximab (100 mg) is also effective and patients are exposed to lower risks of potentially severe side effects [40, 41]. A retrospective study showed that RTX offered limited and partial improvement for active moderate-to-severe TAO with a long duration of disease [42]. But another randomized controlled trial of rituximab had reported conflicting results. Stan et al. concluded that rituximab has no additional benefit to patients compared to placebo. Note that 10 patients (4 in RTX group and 6 in the placebo, $p < 0.33$) treated with corticosteroids had completed therapy at least 1.5 months prior to trial enrollment and all patients reported worsening of the disease after corticosteroids were discontinued [43]. Because of these conflicting results, the role of rituximab in moderate-to-severe TAO remains to be defined by a larger, multicenter RCT [44].

Therapy targeting TSHR

A small molecule TSHR antagonist (NCGC00229600) reduce the productions of cAMP, pAkt, and HA, which are activated via TSHR signaling and are vital to the pathogenesis of TAO. It may be beneficial to TAO with therapeutic potential [45]. The human monoclonal autoantibody K1–70 binds to the TSHR with high affinity and blocks TSHR cyclic AMP stimulation by TSH and thyroid stimulating autoantibodies. The study from Furmaniak et al. aimed to provide important toxicity, safety and pharmacokinetics information to design the first in human clinical trial with K1–70 [46]. Marcinkowski et al. showed that S37a, a novel highly selective inhibitor for the TSHR, not only inhibits the TSHR activation by thyrotropin itself but also activation by monoclonal TSAb M22 (human), KSAb1 (murine), and the allosteric small-molecule agonist C2. It has promising potential for further development for the treatment of TAO [47].

Teprotumumab

Teprotumumab (TMB) is a fully recombinant human monoclonal antibody of immunoglobulin G1 that binds to the cysteine-rich region of insulin-like growth factor-1 receptor (IGF-IR) with high affinity and specificity [10, 48]. Kumar suggested that blocking IGF-1R with a monoclonal antibody (mAb) may reduce TSHR and IGF-1R dependent signaling, thereby blocking pathological activity initiated by both receptors [49]. Although teprotumumab is specific for IGF-1R, Smith and his colleagues have shown that it can also inhibit the signaling of TSH-R in vitro because the two receptors form a physical complex [50].

Chen's study is consistent with previous reports. The expression of IGF-1R and TSHR on the surface of untreated fibroblasts is relatively high [51, 52]. It showed that Teprotumumab does not interfere with the detection of either receptor on the cell surface [10]. Then they investigated teprotumumab does not alter IGF-1R expression after incubation and found a significant decrease in surface IGF-1R levels after 12 hours [10]. Because IGF-1R and TSHR form a physical complex [9], the effect of teprotumumab on TSHR display was also investigated. Similar to IGF-1R, TSHR levels declined after treatment with teprotumumab, reaching a nadir after 12 hours [10]. Fibrocytes from GD patients also showed a significant reduction in surface IGF-1R and TSHR due to teprotumumab treatment [10].

Previous studies have shown that IL-6 and IL-8 seem to be related to the pathogenesis of TAO [53, 54]. Subsequently, Chen H et al. detected the molecular mechanism of Teprotumumab's effect on bTSH-induced cytokines in fibroblasts of healthy donors and GD patients. The mAb failed to alter basal steady-state IL-6 and IL-8 mRNA levels. TSH increased IL-6 transcripts in fibrocytes from healthy donors and patients with GD by 400-fold and 2000-fold respectively. Teprotumumab significantly inhibited the induction by bTSH of IL-6 mRNA in fibrocytes from healthy donors and patients with GD ($p < 0.001$ and $p < 0.0001$). Similar results were observed in the measurement of IL-8 mRNA [10]. Meanwhile, teprotumumab partially blocked the Akt phosphorylation induced by TSH and IGF-1 [10, 55].

Recent studies have shown that teprotumumab, as a pharmacological and functional inhibitor, blocks the activation of IGF-1R through its endogenous ligands (IGF-1 and IGF-2), and causes receptor internalization [32, 48, 56]. TMB exerts its pharmacological effects through functional inhibition of the IGF-1R pathway, leading to complete closure of IGF-1R signaling by a combination of two mechanisms: upon binding to the cysteine-rich domain of human IGF-1R, TMB blocks the binding pocket for both endogenous ligands, IGF-1 and IGF-2, and prevents them from activating the IGF-1R signaling cascade; and binding of TMB induces internalization and subsequent degradation of IGF-1R, in vitro and in vivo, resulting in cell surface accessible 95 % reduction in body protein [32].

Two multicenter, double-blind, randomized, placebo-controlled trials based on basic researches had showed that it significantly reduced the degree of exophthalmos [57, 58].

