Int Ophthalmol (2020) 40:1035–1048
https://doi.org/10.1007/s10792-019-01258-7

REVIEW

Thyroid eye disease: current and potential medical management

Jessica M. Pouso-Diz · Jose M. Abalo-Lojo · Francisco Gonzalez

Received: 27 April 2019 / Accepted: 28 December 2019 / Published online: 9 January 2020
© Springer Nature B.V. 2020

Abstract
Introduction Thyroid eye disease (TED) is the most frequent extra-thyroid manifestation of Graves' disease and it is more frequent in middle age and in female gender. Nowadays, the causal mechanisms of this disease are not completely understood, but the current available studies suggest that the main causative factor is the thyroid stimulating hormone receptor.
Materials and methods To collect reports on TED medical management, a thorough literature search was performed in PubMed database. An additional search was made in Google Scholar to complete the collected items.
Results Among the indentified risk factors, tobacco habit is the most relevant. The main criteria to choose a suitable treatment are the activity and severity of the disease. Support measures can be used to improve the patient's symptoms in any phase of the disease. There is a large number of drugs proposed to manage TED, although with different reported rates of success.
Conclusions Currently, the drugs of choice are corticosteroids in moderate-to-severe and in sight-threatening forms. The main problem of corticosteroids is their spectrum of side effects. Therefore, other alternatives are being suggested for medical management of this disease. The efficacy of these alternatives remains unclear.

Keywords Thyroid eye disease · Graves' disease · TSHR · Corticosteroids

Introduction

Graves' disease is an autoimmune disorder that is more frequent in middle age and in females. The signs and symptoms of this disease are thyrotoxicosis, goiter, pretibial myxedema, and thyroid eye disease (TED) [1]. The incidence of Graves' disease is 210 cases/million/year in Sweden, with a peak incidence between 30 and 60 years and a female/male ratio of approximately 4/1 [2]. The most frequent extra-thyroid presentation of this disease is TED [3, 4]. Although TED appears mostly, in patients with Graves' disease, it can also be present in other thyroid disorders, such as Hashimoto's thyroiditis, hyperthyroidism, hypothyroidism, and thyroid carcinoma [5, 6].

TED is an orbital disorder characterized by an inflammatory process in the periocular soft tissues. It has low incidence and prevalence, mostly in its severe

J. M. Pouso-Diz (✉) · F. Gonzalez
Department of Surgery and Medicosurgical Specialties and CIMUS, University of Santiago de Compostela, Santiago de Compostela, Spain
e-mail: jessy7_pd@hotmail.com

J. M. Abalo-Lojo · F. Gonzalez
Service of Ophthalmology and IDIS, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain

www.manaraa.com

presentation [7]. The most prominent clinical manifestations of TED are exophthalmos, strabismus, diplopia, periorbital edema and, in severe cases, dysthyroid optic neuropathy and corneal breakdown [7]. TED appears in about 20% of all Graves' patients [2]. Moderate-to-severe cases of TED have a lower incidence, i.e., 16.1 cases/million/year in Denmark, and are more frequent in females (female/male ratio 5/1) [8]. Dysthyroid optic neuropathy appears in about 5% of patients with TED [9]. The European Group on Graves' Orbitopathy (EUGOGO) studies performed between 2000 and 2012 showed that the current tendency of TED in Graves' patients is to be less active and less severe than previously, probably because of the reduction in the prevalence of smokers and the early diagnosis and treatment of this disease [10].

The main cause of Graves' disease seems to be an abnormal immune response to thyroid-stimulating hormone receptor (TSHR) [11]. TSHR activates the immune system and induces the synthesis of antithyroid antibodies [12]; one of the most relevant is thyroid-stimulating antibody (TSAb) [13]. Since TSHR is also present in orbital tissues, these processes also take place in the orbit, causing TED [14]. Insulin-like growth factor receptor (IGF-1R), related to TSHR [15] and present in B cells, T cells, and fibrocytes [16–18], may also contribute to the development of TED, although its role remains controversial [19]. B-cell-activating factor (BAFF), which is a member of the tumor necrosis factor (TNF) family, also seems to be involved in TED. This molecule has been related to an increase in the survival of B cells in orbital tissues [20, 21]. It is also present in other autoimmune disorders, such as rheumatoid arthritis [22], systemic lupus erythematosus [23], and autoimmune hemolytic anemia [24]. The platelet-derived growth factor (PDGF) seems to be a key factor in the development and maintenance of TED [25, 26], because its expression levels are increased in orbital tissues from TED patients with both active and inactive phases [27]. As a result of the activity of these factors, there is an increase in orbital fibroblasts, differentiation of fibroblasts into adipocytes and myofibroblasts [28], transformation of preadipocytes into adipocytes, production of autoantibodies, increased cytokine and glycosaminoglycan (GAG) levels, and infiltration of extraocular muscles by inflammatory molecules and cells [29, 30]. These events increase inflammation, expansion, remodeling, and fibrosis in periocular tissues [28]. These processes result in the clinical manifestations of TED.

There is no completely reliable, specific, and safe medical drug for TED. Current medical treatments for TED are based on corticosteroid or immunosuppressive therapies. Most of the newly proposed treatments aim to interfere with the mechanisms involved in the pathogenesis leading to TED. To evaluate the outcome of studies or clinical trials testing new drugs of new regimes of drugs already in use to treat TED, it is necessary to assess the results in such a way that comparisons among different studies are possible. Currently, changes in the activity and severity of the disease are used to quantify these outcomes. There is, however, a persistent difficulty in assessing the activity and severity of TED, which may lead to the use of treatments with poor or absent efficacy [7].

