Current Approach to Graves' Ophthalmopathy: Review

Graves Oftalmopatisine Güncel Yaklaşım

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ABSTRACT Graves' ophthalmopathy (orbitopathy; GO) is an autoimmune disorder, representing the commonest and most important extra thyroidal manifestation of Graves' disease. Its association other with thyroid disorders is very rare, majority of cases are mild to moderate severity, with only 3-5 % of cases having a threat to eyesight. The ocular manifestations of GO include eyelid retraction, proptosis, chemosis, periorbital edema, and altered ocular motility with significant functional, social, and cosmetic consequences. The autoantibodies against thyroid antigens, principally thyrotrophin (TSH) receptor antibodies, play a key role in the pathogenesis of GO. The pathological events in this disorder result from complex interplay among orbital fibroblasts, immune cells, cytokines, antibodies, genetics and environmental factors. The onset and progression of GO are influenced by a variety of factors such as smoking, iodine consumption, thyroid dysfunction and treatment modalities for thyrotoxicosis. Determination of the disease activity and degree of its severity is very important for the choice and application of treatment modality. So far, there are no effective means of preventing the disease or reliably altering its course. Current therapeutic options include corticosteroids, external orbital radiotherapy, steroid-sparing immunosuppressive agents for reducing the inflammation during active disease, and surgery for correcting the residual abnormalities secondary to fibrosis in the inactive state of the disease. These interventions are aimed at the consequences of the disease rather than targeting its cause. Management of GO requires a multidisciplinary approach, and available treatments, unfortunately, do not prevent or reverse the pathological changes in the orbital tissues.

Key Words: Graves disease; Graves ophthalmopathy; thyroid (USP)

ÖZET Graves oftalmopatisi (GO), Graves hastalığının en yaygın ve en önemli tiroid dışı bulgusu olarak ortaya çıkan otoimmün bir bozukluktur. Diğer tiroid hastalıkları ile birlikteliği nadir olup, olguların çoğu hafif-orta şiddetlidir. Görmeyi tehdit eden vakaların oranı ise sadece %3-5'dir. GO göz bulguları göz kapağı retraksiyonu, proptozis, kemozis, periorbital ödem ve önemli fonksiyonel, sosyal ve kozmetik sonuçları olan göz hareketlerindeki değişiklikleri içerir. Tiroid antijenlerine karşı, esas olarak TSH reseptörü antikorları, GO patogenezinde anahtar bir rol oynamaktadır. Bu bozuklukta patolojik olaylar; orbital fibroblastlar, bağışıklık hücreleri, sitokinler, antikorlar, genetik ve çevresel faktörler arasındaki karmaşık etkileşim sonucu ortaya çıkmaktadır. GO başlangıcı ve ilerlemesi sigara içimi, iyot tüketimi, tiroid disfonksiyonu ve tirotoksikozun tedavi yöntemleri gibi çeşitli faktörlerden etkilenir. Hastalık aktivitesi ve şiddetinin derecesi tedavi yönteminin seçimi ve uygulaması için çok önemlidir. Şu ana kadar hastalığı önleyen veya seyrini değiştiren etkili bir yöntem bulunamamıştır. Güncel tedavi seçenekleri, kortikosteroidler, eksternal orbital radyoterapi ve aktif dönemde steroid dışı immünosüpresif ajanlardır. Hastalığın inaktif olduğu durumda sekonder fibrozise bağlı anormallikler için cerrahi de bir seçenektir. Bu girişimler sorunun nedenlerinden ziyade hastalığın sonuçlarına yöneliktir. GO yönetimi multidisipliner bir yaklaşım gerektirmektedir ve maalesef mevcut tedaviler orbital dokulardaki patolojik değişiklikleri geri döndüremez ve önleyemez.

Anahtar Kelimeler: Graves hastalığı; Graves oftalmopatisi; tiroid (USP)

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Graves'ophthalmopathy (GO), is an autoimmune disorder seen in Graves' disease, the major features of which are orbital tissue involvement, increase in palpebral fissure, proptosis, eyelid edema, conjunctivitis and extra ocular muscle involvement.[1] Graves' ophthalmopathy is referred to by names such as thyroid related eye disease and concomitant thyroid ophthalmopathy.