The primary endpoints in studies about the immunotherapies of TAO usually include reduction of clinical activity score (CAS). Secondary end points usually include clinically significant improvement in proptosis, lid fissure width, diplopia score, lagophthalmos, disease severity, changes in those parameters, orbital fat/ muscle volume and quality-of-life, each item of the clinical activity score, patient self-assessment and so on [28, 42, 43]. In most studies it is sufficient to achieve the primary outcome with an improvement in the disease activity. Only a few studies call for an improvement in exophthalmos or mobility mandatory to reach primary outcome.

Primary and secondary outcomes in teprotumumab RCTs will be introduced in detail in the following sections.

How IGF-1R Antibody Act on the Treatment of TAO?

TSHR as Autoantigen in TAO

At the heart of Graves' disease is the loss of immune tolerance to the thyroid stimulating hormone receptor (TSHR) and the production of activated antibodies against this receptor protein, known as thyroid stimulating immunoglobulin (TSI) [2, 59], these autoantibodies can be detected in most GD patients with or without eye disease [60]. TSH is expressed by the orbital fibrocyte [51, 61], which suggests that it may be involved in ophthalmopathy. The expression of TSH receptor in orbital fibroblasts and preadipocytes was relatively low, but increased with retro-orbital adipocyte differentiation [51]. The expression in the active stage was higher than that in the inactive stage, which was directly related to IL-1β [62]. CD34 + fibroblasts from bone marrow were detected in the orbital tissue of TAO, but not in the normal orbit [51]. TSHR expressed by fibroblasts is functional and can upregulate the expression of cytokines IL-6 and TNF-α [51]. CD40-CD40L activating orbital fibroblasts may be an important mechanism for upregulation of local orbital IL-6 and IL-8 expression, and induce orbital fibroblasts to synthesize excess hyaluronic acid [63, 64]. A monoclonal TSHR-stimulating antibody M22 stimulates hyaluronic acid secretion and M22 was specific for TSHR [65].

It has been reported that TSI levels may be associated with disease activity and predict whether patients may develop into serious diseases in the future [66]. However, although antibody levels in patients with more severe and active TAO appear to be higher, the utility of TSI levels as a clinical management guideline has not been established in appropriate controlled studies [48]. In some severe cases, undetectable TSI [60, 67], suggests that there may be additional autoantigens to play a role in TAO.

IGF-1R as Autoantigen in TAO

Insulin-like growth factor-1 receptor (IGF-IR) is a membrane tyrosine kinase receptor that plays a role in cell growth and metabolism [68], it also regulates immune function and may be used as a therapeutic target in autoimmune diseases [6, 69]. Recent studies provide evidences for the role of IGF-1R in the pathogenesis of GO [48, 70].

Weightman and his colleagues provided the first clue that IGF-IR might be involved in TAO [71]. They speculated that immunoglobulin (GD-IgG) stimulation of fibroblasts and extraocular muscle cells may act through IGF-IR [71]. IgG collected from patients with GD, whet her or not manifested as TAO, can replace the IGF-I radiolabeled on the surface binding site of orbital fibroblasts transplanted from extraocular muscle tissue. In contrast, IgG in the healthy control failed to change the binding of IGF-I to cells [71].

Subsequent study supported the presence of antibodies against IGF-1R, in which it was found that IgG from GD patients induced the expression of T-cell chemokines in auto fibroblasts from thyroid, orbit and skin. These effects did not exist in normal control fibroblasts [72]. These IgG were later shown to target IGF-1R [73]. This triggers local inflammatory and immune responses, leading to fibroblast proliferation and differentiation, tissue expansion, extracellular matrix augmentation, edema, and extensive orbital tissue remodeling [69, 74].

Smith's basic research identified the important role of IGF-1R [10, 50], which described the overexpression of IGF-1R in fibroblasts and its activation by IgG in Graves' disease, leading to inappropriate expression of inflammatory factors, production of hyaluronic acid and cell activation in Graves' orbital fibroblasts, which lack of function in the culture of healthy donors [74, 75]. Many subsequent studies have demonstrated the central role of orbital fibroblasts and the overexpression of IGF-1R in Graves patients [9, 75, 76].

Pritchard et al. used the inhibitory anti-IGF-IR antibody 1H7 or DN mutant receptor 486/STOP transfected into GD fibroblasts to block IGF-IR activity, which could block GD-IgG-dependent increases in IL-16 and RANTES expression [73]. The signaling pathway that mediates the action of GD IgG in these cells has been mapped to Akt/FRAP/mTOR/p70sk6 [72]. This signaling leads to the induction of two T-cell chemokines, IL-16 and RANTES, which are not found in healthy human fibroblasts [72]. In addition, Tsui et al. demonstrated that 1H7 can attenuate the ERK signal transduction initiated by TSHR in TAO orbital fibroblasts [9]. Subsequent vitro studies of orbital fibroblasts and fibroblasts showed that the antibody inhibiting IGF-IR could weaken the effects of IGF-I, thyrotropin and thyroid-stimulating immunoglobulin [9, 10]. Furthermore, functional IGF-1R was found in professional immune cells, including lymphocytes (B cells and T cells) and monocytes, which indicated that IGF-1R may play a role not only in the pathogenesis of GO, but also in the immune system [48].