To assess the activity of TED, a Clinical Activity Score (CAS) has been proposed. It has seven items, each of them worth one point [4, 31]; TED is in the active phase when CAS $\geq$ 3/7 [32]. Three more items have been added for follow-up purposes [31, 33], so active disease is considered in this case when the patient has $\geq$ 4/10 points [32]. To assess the severity of TED, three scoring systems have been proposed, namely the VISA, modified NOSPECS, and EUGOGO classifications [3, 34, 35]. In the EUGOGO classification, TED is divided into three groups: mild, moderate-to-severe and sight-threatening or very severe [4].

The aim of this paper is to provide an overview of the currently available medical treatments and to introduce novel drugs that, because of their biological properties, could result beneficial for TED patients.

Materials and methods

To collect reports on TED medical management, a thorough literature search was performed in PubMed database up to March 11, 2018, and restricted to those items written in English language. The words used in the searching included the following: active, adalimumab, antibody, BAFF, cyclosporine, corticosteroids, disease, euthyroid, exophthalmos, eye, fibroblast, Graves, hyperthyroidism, management, medical, methotrexate, mycophenolate, ophthalmopathy, orbitopathy, PDGF, radiotherapy, rituximab, selenium, smoking, teprotumumab, therapy, thyroid,

المنارة للاستشارات
www.manaraa.com

tocilizumab, and TSHR. They were used alone or in combination. An additional search was made in Google Scholar to complete the collected items. Reports referenced in the items found in the mentioned search and deemed to be relevant were also included. Those articles not reporting medical treatment of TED were not included in this study.

Results

Preventive actions on TED

There are several actions reported to prevent the occurrence of TED and to avoid the progression of this condition, which include stop smoking, keeping euthyroidism, prophylaxis with corticosteroids, antithyroid drugs and thyroidectomy and selenium.

Smoking

Stopping smoking seems to play an important role in reducing the risk of having and aggravating TED [36, 37]. There is a higher prevalence of TED among smokers [38] and a lower risk of exophthalmos and diplopia if the patients withdraw smoking [39]. Since tobacco decreases the effect of immunosuppressive drugs, smokers have a weaker and slower response to treatment [38, 40, 41]. Several studies show that the effect is dose-dependent [39, 40]. Passive smokers are also harmed, mostly children [42]. The reason why tobacco impairs TED is unknown, but it seems that it may be related to hypoxia and/or increased production of free radicals [41].

Euthyroidism

Both the up- and down-regulation of thyroid activity increase the risk of TED [7, 41] whereas euthyroidism improves TED [7, 32]. The process that causes the impairment of TED can be related to TSHR activation by TSHR antibodies (resulting in hyperthyroidism) and by TSH (thyroid-stimulating hormone) malfunction (resulting in hypothyroidism) [41]. There are however some studies reporting that both antithyroid drugs or thyroidectomy do not have effect on TED [32]. Although there are cases of TED in euthyroid patients [43–45], those represent only 6% of cases [46].

Prophylaxis with corticosteroids

This drug can be used before radioiodine [47–49]. Radioiodine is frequently used for treatment of Graves' hyperthyroidism in some countries [50]. Without corticosteroid prophylaxis, the risk of development or impairment of orbital affectation is 15% [48, 51], being in 5% of cases persistent [48]. The risk seems to be higher in smokers [48, 52] and when the subsequent secondary hypothyroidism is not corrected promptly [53, 54]. In a study, 0.2 mg/kg of prednisone starting 1 day after radioiodine for 6 weeks has been proposed to avoid orbital impairment [49], although another study reports that this is not effective [55]. Another proposed option is 500 mg/week of methylprednisolone i.v. for 2 weeks, followed by 250 mg/week for the next 2 weeks, beginning 1 week after the radioiodine treatment [51].

Antithyroid drugs and thyroidectomy

Some studies show a relationship between the active phase of TED and the serum level of TSHR autoantibodies [56]. Other studies suggest that these antibodies can be useful to detect patients with tendency to develop severe TED [57]. The decrease of these antibodies could be achieved with antithyroid drugs or thyroidectomy [7] and therefore reduce the autoimmune response.

Selenium

This drug could reduce the symptoms, the quality of life, and the risk of development of severe forms of TED. Selenium can be used in mild forms of TED. It was reported that doses of 100 µg twice a day for 6 months were associated with an improved quality of life, less eye involvement, and slower progression of TED as compared with placebo [58].

Supportive management of TED

There are several treatments and procedures that may improve the symptoms and reduce complications of TED. They include artificial tears and moisture chambers to reduce the corneal exposure and ocular dryness, botulinum toxin injections to palliate palpebral retraction [59–61], sunglasses to avoid the photophobia, prismatic lenses or monocular occlusion

المنارة للاستشارات
www.manaraa.com

to improve diplopia [62, 63], and keeping the head elevated while sleeping to reduce palpebral edema [64].

Currently available drugs for medical management of TED

This section describes current treatment for TED. Below, their action mechanisms, posology, advantages, inconveniences, and side effects will be explained.

Selenium

This microelement is incorporated into selenoproteins, most of which are expressed in the thyroid gland [65]. Low levels of selenium seem to increase the risk of thyroid disease [66]. Supplementation with this element reduces the levels of oxygen free radicals that could induce or exacerbate TED [67–70]. It also has immunomodulatory properties. In selenium deficiency, suppressor T cells do not inhibit the production of interleukins that are responsible for stimulating autoreactive T cells and increasing autoantibody production [70, 71]. Some studies have shown that, combined with antithyroid drugs, selenium helps to achieve control and stabilization of thyroid hormone levels in comparison with antithyroid drug monotherapy [72]; however, a current study [73] shows that selenium supplementation has not effects about recurrence or hyperthyroidism. In one study, selenium was administered orally for 6 months (100 μg twice daily) and was found to improve quality of life, eyelid aperture and soft tissue changes and slow down disease progression [58]. The most adequate administration form of selenium is the organic form, known as selenomethionine [70]. Levels of selenium in plasma should not exceed 122 μg/l [74], because it can cause diabetes mellitus type 2 and hyperlipidemia [75–77]. Selenosis occurs when levels exceed 400 μg/day, resulting in nausea, vomiting, abdominal pain, diarrhea, hair loss, nail fragility, peripheral neuropathy, and the smell of garlic in sweat and breath [70].