The frequency of thyroid ophthalmopathy ranges between 13 to 69% and its incidence is about 16/100.000 in women and 3/100.000 in men.[2-4]. GO is seen in about 1/3 of the Graves' disease cases and the majority of cases are in mild or moderate severity.[5] GO may initiate with other clinical symptoms of Graves' disease or occur lately. In some cases, other clinical signs may be absent (euthyroid Graves'). Although GO is bilateral in most cases, it can be unilateral rarely. A careful examination may reveal the disorder in the other eye in unilateral cases.

Although intensive studies have been made in etiopathogenesis, clinical course and treatment, there is not any effective method in the prevention or treatment of GO. Current developments related to the GO will be outlined here.

RISK FACTORS

Thyroid ophthalmopathy almost always arises in Graves' patients, and is hardly ever seen in other thyroid diseases. The level of ophthalmopathy, response to treatment and outcome may vary for each patient. Disease that occur in a short time, or such as in cases of diseases like hypertension, diabetes mellitus, hyperlipidemia, and smoking may increase the severity of GO. Ophthalmopathy is more frequently seen in patients with certain risk factors such as some races, female sex, small orbital volume, long duration of thyroid dysfunction, smoking and radioactive iodine (RAI) administration.[6] Some of these are modifiable risk factors, but some are not (Table 1). Although many genes have been blamed for development of GO, it has not been clearly demonstrated. Of environmental factors, particularly smoking and GO show a tight association in studies. Some chemical agents in cigarette have been suggested to induce cytokine production in orbital tissues.[7]

TABLE 1: Risk factors of Graves' ophthalmopathy.

Age
Gender
Genetic
Small orbita
Smoking
Hyperthyroidism / Hypothyroidism
Radioactive iodine therapy
TSH receptor antibodies
Selenium deficiency

In some studies, exacerbations in ophthalmopathy have been shown in Graves' disease with the implementation of RAI.[8,9] There are some studies showing that concomitant implementation of corticosteroids with RAI therapy would be more appropriate in patients with ophthalmopathy (when severe cases excluded).[10]

PATHOPHYSIOLOGY

GO occurs with the development of autoimmune events in orbital soft tissues. Edema due to inflammation in the orbital space soft tissue and the extraocular muscles, growth in the soft tissues and fibrosis occurs in later periods. This inflammation results in the swelling of the eyelids, conjunctival hyperemia, the lid range remaining open (lagophthalmus), the restriction of the eye movements, and the eyeball extending forward (proptosis= exophthalmos) as the clinical symptoms.

How the auto inflammation in the orbital soft tissue starts is not fully known, but it is suggested that there are thyroid antigens on the orbital tissues and reaction of autoantibodies against these antigens leads to the final event.[11] The most emphasized agents about this issue are thyrotrophin (TSH) receptor antibodies (TRAb).[12] TRAb interacts with the TSH receptor in orbital tissues, especially in fibroblasts. The stimulation of these receptors by TRAb leads to a chain of inflammatory reactions such as fibroblast activation, proinflammatory cytokine production,

increased collection of inflammatory cells, new adipocyte formation and changes in extra ocular muscle.

Insulin-like growth factor 1 receptor (IGF-1R) antibody levels were also high in patients with GO. The binding of these antibodies to orbital tissues receptors may lead to increases in cytokine secretion, orbital immune cell accumulation and connective tissue intermediate material synthesis.[13,14] Orbital fibroblasts can be changed into adipocytes under induction of various cytokines.[15] Intraorbital adipose tissue growth causes the propulsion of the eyeball forward (proptosis). Extraocular muscle movement disorders, limitation of eye movement and diplopia occur as a result of increase in fat and connective tissue, fibrosis and edema. In some severe cases, an optic nerve disorder occurs (dysthyroid optic neuropathy).

In the histopathological examination of the orbital tissue, orbital fat and intermediate tissue accumulation, extraocular muscle enlargement and propulsion of the eyeball are seen. Microscopically, the acute phase involves mixed cellular infiltration consisting of lymphocytes, plasma cells, macrophages and eosinophils, increased glycosaminoglycans, collagen deposition, and hyperplasia of fibroblasts, rise in adipocytes; and the chronic phase shows fibrosis and muscle degeneration.[16]

CLINICAL SIGNS

In mild cases, eye symptoms may not be apparent. The most common symptom is the increased palpebral gap and patients appear to be staring. Swelling of the eyelids, conjunctival hyperemia, limitation of eye movements depending on the involvement of the eye muscles, double vision, convergence disorder and forward dislocation of the eyeball (proptosis) are the main symptoms. In more severe cases, loss of vision from optic nerve damage can occur.