Based on these findings, several attempts to test the functional autoantibody (IGF-1RAb) against IGF-1R have yielded conflicting results, and some have questioned the existence and significance of IGF-1RAb [77–84]. IGF-1R antibodies are unlikely to be a useful biomarker because they are only found in a quarter of Graves' patients, regardless of the presence or absence of TAO [85].

TSHR and IGF-1R complex

Proving the physical and functional interaction of IGF-1R and TSH-R is the key to the ultimate treatment. Studies by Tramontano et al. provided preliminary clues to the possible functional interaction between IGF1 and TSH, with IGF-1 enhancing the effect of TSH in culture on thyroid epithelial cells FRTL-5, including cell proliferation and DNA synthesis [86]. Conditional knockout of the IGF-1R gene in the thyroid gland significantly reduces its response to TSH [87]. The two receptors signaling pathways overlap, indicating the potential for functional interactions between receptor proteins [88, 89]. Tsui et al. found that the two proteins actually interact physically, which directly proved that IGF- 1R and TSHR form a protein complex, and IGF-1R was trans activated by the complex [9]. Inhibition of IGF-IR activity in orbital fibroblasts, fibroblasts, or thyroid epithelial cells leads to decreased activation of both receptors [9, 48], supporting the role of IGF-1R in the pathogenesis of GO. In general, they are called GD immunoglobulin G (GD IgG). Whether their activity is caused by TSI or by a unique anti IGFIR antibody, altering their interaction with orbital autoantigens or altering the signal events generated by these antibody antigen interactions

seems to be a potentially useful therapeutic target. M22 stimulates hyaluronic acid secretion, Neumann et al latest study showed that M22 binds to TSHR but does not bind to IGF-1R and provided additional evidence that immunoglobulins from patients with GO (GO-Igs) do not directly activate IGF1R. Stimulation of HA secretion initiated by TSHR activation is independent of autocrine/paracrine effects of IGF1 generation [65].

Therapeutic Trials of Teprotumumab in TAO

Phase II

Smith et al. conducted a multicenter, double-blind, randomized, placebo-controlled trial (NCT 01868997) to conclude the effectiveness and safety of teprotumumab in patients with moderate-to-severe active TAO [57]. A total of 88 patients were randomly assigned to receive either placebo or active drugs. The primary outcome was the response in the study eye compared with placebo. This end point comprised a reduction of 2 mm or more in proptosis in the study eye and a reduction of 2 points or more in the Clinical Activity Score at 24th week. Secondary outcomes, measured as continuous variables, included proptosis, the Clinical Activity Score, and results on the Graves' ophthalmopathy–specific quality-of-life questionnaire. In the trial, 29 of the 42 patients (69 %) who received teprotumumab had a response at week 24, while 9 of the 45 patients (20 %) who received placebo responded ($p < 0.001$). The time to first response was shorter and the fraction of patients achieving response was higher in the teprotumumab group at weeks 6, 12 and 18 ($p < 0.001$ at all comparisons). In addition, QoL and visual function of TMB group were prominently improved at all assessment time points, which was higher than that of placebo. The remarkable reduction of proptosis was similar to the report after decompression surgery [25, 90]. However, orbital surgery may lead to the recurrence of ophthalmopathy and may cause or aggravate diplopia [25, 57, 91]. No significant reduction in proptosis had been reported in any previous placebo-controlled trials of other drugs for TAO.

Phase III

A randomized, double-blind, placebo-controlled, multicenter phase 3 trial (NCT 03298867) of teprotumumab had been completed which including 41 patients assigned to the teprotumumab group and 42 to the placebo group [58]. It was similar to that of the phase 2 trial in which 8 infusions of teprotumumab or placebo were administered over a 24 week. The difference is that assessment time point was simplified to a proptosis reduction of > 2 mm in the examined eye only at week 24. At week 24, the percentage of patients in teprotumumab group with a proptosis response was higher than with placebo (83 vs.10 %, $p < 0.001$). And the secondary outcomes among the patients in the teprotumumab group were significantly better than in the placebo group. The orbital imaging performed in the six patients in the teprotumumab group (at one trial site) indicated reductions in extraocular muscle volume, orbital fat volume, or both. In phase 2 trial, orbital imaging was not performed and it was not possible to determine which orbital tissues were affected by teprotumumab. Another limitation is lack of long-term follow-up. The collection of data on the durability of efficacy and relapses are ongoing in either trial. In the phase 2 trial, the efficacy of teprotumumab was maintained for up to 48 weeks of follow-up in most of the patients who had a proptosis response and a diplopia response. An extension of the phase 3 OPTIC trial, OPTIC-X (NCT03461211), is currently ongoing for patients who did not have a proptosis response and have a relapse during the follow-up period.