Corticosteroids

This group of drugs reduces the production of GAG by orbital fibroblasts, inhibits the expression of HLA-DR, the production of cytokines and antibodies and neutrophil and macrophage chemotaxis, and modulates T- and B-cell function [32, 78, 79]. These effects lead to an improvement in orbital inflammation [6, 79]. Although corticosteroids are currently the first-choice drug in TED, they show poor or non-existent response in 20–30% of cases [80, 81]; 10–20% of patients have a relapse when the drug is withdrawn [32]. Corticosteroids can be administered orally, intravenously, or retrobulbarly; the most effective route of administration is intravenous [82]. As intravenous administration achieves a greater decrease in the CAS and has fewer side effects than oral administration [82]. There is no significant difference between oral and retrobulbar administration, but the latter causes fewer gastric problems and lower weight gain than oral administration [83]. Some authors recommend intravenous administration as the first choice [32, 64, 74]. A recommended corticosteroids and dose for i.v. administration is methylprednisolone 500 mg/week for 6 weeks followed by 250 mg/week for six additional weeks [84]. For oral use, the recommended dose starts at 60–100 mg of prednisone and followed by a slow decrease for 5–6 months until complete withdrawal [85]. Another recommended protocol is prednisone 1 mg/kg/day, then a gradual decrease of 10 mg/week until a dose of 20 mg/day is reached, and finally declining to 5 mg/week [64]. The cumulative dose should not exceed 8 g, because higher cumulative doses increase morbidity, including an increased risk of acute liver failure [84, 86] and mortality [80]. In a clinical trial [87], three cumulative doses (2.25 g, 4.98 g and 7.47 g) were compared; the conclusion was that the most effective cumulative dose is 7.47 g, as assessed by the CAS. However, because this benefit is transient and is associated with greater toxicity, it was suggested that an intermediate dose regimen should be used in most cases. The main disadvantages of corticosteroids are their side effects, of which the most relevant are cardiovascular diseases [80, 81] and acute liver failure [84, 86]. Liver damage is caused by dose-dependent toxicity that has a direct effect on hepatocytes. To avoid this problem, screening for hepatotropic viruses and a check for the existence of antibodies against the liver [32] is recommended; moreover, statin therapy should be withdrawn [88]. The most frequent effect on the liver is an asymptomatic elevation in transaminases [32, 89]. Other reported side effects are

المنارة للاستشارات
www.manaraa.com

osteoporosis, increased risk of infection, hyperlipidemia, diabetes mellitus, avascular osteonecrosis, redistribution of fat, cataracts, major depression and psychosis, and polymenorrhea [80, 90, 91].

Cyclosporine

Cyclosporine is an immunosuppressive agent that specifically and reversibly inhibits Th1 helper cells, which in turn causes a decrease in IL-2 and IFN-γ expression [92]. Cyclosporine orally as monotherapy (7.5 mg/kg/day for 12 weeks) has less effect than oral corticosteroids (prednisone 60 mg/day followed by a tapered of 20 mg/day) [93], so it should be used in combination with other drugs. Some authors advise administering cyclosporine with oral corticosteroids in steroid-resistant patients and as a steroid-sparing therapy [93, 94]. The most relevant side effects of cyclosporine are dose-dependent and include renal and liver toxicity and gingival hyperplasia [4].

Rituximab

This drug is a chimeric antibody against the antigen CD20 present on B cells. Rituximab could be useful in TED because it prevents antigen presentation by B cells, therefore reducing the production of TSRH antibodies and inflammatory cytokines [95–97]. This drug can be used to treat moderate-to-severe forms of TED [96]. Some studies have shown that rituximab can be useful in the management of TED [96, 97]. A recent study that compared rituximab (first infusion of 1000 mg twice and then 500 mg once) with i.v. corticosteroids (methylprednisolone 7.5 g) showed better outcomes in moderate-to-severe patients treated with rituximab [98]. These patients showed improved eye motility, visual function and quality of life, and underwent fewer surgical procedures. Other studies, however, report no significant differences with placebo [99] and suggest that this drug can be counterproductive because it may induce dysthyroid optic neuropathy, probably caused by the orbital tissue expansion subsequent to massive B-cell lysis [32, 100]. The main side effects of rituximab are dose-dependent and include increased number of infection episodes and hypogammaglobulinemia [101]. A reaction to the initial administration occurs in 10% of patients apparently caused by its chimerical nature. This reaction is reversible but, in some cases, it could be severe [102].

Anti-TNF-α

TNF-α is a molecule produced by fibrocytes when they are stimulated by TSH or by thyroid-stimulating immunoglobulins. This molecule causes relevant effects, such as the production of adhesion molecules and chemokines in fibroblasts and the recruitment of inflammatory cells to local tissues [103]. Therefore, anti-TNF-α drugs could be useful despite their side effects [64, 74], which include higher risk of infections, lupus-like reactions, immunogenicity, and demyelinating disorders [81, 104]. There are three important drugs in this group, i.e., infliximab, etanercept, and adalimumab. Infliximab is a monoclonal antibody. A case report on a single-dose administration of infliximab showed positive effects in a patient with active TED, with reduced inflammation, improved visual function and scores on the CAS and NO SPECS scales, without noticeable short-term side effects [105]. Etanercept is a recombinant fusion protein of the extracellular ligand-biding portion of the TNF receptor [32]. In one study, it was observed that the administration of 25 mg of etanercept twice weekly for 12 weeks reduced the CAS score, periocular chemosis, and redness without serious side effects [106]. Both etanercept and infliximab may reduce inflammatory signs in steroid-resistant patients, and patients with more severe affectation show better improvement [81]. Adalimumab is a human monoclonal antibody that has the advantage of being administered subcutaneously every 2 weeks, while etanercept is administered twice per week and infliximab requires i.v. administration. A recent report suggested that subcutaneous adalimumab (80 mg followed by biweekly 40 mg administered for at leats 10 weeks) may have a role in the treatment of active TED [81].