Besides ophthalmological examination in the evaluation of ophthalmopathy, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), etc. can also be utilized as imaging techniques, and CT is the most appropriate of them.[17]

A variety of approaches are available in the clinical evaluation of the severity of GO and one of these is denoted as NO SPECS classification (Table 2).[18]

Several scoring systems may be used outside of this classification to determine disease activity. In this scoring system, eye movements to be painful, limited range of motion of the eyeball, optic nerve effective resistance, etc. are taken into consideration. GO is proposed to be classified by Graves' ophthalmopathy workgroup (EUGOGO).[19]

EUGOGO recommends the following assessments for patients with GO in specialist centers. Activity measures based on the classical features of inflammation: clinical activity score (CAS) is the sum of all items present. A CAS R3/7 indicates active GO.

- Spontaneous retrobulbar pain
- Pain on attempted up or down gaze
- Redness of the eyelids
- Redness of the conjunctiva
- Swelling of the eyelids
- Inflammation of the caruncle and/or plica
- Conjunctival edema

EUGOGO severity classifications in GO:

1. Sight-threatening GO: Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown. This category warrants immediate intervention.

2. Moderate-to-severe GO: Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical inter-

TABLE 2: NO SPECS classification.

1) No sign or symptom
2) Only signs
3) Soft tissue involvement
4) Proptosis
5) Extraocular muscle involvement
6) Corneal involvement
7) Sight loss

vention (if inactive). Patients with moderate-to-severe GO usually have any one or more of the following: lid retraction ≥2 mm, moderate or severe soft tissue involvement, exophthalmos ≥3 mm above normal for race and gender, inconstant, or constant diplopia.

3. Mild GO: patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have only one or more of the following: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos <3 mm above normal for race and gender, transient or no diplopia, and corneal exposure responsive to lubricants.

Another classification in determining the severity of GO is defined as VISA classification (**V**ision, **I**nflammation, **S**trabismus, **A**ppearance).[20]

There are several approaches to determine whether GO is in the active phase, and the most widely accepted of them is shown in the following table (Table 3).

DIFFERENTIAL DIAGNOSIS

With typical clinical signs of thyrotoxicosis, increased serum thyroid hormones, a suppressed TSH and positive TRAb, it is not difficult to diagnose thyroid ophthalmopathy. However, the diagnosis can be difficult in some rare cases such as the absence or dimming of clinical symptoms related to thyrotoxicosis, or when serum thyroid hormones are normal. In such cases, especially TRAb positivity is very helpful in the diagnosis of GO. In the following table differential diagnosis of GO are given (Table 4).

TREATMENT

As ophthalmopathy is the "very public" complaint of Graves' disease, ophthalmopathy treatment in these patients is vital. Graves' ophthalmopathy is seen in the majority of cases, although most of them are mild to moderate in severity, more serious of them are up to 3-5% of cases.

Interventions to be made in the treatment of GO depends on the severity of ophthalmopathy, and treatment requires a multidisciplinary approach. Therefore, the severity of ophthalmopathy and clinical activity of the situation should be very well determined. So, the orbital pathology should be well introduced with a good ophthalmologic examination, CT or MRI when needed. In very mild cases, supportive therapy in addition to treatment of thyrotoxicosis (protective goggles, eye drops) is

TABLE 3: Clinical activity score (CAS).

1. Spontaneous orbital pain.
2. Gaze evoked orbital pain.
3. Eyelid swelling that is considered to be due to active (inflammatory phase) GO.
4. Eyelid erythema.
5. Conjunctival redness that is considered to be due to active (inflammatory phase) GO.
6. Chemosis.
7. Inflammation of caruncle or plica.
Patients assessed after follow-up can be scored out of 10 by including items 8-10.
8. Increase of > 2mm in proptosis.
9. Decrease in uniocular ocular excursion in any one direction of > 8º.
10. Decrease of acuity equivalent to 1 Snellen line.

TABLE 4: The differential diagnosis of Graves' ophthalmopathy.

Inflammatory diseases: Graves' disease, orbital cellulitis, Wegener's granulomatosis, Erdheim disease, mucormycosis, pseudotumor cerebri, dakrioadenit.
Neoplasia: Leukemia, menigioma, hemangioma, Hans-Schuller-Christian disease
Vascular diseases: Carotid-cavernous fistula, aortic valve regurgitation
Others: Orbital fracture, retrobulbar hemorrhage, Cushing's syndrome, Pfeiffer syndrome, dermoid cyst, orbital structural pathologies

sufficient. Many approaches can be applied in moderate and severe cases. Treatment success rate decreases with the severity of GO. There are a variety of treatment methods in GO (Table 5).