Safety of Teprotumumab

In the phase 2 clinical trial, the only adverse event related to the drug was hyperglycemia in diabetic patients; the event was controlled by adjusting the diabetic drug [57]. In the phase 3 trial, most adverse events were mild or moderate in the teprotumumab group; including muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dry skin, dysgeusia, and headache. One of the two serious events is that an infusion reaction leading to treatment discontinuation [58]. Several monoclonal antibodies against IGF-1R have been tested in clinical trials to look forward to their therapeutic effects on various types of cancer. Although the therapeutic effects of these drugs are disappointing, they generally show satisfactory safety [92]. Ma and Zhang summarized the adverse reactions of anti IGF-1R monoclonal antibody in tumor treatment. The total incidence of hyperglycemia was 14.4 %, but metformin and other hypoglycemic drugs seemed to be easy to control [93]. A complicated mechanism to explain hyperglycemia is as follows: Besides tumor cells, IGF-IR monoclonal antibodies also act on normal tissues. Most of all, IGF-IRs in the hypothalamic-pituitary axis that are involved in homeostatic feedback control is also targeted. This reduces the feedback inhibition of growth hormone secretion, thus lead to elevation in growth hormone (GH). Elevation of GH can cause insulin resistance in classic insulin target organs, increased gluconeogenesis, and thus leading to elevations in glucose concentrations. This in turn results in increased insulin secretion which commonly corrects hyperglycemia to some extent [93]. Thrombocytopenia, neutropenia, anemia, and fatigue reported in previous cancer studies were not observed in patients with ophthalmopathy [93, 94].

Although some IGF-1R monoclonal antibodies have shown good safety in the targeted treatment of tumor, the population of teprotumumab is limited, and the new immunomodulator still has potentially fatal risks, including serious infection, malignant tumor, etc. In view of these potential adverse events, immunomodulatory therapy must be performed in experienced centers that can safely monitor and manage potential serious adverse events.

Current Situation

Based on the positive results over two randomized clinical trials, the Food and Drug Administration (FDA) and Dermatology and Ophthalmology Drug Advisory Committee(DODAC) unanimously supported teprotumumab in the treatment of active Thyroid-associated ophthalmopathy which potential benefits outweigh the risks.

Discussion

The completed trial was designed to examine the effectiveness and safety of IGF-IR inhibition in active TAO. It could not address the issue of whether this therapeutic strategy might also be effective in stable disease. Whether teprotumumab is effective and safe in inactive patients still needs to be evaluated.

Stable normal thyroid function may contribute to the spontaneous improvement of mild TAO and may help to optimize the potential reactivity of immunosuppressive therapy [95, 96]. Therefore, whether there is difference in the therapeutic effect of Teprotumumab on moderate-to-severe active TAO with normal thyroid function or dysthyroidism is not sure.

Further studies that directly compare teprotumumab with current first-line therapy rather than placebos will help to confirm the superiority of its efficacy.

Thyroid skin lesions occur in 1–4 % of Graves' disease patients, and almost always in patients with severe ophthalmopathy [97]. The mechanism of pretibial myxedema is not clear. TSHR is also expressed in fibroblasts with pretibial myxedema. Is there IGF-1R and TSH-R complex in the anterior tibial tissue, and is Teprotumumab beneficial to pretibial myxedema?

There are many IGF-1R monoclonal antibodies, but it is not sure whether Teprotumumab has physical/biological characteristics, which makes its clinical efficacy and safety different from other IGF-1R antibodies. Another mAb 1H7 blocked by IGF-1R can also attenuate TSHR activated signal transduction in TAO orbital fibroblasts [9].

Conclusion

In the last few years, so many new findings have emerged that now allow targeted therapy. IGF-1R as an autoantigen may be a mechanism for thyroid-associated ophthalmopathy. The apparent effectiveness and relative security of teprotumumab offer hope for improving the quality of life for ophthalmopathy patients. The drug has achieved registration by the U.S. FDA. It is possible that some patients may achieve substantial benefit and durable enough as to lessen the need for many remedial surgeries. In addition, a longer follow-up period would allow investigators to assess clinical and subjective improvements in diplopia and proptosis. Additional studies, including an extension of the phase III OPTIC trial, OPTIC-X (NCT03461211), are currently underway.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Wang Y, Smith TJ. Current concepts in the molecular pathogenesis of thyroid-associated ophthalmopathy. Invest Ophthalmol Vis Sci 2014; 55: 1735–1748

[2] Smith TJ, Hegedus L. Graves' Disease. N Engl J Med 2016; 375: 1552–1565

[3] Douglas RS, Gupta S. The pathophysiology of thyroid eye disease: Implications for immunotherapy. Curr Opin Ophthalmol 2011; 22: 385–390