Tocilizumab

This drug is a recombinant humanized monoclonal antibody to the IL-6 receptor [64, 74]. IL-6 is a proinflammatory cytokine present in Th1 immune response [32]. Tocilizumab can be used in steroid-resistant patients [64, 74, 107]. One report showed that tocilizumab (8 mg/kg/month i.v., 16 months) improved the CAS score (proptosis in 72% of patients, extraocular motility in 83% of patients, and diplopia in 54% of patients) in steroid-resistant patients [108].

المنارة للاستشارات
www.manaraa.com

The same study reported that, in one case with acute dysthyroid optic neuropathy, administration of this drug prevented orbital decompression. In a recent clinical trial [109], it was found that tocilizumab (8 mg/kg i.v. at weeks 0, 4, 8, and 12) offers a meaningful improvement in activity and severity in corticosteroid-resistant TED. The relevant side effects were increased transaminases in one patient and acute pyelonephritis in another patient. Another recent study observed a reduction in extraocular muscle thickness and conjunctival chemosis after four doses of tocilizumab [107]. The main side effects found in patients with rheumatoid arthritis that use this drug are an increased rate of infections, malignancy, gastrointestinal perforation, lipid changes, and cardiac dysfunction [110].

IGF-1R blockers

IGF-1R is a molecule that is elevated in orbital fibroblasts [15] and in B [17] and T [16] cells in patients with Graves' disease, but it does not seem to be specific to this disease [7, 18, 111]. IGF-1R blockers bind to IGF-1R on fibrocytes and attenuate TSH-dependent signals, leading to a decrease in IL-6 and IL-8 expression [111]. The most relevant member of this group is teprotumumab. This drug is a monoclonal antibody that decreases the action of IGF-1, TSH, and thyroid-stimulating immunoglobulins on orbital fibroblasts and fibrocytes derived from patients with Graves' disease in in vitro studies [15, 111]. Some studies have shown that teprotumumab can decrease orbital symptoms in TED patients [64]. In one trial, patients receiving eight intravenous injections with an initial dose of 10 mg/kg every 3 weeks, followed by 20 mg/kg for the remaining seven infusions, were more effective than placebo in reducing proptosis and CAS [18]. The most relevant observed side effect was increased glycemia in diabetic patients. Other side effects were diarrhea and muscle spasms [18].

Mycophenolate mofetil

Mycophenolate mofetil is an immune modulator drug that inhibits inosine monophosphate dehydrogenase, leading to inhibition of the de novo pathway of guanosine monophosphate synthesis and in turn reducing the proliferation of lymphocytes [74]. A study comparing the efficacy and safety of mycophenolate mofetil (administered orally twice a day a total dose of 1000 mg/day, being the maximum dose 500 mg per dose, for 24 weeks) and corticosteroids (methylprednisolone i.v. 0.5 g/day for 3 consecutive days per week for 2 weeks, followed by oral prednisone 60 mg/day for 8 weeks and then a gradual decrease of 5 mg/week for 14 weeks) in patients with moderate-to-severe forms and in the active phase of TED showed that this drug is effective, safe, achieves better CAS scores, improves proptosis and diplopia, and has lower relapse rate [112]. Another current study [113] compare the use of intravenous methylprednisolone alone (500 mg/week for 6 weeks followed by 250 mg/week for 6 weeks) vs methylprednisolone plus mycophenolate (360 mg twice per day for 24 weeks) did not find significant difference in the rate of response at 12 weeks or rate of relapse at 24 and 36 weeks, but subsequent analyze seems to show an improvement in rate of response by 24 weeks in patients with active and moderate-to-severe TED. For this reason, more studies are necessary. The main side effects are reactivation of infections and gastrointestinal and hematological disorders [112].

Methotrexate

Methotrexate inhibits the dihydrofolate reductase and reduces synthesis of DNA, RNA and proteins [114]. Patients receiving a maximum dose of 15–25 mg/week (with folate supplementation) show improved ocular conditions, mostly regarding soft tissues, extraocular muscles, and visual acuity [91]. It could be used as an alternative to corticosteroids or for corticosteroid sparing [115, 116]. Also, it can be administered for long time to prevent relapses [74]. Side effects include gastrointestinal irritation, liver toxicity, bone marrow depression [6], opportunistic infections, and interstitial pneumonitis [6, 115]. To avoid these side effects, folic acid administration is recommended [6].

Somatostatin analogs

In TED, there is upregulation of somatostatin receptors 1 and 5 on orbital fibroblasts [117]. The members of this group are octreotide, lanreotide, and pasireotide. Several studies have shown that these drugs have little to no effect in TED [118, 119]. For instance, one

المنارة للاستشارات
www.manaraa.com

study showed no differences between an im injection of 30 mg of lanreotide every 2 weeks for 12 weeks and placebo [120]. Pasireotide could be more useful because it has higher affinity for somatostatin receptors 1 and 5 [121], but there are very few studies addressing the effectiveness of this drug in TED. The side effects of pasireotide include nasopharyngitis, glycemia disorders, diabetes mellitus, constipation, and liver function abnormalities [122]. Since octreotide is only taken up by orbital tissues during the active phase of TED and it can be detected by scintigraphy, this drug can be used as a probe to assess TED activity [123].

Potential new drugs to treat TED

This section describes possible future alternatives to treat TED. They have not yet been tested in humans, but could be useful because of the observed in vitro results.