SUPPORTIVE/PROTECTIVE METHODS

The implementation of simple measures such as cessation of smoking, avoiding stress, using noniodinized salt, high retention of the head while lying in bed, dark glasses and eye drops are quite useful in the treatment of patients with GO.

ANTITHYROID DRUGS (FOR THE TREATMENT OF THYROTOXICOSIS)

It is important to achieve and sustain euthyroidism in patients with GO. For this, antithyroid agents, beta-blockers, dexamethasone, and other agents in some cases are used. Propylthiouracil and methimazole are antithyroid drugs. Both drugs are very similar in terms of efficacy and side effects. With having a mild immunosuppressive effect, reducing peripheral conversion of thyroxine (T4) to triiodothyronine (T3) and being more reliable in the first trimester of pregnancy, propylthiouracil have the advantages over the other. Propylthiouracil is used at a dose of 300-600 mg per day, and methimazole is used in the dose of 30-60 mg/day. Both drugs have minor (approximately 5-10% of cases; skin rash, itching, increased transaminases, etc.) and major (in the 0.3-1% of cases; agranulocytosis, aplastic anemia, etc.) side effects. Antithyroid drugs are usually not recommended for use for more than 2 years. Thyroid function should be checked at 4-6 weeks intervals initially, and at longer intervals after achieving euthyroidism.

Beta-blockers are frequently used to reduce the sympathomimetic symptoms (tremor, tachycardia, sweating, etc.). Classically, propranolol (40-160 mg/day) or other beta blockers are used.

Selenium, a trace element contained in the form of selenoproteins, at doses of 200 mcg a day has been found useful in the treatment of patients with mild GO.[21]

THYROIDECTOMY

Thyroidectomy is one of the methods in the treatment of hyperthyroidism. Thyroidectomy may be preferred in large goiter, nodules, malignancy, pressure symptoms, pregnancy, major side effects of antithyroid drugs and in the presence of moderate-to-severe exofthalmus. It has been suggested that the course is better if thyroidectomy is made in GO cases, but there is no consensus on this issue.[22,23] Total or subtotal thyroidectomy may be done, but relapses can occur in subtotal cases.

CLASSICAL IMMUNOSUPPRESSIVE TREATMENT

Approaches targeting the immune system in the treatment of GO is gaining more and more importance. Suppressing the immune system with corticosteroids, methotrexate, cyclosporine, azathioprine, intravenous (IV) immunoglobulins, etc. have been used.

Immunosuppressive agents that are most often used in the treatment of GO are corticosteroids.[24] Corticosteroid treatment applications should be considered in terms of possible side effects; clinicians should be careful in diabetic, obese, hyper-

TABLE 5: Methods of the Graves' ophthalmopathy treatment.

Supportive/Protective Methods
Anti-thyroid drugs
Classical immune-suppressive therapy (corticosteroids, azathioprine, cyclosporine, etc.)
Radiotherapy
Surgery
New immune-modulatory agents (monoclonal antibodies: anti-CD20, anti-TNF, anti-IGF-1 Ab, anti-IL6)
Others (anti-TSH receptor molecules, quercetin, colchicine, somatostatin analogs, etc.)

tensive patients or in patients with active infections. Corticosteroids may be administered through oral, IV or intra orbital routes. When administered orally, it can be started at high doses (e.g., 60 to 100 mg prednisone or equivalent), and the dose should be reduced gradually over time and withdrawn. Oral corticosteroid therapy response rate averages around 50%.[25] The treatment of choice for moderate-to-severe and active (CAS ≥3/7) GO is pulses of i.v. glucocorticoids (GCs). This treatment should be undertaken in centers with appropriate expertise.[19] It has been shown that a high dose pulse IV steroid administration once or twice a week was more effective.[26] Thus in practice generally 1 g/a week, not exceeding the maximum dose of 8 g of methylprednisolone administration may be used in treatment. High doses of corticosteroids can cause side effects such as immunosuppression, hyperglycemia, osteonecrosis, osteoporosis, gastric bleeding, weight gain, hypertension, Cushing's syndrome, and more rarely, hepatic failure and death.[27] Bisphosphonates are recommended when long-term (>3 months) oral GC therapy (average daily dose >5 mg prednisone or equivalent) is used. It is reasonable to suggest the use of antiresorptive agents also when GCs are used i.v.