[4] Cyranska-Chyrek E, Olejarz M, Szczepanek-Parulska E et al. Severe unilateral orbitopathy in a patient with Hashimoto's thyroiditis - a case report. BMC Ophthalmol 2019; 19: 9

[5] Gillespie EF, Smith TJ, Douglas RS. Thyroid eye disease: towards an evidence base for treatment in the 21st century. Curr Neurol Neurosci Rep 2012; 12: 318–324

[6] Smith TJ. TSHR as a therapeutic target in Graves' disease. Expert Opin Ther Targets 2017; 21: 427–432

[7] Bhatti MT, Dutton JJ. Thyroid eye disease: Therapy in the active phase. J Neuro-Ophthalmol 2014; 34: 186–197

[8] Smith TJ. Pathogenesis of Graves'orbitopathy: A 2010 update. J Endocrinol Invest 2010; 33: 414–421

[9] Tsui S, Naik V, Hoa N et al. 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

[10] Chen H, Mester T, Raychaudhuri N et al. Teprotumumab, an IGF-1R blocking monoclonal antibody inhibits TSH and IGF-1 action in fibrocytes. J Clin Endocrinol Metab 2014; 99: E1635–E1640

[11] Bartalena L, Baldeschi LBoboridis et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J 2016; 5: 9–26

[12] Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M et al. Treatment modalities for Graves' ophthalmopathy: Systematic review and metaanalysis. J Clin Endocrinol Metab 2009; 94: 2708–2716

[13] Zhu W, Ye L, Shen L et al. A prospective, randomized trial of intravenous glucocorticoids therapy with different protocols for patients with Graves' ophthalmopathy. J Clin Endocrinol Metab 2014; 99: 1999–2007

[14] Bartalena L, Baldeschi L, Dickinson A et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol 2008; 158: 273–285

[15] Bartalena L, Krassas GE, Wiersinga W et al. 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

[16] Marcocci C, Watt T, Altea MA et al. Fatal and non-fatal adverse events of glucocorticoid therapy for Graves' orbitopathy: A questionnaire survey among members of the European Thyroid Association. Eur J Endocrinol 2012; 166: 247–253

[17] Sisti E, Coco B, Menconi F et al. Intravenous glucocorticoid therapy for Graves' ophthalmopathy and acute liver damage: an epidemiological study. Eur J Endocrinol 2015; 172: 269–276

[18] Tanda ML, Bartalena L. Efficacy and safety of orbital radiotherapy for Graves' orbitopathy. J Clin Endocrinol Metab 2012; 97: 3857–3865

[19] Mourits MP, van Kempen-Harteveld ML, García MBG et al. Radiotherapy for Graves' orbitopathy: randomised placebo-controlled study. Lancet 2000; 355: 1505–1509

[20] Prummel MF, Terwee CB, Gerding MN et al. A randomized controlled trial of orbital radiotherapy versus sham irradiation in patients with mild Graves' ophthalmopathy. J Clin Endocrinol Metab 2004; 89: 15–20

[21] Johnson KT, Wittig A, Loesch C et al. A retrospective study on the efficacy of total absorbed orbital doses of 12, 16 and 20 Gy combined with systemic steroid treatment in patients with Graves' orbitopathy. Graefes Arch Clin Exp Ophthalmol 2010; 248: 103–109

[22] Oeverhaus M, Witteler T, Lax H et al. Combination therapy of intravenous steroids and orbital irradiation is more effective than intravenous steroids alone in patients with graves' orbitopathy. Horm Metab Res 2017; 49: 739–747

[23] Rajendram Rathie, Taylor Peter N, Victoria J Wilson et al. Combined immunosuppression and radiotherapy in thyroid eye disease (CIRTED): a multicentre. 2 × 2 factorial, double-blind, randomised controlled trial. Lancet Diabetes Endocrinol 2018; 6: 299–309

[24] Gao G, Dai J, Qian Y et al. Meta-analysis of methylprednisolone pulse therapy for Graves' ophthalmopathy. Clin Exp Ophthalmol 2014; 42: 769–777

[25] Wu CY, Niziol LM, Musch DC et al. Thyroid-related orbital decompression surgery: a multivariate analysis of risk factors and outcomes. Ophthalmic Plast Reconstr Surg 2017; 33: 189–195

[26] Garrity JA, Fatourechi V, Bergstralh EJ et al. Results of transantral orbital decompression in 428 patients with severe graves' ophthalmopathy. Am J Ophthalmol 1993; 116: 533–547

[27] Gortz GE, Horstmann M, Aniol B et al. Hypoxia-dependent HIF-1 activation impacts on tissue remodeling in graves' ophthalmopathy-implications for smoking. J Clin Endocrinol Metab 2016; 101: 4834–4842