Anti-BAFF

BAFF is a factor that is part of the TNF superfamily and is expressed by orbital fibroblasts [124]. This factor increases in B-cell survival, which in turn induces and maintains inflammation in the active phase of TED [98, 125, 126]. BAFF is produced by the interaction between fibroblasts and T cells. In this process, several cytokines and chemokines, such as IFN-γ and TNF-α, are produced. All these actions promote B-cell survival [124]. Currently, there are no studies on the effect of anti-BAFF drugs for the treatment of TED, but they may be useful because of their biological effects. Atacicept and belimumab are two relevant anti-BAFF members. Atacicept is a recombinant fusion protein, and its side effects are hypersensitivity, injection side reaction, diarrhea, gastritis, and pruritus [127]. Belimumab is a fully humanized monoclonal antibody [128]; its main side effects are post-infusion systemic reactions, influenza, and nausea [129].

Tyrosine kinase inhibitors

PDGF receptors have tyrosine kinase activity. Tyrosine kinase inhibitors block the BB isoform of PDGF receptors [25, 130]. PDGF is elevated by two- to three-fold in orbital tissues in patients with TED in all phases of TED [27, 130, 131]. The main effects of PDGF receptor activation on orbital tissues is an increase in the production of cytokines (IL-6, IL-8, CCL-2, CCL-5, and CCL-7) and GAG by orbital fibroblasts [130]. It also increases the response of fibroblasts to TSHR antibodies [26]. For these reasons, tyrosine kinase inhibitors could play a role in restructuring orbital tissues [32]. This group of drugs includes imatinib mesylate, nilotinib, and dasatinib. The first two drugs were tested using in vitro studies and led to a reduction in hyaluronan (a type of GAG) production [131]. However, when used in other diseases (i.e., chronic myeloid leukemia), they were found to have severe side effects such as periorbital edema, occlusion of peripheral arteries, and cerebrovascular accidents [132]. Furthermore, high doses of imatinib mesylate can increase adipogenesis in orbital fibroblasts [133]. Dasatinib is a second-generation tyrosine kinase inhibitor that is better tolerated and does not induce adipogenesis in orbital fibroblasts [134]. Some side effects include pleural effusion, rash, vomiting, diarrhea, tiredness, headache, anemia, thrombocytopenia, and neutropenia [27, 135].

PIK3/mTORC1 cascade inhibitors

In vitro studies have suggested that these drugs reduce adipogenesis and hyaluronan accumulation [136]. The first generation of these drugs includes wortmannin, LY 294002, and rapamycin. Unfortunately, they have many side effects such as diarrhea, mucositis, hyperglycemia, and anorexia [137]. Currently, there are no studies available related to their use in TED [32].

TSHR ligands

These are molecules of a low molecular weight that have several effects on TSHR as agonists, neutral antagonists, and inverse agonists [32] and therefore could be useful in TED. Currently, there are only in vitro and mouse studies available [138].

Anakinra

This molecule is an antagonist of IL-1. IL-1 receptor is elevated in the orbital fibroblasts of patients with TED, mostly in smokers [32]. The main side effects when used for other conditions are injection-site reactions

المنارة للاستشارات
www.manaraa.com

and infections [139]. No studies have been done yet with anakinra in TED.

CD3 antibodies

This group includes otelixizumab and teplizumab. They cause the depletion of T cells in some diseases [140]. Owing to the relevant function of T cells in TED, they could be useful to treat this disease [10]. There is a lack of published studies with these two drugs in TED patients.

Tanshinone (Tan IIA)

This molecule was isolated from a plant (*Salvia miltiorrhiza*). Tan IIA, when tested in vitro, led to a reduction in IL-6 and IL-8 expression in orbital fibroblasts. Moreover, these studies showed anti-inflammatory, antioxidant, and antiadipogenic effects in orbital fibroblasts from TED patients [141]. However, further studies in humans are needed to confirm these results.

Conclusion

To find out about the available medical drugs of proven or potential use to treat TED, we first performed an initial search in the PubMed database and expanded it further to the most relevant references provided by the papers found in the initial search. As reported in a previously reported meta-analysis [82], we found that the most commonly used drugs are corticosteroids, administered orally or i.v. However, the adverse event profile of corticosteroids is important and should be kept in mind.

The results provided here show that additional medical treatments are available and can be used to treat patients with TED. These include drugs already tested in TED patients with different rates of success such as selenium, cyclosporine, rituximab, anti-TNF-α drugs, tocilizumab, IGF-1R blockers, mycophenolate mofetil, methotrexate, and somatostatin analogs. There are other drugs that, though not tested yet in TED patients, on the basis of their biological effects, can potentially be used to treat this disease. These drugs include anti-BAFF drugs, tyrosine kinase inhibitors, PIK3/mTORC1 cascade inhibitors, TSHR ligands, anakinra, CD3 antibodies, and tanshinone.

Our review of the literature did not attempt to propose medical treatment guidelines for TED, but rather to provide a list of available drugs, their biological mechanism of action, and their effects on this disease. To evaluate the efficacy of a specific treatment, a reliable scoring system of the disease status is needed in order to make comparisons among the available reported studies. The CAS scoring system evaluates disease activity, but does not fully describe the status of the disease. There is a known interobserver variability in the evaluation of the orbitopathy status that may introduce some bias in the definition of mild, moderate or severe affectation, which in turn makes difficult to establish comparisons among the reported studies or trials. Nevertheless, some conclusions can be drawn.

TED patients require preventive measurements consisting mainly of smoking cessation and maintaining euthyroid status. Some support measures such as artificial tears, botulinum toxin, sunglasses, or prismatic lenses may improve the symptoms and reduce complications.