Glucocorticoids (GCs) and surgical decompression of the orbit are the only treatments proved to be effective in patients with dysthyroid optic neuropathy (DON). High-dose i.v. GCs is the preferred first-line treatment for DON. If the response to i.v. GCs is absent or poor after 1-2 weeks, or the dose/duration of steroid required induces significant side effects, prompt orbital decompression should be carried out. Orbital decompression should be offered promptly to patients with DON or corneal breakdown who cannot tolerate GCs. Both i.v. GC therapy and orbital decompression surgery should only be undertaken in centers with appropriate expertise.[19]

Steroids can also be given with an intraorbital (retrobulbar) application. In 29 GO patients treated in this way ophtalmopathy was improved, moreover, the orbital steroid injection have been reported to be associated with less side effects.[28]

Methotrexate has also been used in the treatment of GO and has been shown to be useful.[29] Methotrexate can be used in patients which are corticosteroids are not appropriate (GO with diabetes mellitus, obesity, hypertension, etc.).

ORBITAL RADIOTHERAPY

Orbital radiotherapy should be applied in selected cases and in experienced centers. This treatment approach can be useful in 60% of cases.[30-32] Orbital radiation has been thought to be most effective in the inflammatory manifestations of active GO. In a retrospective analysis of 200 GO cases, orbital radiotherapy was quite beneficial on GO results, and long-term complications such as cataract, radiation retinopathy and fibrosis were not more than expected.[33]

Orbital radiotherapy may be administered in each eye as a total dose of 20 Gray (Gy) in 15-20 days fractionally or as 1 Gy in a week for 20 weeks. Lower than classic doses (10 Gy) may be helpful.[34] Higher doses are not more effective. Orbital radiotherapy (OR) is generally well tolerated but sometimes it can cause a temporary increase in eye symptoms. Simultaneous administration of glucocorticoids in these patients is useful. After orbital radiotherapy, particularly in diabetic patients, there may be a slight increase in cataract and retinal microvascular disorders. Given all these data, the orbital radiotherapy should be tried in severe GO cases resistant to other treatments, and should not be administered in mild-to-moderate cases.[35] In another study, orbital irradiation after corticosteroid pulse therapy had no beneficial therapeutic effects on rectus muscle hypertrophy or proptosis of active Graves' ophthalmopathy during the 6-month follow-up period.[36] Combination of GC (either orally or locally) with OR is more effective than either treatment alone. It is unclear whether i.v. GCs with OR are more efficacious than i.v. GCs alone.

ORBITAL SURGERY

Rehabilitative surgery should only be performed in patients who have had inactive GO for at least 6 months. Rehabilitative surgery includes one or

more of the following procedures: (a) orbital decompression (the usual indications being disfiguring exophthalmos, troublesome retroocular pain/discomfort, and/or grittiness associated with minor exposure keratopathy not amenable to topical therapies; (b) squint correction; (c) lid lengthening; (d) blepharoplasty/browplasty.

Orbital decompression for disfiguring exophthalmos is best deferred until the orbitopathy has been inactive for at least 6 months. However, orbital decompression can be considered also in patients with active GO who are intolerant or nonresponsive to GCs, if waiting for spontaneous inactivation of GO can potentially be hazardous for visual function. Eye muscle and lid surgeries are effective treatments for correcting diplopia and improving lid function and appearance.

Various surgical techniques are applied for orbital decompression, combined medial and lateral wall decompression, as well as endoscopic decompression.[37,38] In 56 patients with Graves' ophthalmopathy, orbital bone and fat decompression led to a 5.40 mm decrease in proptosis, when simple orbital fat decompression led to an average of 3.40 mm reduction in proptosis.[39] In the GO treatment, the success of the surgery is often associated with the experience of the expert. Moreover, severity and duration of orbitopathy affects the success.

NEW IMMUNOMODULATORY AGENTS

As the details of the pathogenesis of thyroid ophthalmopathy are reached, more effective therapeutic agents are on the way of development. Inhibition of lymphocyte accumulation in the orbital tissues, blocking of IGF-1 receptors present at the surface of fibroblasts, blocking TNF receptors, etc. are some of these stages. Anti-CD20, anti-TNF, anti-IGF-1 antibodies, etc. are available drugs which modulate the immune system.