[28] Kahaly GJ, Riedl M, König J et al. Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): A randomised, observer-masked, multicentre trial. Lancet Diabetes Endocrinol 2018; 6: 287–298

[29] Bahn RS. Graves' Ophthalmopathy. N Engl J Med 2010; 362: 726–738

[30] Scott LJ. Etanercept: a review of its use in autoimmune inflammatory diseases. Drugs 2014; 74: 1379–1410

[31] Paridaens D, van den Bosch WA, van der Loos TL et al. The effect of etanercept on Graves' ophthalmopathy: a pilot study. Eye (Lond) 2005; 19: 1286–1289

[32] Kahaly GJ. Immunotherapies for thyroid eye disease. Curr Opin Endocrinol Diabetes Obes 2019; 26: 250–255

[33] Jones TH. Interieukin-6 an endocrine cytokine. Clin Endocrinol 1994; 40: 703–713

[34] Scott LJ. Tocilizumab: A Review in Rheumatoid Arthritis. Drugs 2017; 77: 1865–1879

[35] Yokota S, Imagawa T, Mori M et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet 2008; 371: 998–1006

[36] Salvi Mario, Girasole Giuseppe, Pedrazzoni Mario et al. Increased serum concentrations of Interleukin-6 (IL-6) and soluble IL-6 receptor in patients with Graves' disease. Clin Endocrinol Metab 1996; 81: 2976–2979

[37] Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR et al. Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant graves orbitopathy: A randomized clinical trial. Am J Ophthalmol 2018; 195: 181–190

[38] Perez-Moreiras JV, Alvarez-Lopez A, Gomez EC. Treatment of active corticosteroid-resistant Graves' orbitopathy. Ophthalmic Plast Reconstr Surg 2014; 30: 162–167

[39] Minakaran Neda, Ezra DG. Rituximab for thyroid-associated ophthalmopathy (Review). Cochrane Database Syst Rev 2013; 5: 1–23

[40] Salvi M, Vannucchi G, Curro N et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. J Clin Endocrinol Metab 2015; 100: 422–431

[41] Insull EA, Sipkova Z, David J et al. Early low-dose rituximab for active thyroid eye disease: An effective and well-tolerated treatment. Clin Endocrinol (Oxf) 2019; 91: 179–186

[42] Eid Laura, Coste-Verdier Valentine, Longueville Eric et al. The effects of Rituximab on Graves'orbitopathy: A retrospective study of 14 patients. Eur J Ophthalmol 2019; 1–6

[43] Stan MN, Garrity JA, Carranza Leon BG et al. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. J Clin Endocrinol Metab 2015; 100: 432–441

[44] Wiersinga WM. Advances in treatment of active, moderate-to-severe Graves' ophthalmopathy. Lancet Diabetes Endocrinol 2017; 5: 134–142

[45] Turcu AF, Kumar S, Neumann S et al. A small molecule antagonist inhibits thyrotropin receptor antibody-induced orbital fibroblast functions involved in the pathogenesis of Graves ophthalmopathy. J Clin Endocrinol Metab 2013; 98: 2153–2159

[46] Furmaniak J, Sanders J, Clark J et al. Preclinical studies on the toxicology, pharmacokinetics and safety of K1-70(TM) a human monoclonal autoantibody to the TSH receptor with TSH antagonist activity. Auto Immun Highlights 2019; 10: 11

[47] Marcinkowski P, Hoyer I, Specker E et al. A new highly thyrotropin receptor-selective small-molecule antagonist with potential for the treatment of graves' orbitopathy. Thyroid 2019; 29: 111–123

[48] Mohyi M, Smith TJ. IGF-I receptor and thyroid-associated ophthalmopathy. J Mol Endocrinol 2018; 61: T29–T43

[49] Kumar S, Iyer S, Bauer H et al. A stimulatory thyrotropin receptor antibody enhances hyaluronic acid synthesis in Graves' orbital fibroblasts: Inhibition by an IGF-I receptor blocking antibody. J Clin Endocrinol Metab 2012; 97: 1681–1687

[50] Douglas RS. Teprotumumab, an insulin-like growth factor-1 receptor antagonist antibody, in the treatment of active thyroid eye disease: A focus on proptosis. Eye (Lond) 2019; 33: 183–190

[51] Douglas RS, Afifiyan NF, Hwang CJ et al. Increased generation of fibrocytes in thyroid-associated ophthalmopathy. J Clin Endocrinol Metab 2010; 95: 430–438

[52] Gillespie EF, Papageorgiou KI, Fernando R et al. Increased expression of TSH receptor by fibrocytes in thyroid-associated ophthalmopathy leads to chemokine production. J Clin Endocrinol Metab 2012; 97: E740–E746

[53] Ujhelyi B, Gogolak P, Erdei A et al. Graves' orbitopathy results in profound changes in tear composition: A study of plasminogen activator inhibitor-1 and seven cytokines. Thyroid 2012; 22: 407–414