The medical treatment should be administered according to the degree of orbital affectation. In mild cases, selenium can be used. Low-dose corticosteroids can be administered if the quality of life of the patient is altered by the disease [7]. In those cases of moderate-to-severe symptoms, high doses of corticosteroids are the first line of treatment [6, 7, 32]. Although a cumulative dose of 7.47 g of methylprednisolone provides a short-term advantage over lower doses, this benefit is transient. Because of the toxicity observed with this cumulative dose, a lower dose regime may be used in most cases and the high dose regime be reserved for severe cases of TED [87]. If corticosteroids do not have effect or they have no clear effect, the next option is to repeat a corticosteroid cycle. If this measure is still not effective, the next measure is to administer corticosteroids with adjuvant orbital radiotherapy or cyclosporine [7]. Other authors propose methotrexate as alternative to corticosteroids, mostly in patients with dependence or resistance to corticosteroids [74]. It is possible to use monoclonal antibodies as well, such as etanercept, infliximab, adalimumab, tocilizumab, or teprotumumab, to reduce the inflammation and to prevent relapses. However, more studies are needed to evaluate the effectiveness of these antibodies in TED patients.

المنارة للاستشارات
www.manaraa.com

In sight-threatening cases, the first-line treatment is high doses of methylprednisolone [7, 32, 74], although this is effective only in about one half of cases. The recommended dose is 500–1000 mg/day for three consecutive days and repeated 1 week later [32]. This therapy may be continued with corticosteroids i.v., but the cumulative dose should not exceed 8 g [32]. If the patient does not have a positive response, orbital decompression may be required [7]. Other studies suggest that 100 mg of rituximab [32, 96] and adalimumab can be useful in dysthyroid optic neuropathy [81].

Unfortunately, currently available therapies are in many cases unsatisfactory, and many patients are unhappy with their treatment results [142]. The reasons for this outcome may be related to the complexity of the pathogenesis of the disease, which makes it difficult to develop targeted therapies. Additionally, the low incidence and prevalence of TED does not allow the adequate design of randomized clinical trials to test new drugs. Despite our growing knowledge of the molecular, genetic, and immunological mechanisms underlying TED, the results obtained by the reported clinical studies have confounding results, which make it difficult to propose a universally accepted treatment recommendation. In conclusion, the review of the available literature shows that corticosteroids are the most frequently used drugs for the treatment of TED. The efficacy of the remaining drugs, either alone or as combined therapy, remains unclear.

Acknowledgements This work has received financial support from ISCIII (RD16/0008/0003) cofounded by European Regional Development Fund (FEDER), and Consellería de Cultura, Educación e Ordenación Universitaria, Xunta de Galicia (Centro Singular de Investigación de Galicia Acreditación 2016–2019, ED431G/05).

Funding This study was funded by ISCIII (RD16/0008/0003) cofounded by European Regional Development Fund (FEDER), and Consellería de Cultura, Educación e Ordenación Universitaria, Xunta de Galicia (Centro Singular de Investigación de Galicia Acreditación 2016–2019, ED431G/05).

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

References

1. De Groot L, Chrousos G, Dungan K et al (2000) Graves' disease and the manifestations of thyrotoxicosis. Endotext, South Dartmouth
2. Abraham-Nordling M, Byström K, Törring O, Lantz M, Berg G, Calissendorf J et al (2011) Incidence of hyperthyroidism in Sweden. Eur J Endocrinol 165:899–905
3. Barrio-Barrio J, Sabater A, Bonet-Farriol E, Velázquez-Villoria Á, Galofré J (2015) Graves' ophthalmopathy: VISA vs EUGOGO classification, assessment, and management. J Ophthalmol 2015:249125
4. Bartalena L, Baldeschi L, Bobodoris K, Eckstein A, Kahaly G, Marcocci C et al (2016) The 2016 European thyroid association/European Group on Graves' Orbitopathy guidelines for the management of Graves' orbitopathy. Eur Thyroid 5:9–26
5. Briceño C, Gupta S, Douglas R (2013) Advances in the management of thyroid eye disease. Int Ophthalmol 53:93–101
6. Rivera-Grana E, Lin P, Suhler E, Rosenbaum J (2015) Methotrexate as a corticosteroid-sparing agent for thyroid eye disease. J Clin Exp Ophthalmol 6:422
7. Bartalena L (2013) Graves' orbitopathy: imperfect treatments for a rare disease. Eur Thyroid J. 2:259–269
8. Laurberg P, Berman D, Bülow Pedersen I, Andersen S, Carlé A (2012) Incidence and clinical presentation of moderate to severe graves' orbitopathy in a Danish population before and after iodine fortification of salt. J Clin Endocrinol Metab 97:2325–2332
9. McKeag D, Lane C, Lazarus J, Baldeschi L, Boboridis K, Dickinson A et al (2007) Clinical features of dysthyroid optic neuropathy: a European Group on Graves' Orbitopathy (EUGOGO) survey. Br J Ophthalmol 91:455–458
10. Wiersinga W (2007) Advances in treatment of active, moderate-to-severe Graves' ophthalmopathy. Diabetes Endocrinol 5:134–142
11. Inaba H, Martin W, De Groot A, Qin S, De Groot L (2006) Thyrotropin receptor epitopes and their relation to histocompatibility leukocyte antigen-DR molecules in Graves' disease. J Clin Endocrinol Metab 91:2286–2294
12. Akamizu T, Mori T, Nakao K (1997) Pathogenesis of Graves' disease: molecular analysis of anti-thyrotropin receptor antibodies. Endocr J 44:633–646
13. Inaba H, De Groot L, Akamizu T (2016) Thyrotropin receptor epitope and human leukocyte antigen in Graves' disease. Front Endocrinol (Lausanne) 7:120
14. Iyer S, Bahn R (2012) Immunopathogenesis of Graves' ophthalmopathy: the role of the TSH receptor. Pract Res Clin Endocrinol Metab 26:281–289
15. Tsui S, Naik V, Hoa N, Hwang C, Afifiyan N, Sinha Hikim A et al (2008) Evidence for an association between