Rituximab: Rituximab is a monoclonal antibody against CD20, a transmembrane protein, which is present on the surface of pre-B lymphocytes and mature B-lymphocytes, and is used to treat non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis. Rituximab effectively reduces the CD20 B-lymphocyte population for 6-9 months. The use of rituximab in GO treatment provides benefits continuing up to 18 months.[40-42] A wide range of doses, such as a single dose of 100 mg or 1000 mg several times were administered. A study conducted very recently in patients with mid-severe ophthalmopathy reported that the use of rituximab led to a decrease in IGF-1R + T-lymphocytes and a clinical improvement.[43] Studies are not sufficient to recommend rituximab use in the treatment of GO, although promising results have been reported by some studies.[44,45]

TNF-α inhibitors: After the observation of overproduction of tumor necrosis factor alpha (TNF α) in orbital tissues of patients with GO, anti-TNF agents such as etanercept, infliximab and adalimumab have been raised in the treatment of GO.[25,46] However, there are insufficient data on this subject yet.

Teprotumumab (anti-IGF-1R monoclonal antibody) Teprotumumab, an IGF-1R antibody, decreases TSH and IGF-1-induced proinflammatory cytokine construction in fibroblast cultures.[47] However, data are lacking for the clinical use of teprotumumab in the treatment of GO.

Tocilizumab (anti-IL-6 monoclonal antibody): Tosiluzumab is an anti-IL-6 monoclonal antibody, and was reported to provide a significant improvement in a case of severe ophthalmopathy.[48] There is not enough data regarding the use of this agent in the treatment of the GO.

Anakinra (IL-1 antagonist): Anakinra is an antagonist of IL-1, and has been shown to reduce cytokine production in orbital fibroblasts cultures, but there are insufficient data on the use in cases of GO.[25]

OTHERS

Besides immunomodulating drugs; many agents such as small molecular weight TSH receptor antagonists, colchicine, pentoxifylline, quercetin, somatostatin analogs, selenium, etc. have been tried in the treatment of GO.

TSH Receptor Antagonists: Small molecular weight substances that bind and inhibit the TSH receptor have been developed. They are still in the experimental stage and, in next years have the potential to take part in the treatment of GO. These molecules have been shown to decrease c-AMP, Akt phosphorylation, and hyaluronic acid synthesis by 50-70% in cultured human thyroid cells.[49]

Quercetin: Quercetin is a natural flavonoid decreasing proinflammatory cytokines (IL-1, IL-6, IL-8 and TNF) in orbital fibroblast cultures of patients with GO.[50] However, in humans, related data is absent.

Colchicine: Colchicine is an alkaloid that reduces production of IL-1, IL-2, TNF and other cytokines by reducing the recruitment of leukocytes motility, chemotaxis, phagocytosis, and fibroblast proliferation.[51] In a comparative study with prednisone and colchicine, it was shown that it could be useful in the treatment of active phase of GO.[52]

Somatostatin analogues have been used in the treatment of GO, however, not any good results were obtained.[53]

Selenium: Selenium can provide positive effects in mild to moderate GO cases by reducing the production of proinflammatory cytokines.[21,54] However, the administration of selenium might be more accurate when the serum level is low, instead of starting routinely in every GO patient.

To summarize GO treatment approach briefly; primarily euthyroidism should be provided and sustained in these patients, modifiable risk factors should be eliminated, severity of ophthalmopathy and clinical activity level should be determined. Supportive and protective treatments are adequate in mild cases, while immunosuppression with corticosteroids should be done in patients with moderate to severe ophthalmopathy in the active stage; and orbital decompression and corrective surgery should be performed for patients in chronic phase. Implementation of other immune modulators in active stage is yet on maturation stage. Orbital radiotherapy can be performed in selected patients in the chronic phase and in experienced centers.

SUMMARY AND CONCLUSIONS

Thyroid ophthalmopathy is one of the most important components of Graves' disease, because it affects visual function and quality of life, and at present there is not an excellent method of treatment or prevention. Genetic and environmental factors can be demonstrated in more detail with research on thyroid ophthalmopathy in the future. Again, the subject of which factors affect the course of the disease is one of the issues that need to be investigated further. More specific and more effective treatment approaches for these mechanisms may arise with increased understanding of the pathogenesis of thyroid ophthalmopathy.

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