[54] Bossowski A, Urban M. Serum levels of cytokines in children and adolescents with Graves' disease and non-toxic nodular goiter. Pediatr Endocrinol Metab 2001; 14: 741–747

[55] Raychaudhuri N, Fernando R, Smith TJ. Thyrotropin regulates IL-6 expression in CD34+ fibrocytes: clear delineation of its cAMP-independent actions. PLoS One 2013; 8: e75100

[56] Smith TJ, JAMJL Janssen. Building the case for insulin-like growth factor receptor-i involvement in thyroid-associated ophthalmopathy. Front Endocrinol (Lausanne) 2017; 7: 167

[57] Smith TJ, Kahaly GJ, Ezra DG et al. Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med 2017; 376: 1748–1761

[58] Douglas RS, Kahaly GJ, Patel A et al. Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med 2020; 382: 341–352

[59] Adams DD, Purves HD, Sirett NE. The response of hypophysectomized mice to injections of human serum containing long-acting thyroid stimulator. Endocrinology 1961; 68: 154–155

[60] Diana T, Wuster C, Kanitz M et al. Highly variable sensitivity of five binding and two bio-assays for TSH-receptor antibodies. J Endocrinol Invest 2016; 39: 1159–1165

[61] Bahn RS, Dutton CM, Natt N et al. Thyrotropin receptor expression in Graves' Orbital adipose/connective tissues: Potential autoantigen in Graves' ophthalmopathy. Endocr Soc 1998; 83: 998–1002

[62] IMMJ Wakelkamp, Bakker O, Baldeschi L et al. TSH-R expression and cytokine profile in orbital tissue of active vs. inactive Graves' ophthalmopathy patients. Clin Endocrinol (Oxf) 2003; 58: 280–287

[63] Cao HJ, Wang H-S, Zhang Y et al. Activation of human orbital fibroblasts through CD40 engagement results in a dramatic induction of hyaluronan synthesis and prostaglandin endoperoxide H synthase-2 expression. Insights into potential pathogenic mechanisms of thyroid-associated ophthalmopathy. J Biol Chem 1998; 273: 29615–29625

[64] Zhang Y, Cao HJ, Graf B et al. CD40 engagement upregulates cyclooxygenase-2 expression and prostaglandin E2 production in human lung fibroblasts. J Immunol 1998; 160: 1053–1057

[65] Krieger CC, Neumann S, Gershengorn MC. TSH/IGF1 receptor crosstalk: Mechanism and clinical implications. Pharmacol Ther 2020; 209: 107502

[66] Jang SY, Shin DY, Lee EJ et al. Relevance of TSH-receptor antibody levels in predicting disease course in Graves' orbitopathy: Comparison of the third-generation TBII assay and Mc4-TSI bioassay. Eye (Lond) 2013; 27: 964–971

[67] Tabasum A, Khan I, Taylor P et al. Thyroid antibody-negative euthyroid Graves' ophthalmopathy. Endocrinol Diabetes Metab Case Rep 2016; 2016: 160008

[68] Gallagher EJ, LeRoith D. Minireview: IGF, insulin, and cancer. Endocrinology 2011; 152: 2546–2551

[69] Smith TJ. Insulin-like growth factor-I regulation of immune function: a potential therapeutic target in autoimmune diseases? Pharmacol Rev 2010; 62: 199–236

[70] Smith TJ, 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

[71] Weightman DR, Perros P, Sherif IH et al. Autoantibodies to IGF-1 binding sites in thyroid associated ophthalmopathy. Autoimmunity 1993; 16: 251–257

[72] Pritchard J, Horst N, Cruikshank W et al. Igs from patients with Graves' disease induce the expression of T cell chemoattractants in their fibroblasts. J Immunol 2002; 168: 942–950

[73] Pritchard J, Han R, Horst N et al. Immunoglobulin activation of T cell chemoattractant expression in fibroblasts from patients with Graves' disease is mediated through the insulin-like growth factor I receptor pathway. J Immunol 2003; 170: 6348–6354

[74] Smith TJ, Hoa N. Immunoglobulins from patients with Graves' disease induce hyaluronan synthesis in their orbital fibroblasts through the self-antigen, insulin-like growth factor-I receptor. J Clin Endocrinol Metab 2004; 89: 5076–5080

[75] Smith TJ, Tsai CC, Shih M-J et al. Unique attributes of orbital fibroblasts and global alterations in IGF-1 receptor signaling could explain thyroid-associated ophthalmopathy. Thyroid 2008; 18: 983–988

[76] Douglas RS, Naik V, Hwang CJ et al. B cells from patients with Graves' disease aberrantly express the IGF-1 receptor: implications for disease pathogenesis. J Immunol (Baltimore, Md 1950; 2008: 5768–5774