المنارة للاستشارات
www.manaraa.com

thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in Graves' disease. J Immunol 181:4387–4405
16. Douglas R, Gianoukakis A, Kamat S, Smith T (2007) Aberrant expression of the insulin-like growth factor-1 receptor by T cells from patients with Graves' disease may carry functional consequences for disease pathogenesis. J Immunol 178:3281–3287
17. Douglas R, Naik V, Hwang C, Afifiyan N, Gianoukakis A, Sand D et al (2008) B cells from patients with Graves' disease aberrantly express the IGF-1 receptor: implications for disease pathogenesis. J Immunol 181:5768–5774
18. Smith T, Kahaly G, Ezra D, Fleming J, Dailey R, Tang R et al (2017) Teprotumumab for thyroid-associated ophthalmopy. N Engl J Med 376:1748–1761
19. Khong J, McNab A, Ebeling P, Craig J, Selva D (2016) Pathogenesis of thyroid eye disease: review and update on molecular mechanisms. Br J Ophthalmol 100:142–150
20. Mackay F, Browning J (2002) BAFF: a fundamental survival factor for B cells. Nat Rev Immunol 2:465–475
21. Lied G, Berstad A (2011) Functional and clinical aspects of the B-cell-activating factor (BAFF): a narrative review. Scand J Immunol 73:1–7
22. Leandro M, Cambridge G (2013) Expression of B cell activating factor (BAFF) and BAFF-biding receptors in rheumatoid arthritis. J Rheumathol 40:1247–1250
23. Theodorou E, Nezos A, Antypa E, Ioakeimidis D, Koutsilieris M, Tektonidou M et al (2018) B-cell activating factor and related genetic variants in lupus related atherosclerosis. J Autoimmun 92:87–92
24. Zhao Y, Li J, Wei B, Xu Z (2015) BAFF level increased in patients with autoimmune hemolytic anemia. Int J Clin Exp Med 8:2876–3882
25. van Steensel L, Dik W (2010) The orbital fibroblast: a key player and target for therapy in Graves' ophthalmopathy. Orbit 29:202–206
26. van Steensel L, Hooijkaas H, Paridaens D, van de Bosch W, Kuijpers R, Drexhage H et al (2012) PDGF enhances orbital fibroblast responses to TSHR stimulating autoantibodies in Graves' ophthalmopathy patients. J Clin Endocrinol Metab 97:944–953
27. Virakul S, van Steensel L, Dalm V, Paridaens D, van Hagen P, Dik W (2014) Platelet-derived growth factor: a key factor in the pathogenesis of Graves' ophthalmopathy and potential target for treatment. Eur Thyroid 3:217–226
28. Dik W, Virakul S, van Steensel L (2016) Current perspectives on the role of orbital fibroblasts in the pathogenesis of Graves' ophthalmopathy. Exp Eye Res 142:83–91
29. Bahn R (2010) Graves' ophthalmopathy. N Engl J Med 362:726–738
30. Smith T (2010) Pathogenesis of Graves' orbitopathy: a 2010 update. J Endocrinol 33:414–421
31. Mourist M, Prummel M, Wiersinga W, Koornneef L (1997) Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf) 47:9–14
32. Campi I, Vannucchi G, Salvi M (2016) Therapy of endocrine disease: endocrine dilemma: management of Graves' orbitopathy. Eur J Endocrinol 175:117–133
33. Salvi M (2012) EUGOGO Atlas: EUGOGO protocol for assessment of Graves' orbitopathy and completion of case record form Milan: EUGOGO
34. Werner S (1969) Classification of the eye changes of Graves' disease. Am J Ophthalmol 68:646–648
35. Werner S (1977) Modification of the classification of the eye changes of Graves' disease. Am J Ophthalmol 83:725–727
36. Prummel M, Wiersinga W (1993) Smoking and risk of Graves' disease. JAMA 169:479–482
37. Wiersinga W (2013) Smoking and thyroid. Clin Endocrinol (Oxf) 79:145–151
38. Bartalena L, Marcocci C, Tanda M, Manetti L, Dell'Unto E, Bartolomei M et al (1998) Cigarette smoking and treatment outcomes in Graves ophthalmopathy. Ann Intern Med 129:632–635
39. Pfeilschifter J, Ziegler R (1996) Smoking and endocrine ophthalmopathy: impact of smoking severity and current vs lifetime cigarette consumption. Clin Endocrinol (Oxf) 45:477–481
40. Eckstein A, Quadbeck B, Mueller G, Rettenmeier A, Hoermann R, Mann K et al (2003) Impact of smoking on the response to treatment of thyroid associated ophthalmopathy. Br J Ophthalmol 87:773–776
41. Bartalena L (2012) Prevention of Graves' ophthalmopathy. Best Pract Res Clin Endocrinol Metab 26:371–379
42. Krassas G, Segni M, Wiersinga W (2005) Childhood Graves' ophthalmopathy: results of a European questionnaire study. Eur J Endocrinol 153:515–521
43. Eckstein A, Lösch C, Glowacka D, Schott M, Mann K, Esser J et al (2009) Euthyroid and primarily hypothyroid patients develop milder and significantly more asymmetrical Graves' ophthalmopathy. Br J Ophthalmol 93:1052–1056
44. Termote K, Decallonne B, Mombaerts I (2014) The influence of prior hyperthyroidism on euthyroid Graves' ophthalmopathy. J Ophthalmol 22:426898
45. Perros P, Hegedüs L, Bartalena L, Marcocci C, Kahaly G, Baldeschi L et al (2017) Graves' orbitopathy are a rare disease in Europe: a European Group on Graves' Orbitopathy (EUGOGO) position statement. Orphanet J Rare Dis 12:72
46. Bartley G, Fatourechi V, Kadrmas E, Jacobsen S, Ilstrup D, Garrity J et al (1996) Clinical features of Graves' ophthalmopathy in an incidence cohort. Am J Ophthalmol 121:284–290
47. Bartalena L, Marccocci C, Bogazzi F, Panicucci M, Lepri A, Pinchera A (1989) Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. N Engl J Med 321:1349–1352
48. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda M, Dell'Unto E et al (1998) Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 338:73–78
49. Lai A, Sassi L, Compri E, Marino F, Sivelli P, Piantanida E et al (2010) Lower dose prednisone prevents radioiodine-associated exacerbation of initially mild or absent graves' orbitopathy: a retrospective cohort study. J Clin Endocrinol Med 95:1333–1337