[77] Krieger CC, Place RF, Bevilacqua C et al. TSH/IGF-1 receptor cross talk in Graves' ophthalmopathy pathogenesis. Clin Endocrinol Metab 2016; 101: 2340–2347

[78] Minich WB, Dehina N, Welsink T et al. Autoantibodies to the IGF1 Receptor in Graves' Orbitopathy. Clin Endocrinol Metab 2013; 98: 752–760

[79] Wiersinga WM. Autoimmunity in Graves' ophthalmopathy: the result of an unfortunate marriage between TSH receptors and IGF-1 receptors? J Clin Endocrinol Metab 2011; 96: 2386–2394

[80] Krieger CC, Neumann S, Marcus-Samuels B et al. TSHR/IGF-1R cross-talk, not IGF-1R stimulating antibodies, mediates graves' ophthalmopathy pathogenesis. Thyroid 2017; 27: 746–747

[81] Smith TJ, Janssen J. Response to Krieger et al. re: "TSHR/IGF-1R Cross-Talk, Not IGF-1R stimulating antibodies, mediates graves' Ophthalmopathy Pathogenesis" (Thyroid 2017;27:746–747). Thyroid 2017; 27: 1458–1459

[82] Marcus-Samuels B, Krieger CC, Boutin A et al. Evidence that Graves' ophthalmopathy immunoglobulins do not directly activate IGF-1 receptors. Thyroid 2018; 28: 650–655

[83] Varewijck AJ, Boelen A, Lamberts SW et al. Circulating IgGs may modulate IGF-I receptor stimulating activity in a subset of patients with Graves' ophthalmopathy. J Clin Endocrinol Metab 2013; 98: 769–776

[84] Pritchard J, Tsui S, Horst N et al. Synovial fibroblasts from patients with rheumatoid arthritis, like fibroblasts from Graves' disease, express high levels of IL-16 when treated with Igs against insulin-like growth factor-1 receptor. J Immunol 2004; 173: 3564–3569

[85] Marino M, Rotondo Dottore G, Ionni I et al. Serum antibodies against the insulin-like growth factor-1 receptor (IGF-1R) in Graves' disease and Graves' orbitopathy. J Endocrinol Invest 2019; 42: 471–480

[86] Tramontano D, Cushing G, Moses A et al. Insulin-like growth factor-I stimulates the growth of rat thyroid cells in culture and synergizes the stimulation of DNA synthesis induced by TSH and Graves'-IgG. Endocrinology 1986; 119: 940–942

[87] Ock S, Ahn J, Lee SH et al. IGF-1 receptor deficiency in thyrocytes impairs thyroid hormone secretion and completely inhibits TSH-stimulated goiter. FASEB J 2013; 27: 4899–4908

[88] Latif R, Morshed SA, Zaidi M et al. The thyroid-stimulating hormone receptor: impact of thyroid-stimulating hormone and thyroid-stimulating hormone receptor antibodies on multimerization, cleavage, and signaling. Endocrinol Metab Clin North Am 2009; 38: 319–341

[89] Morshed SA, Ando T, Latif R et al. Neutral Antibodies to the TSH Receptor Are Present in Graves' Disease and Regulate Selective Signaling Cascades. Endocrinology 2010; 151: 5537–5549

[90] Terwee CB, Dekker FW, Mourits MP et al. Interpretation and validity of changes in scores on the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) after different treatments. Clin Endocrinol 2001; 54: 391–398

[91] Baldeschi L, Lupetti A, Vu P et al. Reactivation of Graves' orbitopathy after rehabilitative orbital decompression. Ophthalmology 2007; 114: 1395–1402

[92] Qu XW, Dong Z, Zhang W et al. Update of IGF-1 receptor inhibitor (ganitumab, dalotuzumab, cixutumumab, teprotumumab and figitumumab) effects on cancer therapy. Oncotarget 2017; 8: 29501–29518

[93] Ma H, Zhang T, Shen H et al. The adverse events profile of anti-IGF-1R monoclonal antibodies in cancer therapy. Br J Clin Pharmacol 2014; 77: 917–928

[94] Robertson JFR, Ferrero J-M, Bourgeois H et al. Ganitumab with either exemestane or fulvestrant for postmenopausal women with advanced, hormone-receptor-positive breast cancer: a randomised, controlled, double-blind, phase 2 trial. Lancet Oncol 2013; 14: 228–235

[95] Marcocci C, Marino M. Treatment of mild, moderate-to-severe and very severe Graves' orbitopathy. Best Pract Res Clin Endocrinol Metab 2012; 26: 325–337

[96] Menconi F, Profilo MA, Leo M et al. Spontaneous improvement of untreated mild Graves' ophthalmopathy: Rundle's curve revisited. Thyroid 2014; 24: 60–66

[97] Fatourechi V. Thyroid dermopathy and acropachy. Best Pract Res Clin Endocrinol Metab 2012; 26: 553–565