www.manaraa.com

50. Negro R, Attanasio R, Grimaldi F, Guglielmi R, Papini E, AME (Associazione Medici Endocrinology) et al (2016) A 2015 Italian survey of clinical practice patterns in the management of Graves' disease: comparison with European and North American surveys. Eur Thyroid J 5:112–119
51. Vannucchi G, Campi I, Covelli D, Dazzi D, Currò N, Simonetta S et al (2009) Graves' orbitopathy activation after radioactive iodine therapy with and without steroid prophylaxis. J Clin Endocrinol Metab 94:3381–3386
52. Träisk F, Tallstedt L, Abraham-Nordling M, Andersson T, Berg G, Calissendorff J et al (2009) Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131. J Clin Endocrinol Metab 94:3700–3707
53. Tallstedt L, Lundell G, Blomgren H, Bring J (1994) Does early administration of thyroxine reduce the development of Graves' ophthalmopathy after radioiodine treatment? Eur J Endocrinol 130:494–497
54. Perros P, Kendall-Taylor P, Neoh C, Frewin S, Dickinson J (2005) A prospective study of the effects of radioiodine therapy for hyperthyroidism in patients with minimally active graves' ophthalmopathy. J Clin Endocrinol Metab 90:5321–5323
55. Watanabe N, Noh J, Kozaki A, Iwaku K, Sekiya K, Kosuga Y et al (2015) Radioiodine-associated exacerbation of Graves' orbitopathy in the Japanese population: randomized prospective study. J Clin Endocrinol Metab 100:2700–2708
56. Gerding M, van der Meer J, Broenink M, Bakker O, Wiersinga W, Prummel M (2000) Association of thyrotropin receptor antibodies with the clinical features of Graves' ophthalmopathy. Clin Endocrinol (Oxf) 52:267–271
57. Eckstein A, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S et al (2006) Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of disease. J Clin Endocrinol Metab 91:3464–6470
58. Marcocci C, Kahaly G, Krassas G, Bartalena L, Prummel M, Stahl M et al (2011) Selenium and the course of mild Graves' orbitopathy. N Engl J Med 364:1920–1931
59. Morgenstern K, Evanchan J, Foster J, Cahill K, Burns J, Holck D et al (2004) Botulinum toxin type a for dysthyroid upper eyelid retraction. Ophthalmic Plast Reconstr Surg 20:181–185
60. Costa P, Saraiva F, Pereira I, Monteiro M, Matayoshi S (2009) Comparative study of Botox injection treatment for upper eyelid retraction with 6-month follow-up in patients with thyroid eye disease in the congestive or fibrotic stage. Eye (London) 23:767–773
61. Nava Castañeda A, Tovilla Canales J, Garnica Hayashi L, Velasco Y Levy A (2017) Management of upper eyelid retraction associated with dysthyroid orbitopathy during the acute inflammatory phase with botulinum toxin type A. J Fr Ophtthalmol 40:279–284
62. Marcocci C, Marinò M (2012) Treatment of mild, moderate-to-severe and very severe Graves' orbitopathy. Best Pract Res Clin Endocrinol Metab 26:325–337
63. Bhatti M, Dutton J (2014) Thyroid eye disease: therapy in the active phase. Best Pract Res Clin Endocrinol Metab 34:186–197
64. Kumari R, Chandra Saha B (2018) Advances in the management of thyroid eye disease: an overview. Int Ophthalmol 38:2247–2255
65. Duntas L, Benvenga S (2015) Selenium: an element for life. Endocrine 48:756–775
66. Wu Q, Rayman M, Lv H, Schomburg L, Cui B, Gao C et al (2015) Low population selenium status is associated with increased prevalence of thyroid disease. J Clin Endocrinol Metab 100:4037–4047
67. Vunta H, Davis F, Palempalli U, Bhat D, Arner R, Thompson J et al (2007) The anti-inflammatory effects of selenium are mediated through 15-deoxy-Delta 12,14-prostaglandin J2 in macrophages. J Biol Chem 282:17964–17973
68. Saranac L, Zivanovic S, Bjelakovic B, Stamenkovic H, Novak M, Kamenov B (2011) Why is the thyroid so prone to autoimmune disease? Horm Res Paediatr 75:157–165
69. Schomburg L (2011) Selenium, selenoproteins and the thyroid gland: interactions in health and disease. Nat Rev Endocrinol 8:160–171
70. Ventura M, Melo M, Carrilho F (2017) Selenium and thyroid disease: from pathophysiology to treatment. Int J Endocrinol 2017:1297658
71. Carlson B, Yoo M, Shrimali R, Irons R, Gladyshev V, Hatfield D et al (2010) Role of selenium-containing proteins in T-cell and macrophage function. Proc Nutr Soc 69:300–310
72. Vrca V, Skerb F, Cepelak I, Romic Z, Mayer L (2004) Supplementation with antioxidants in the treatment of Graves' disease; the effect on glutathione peroxidase activity and concentration of selenium. Clin Chim Acta 341:55–63
73. Kahaly G, Riedl M, König J, Diana T, Schomburg L (2017) Double-blind, placebo-controlled, randomized trial of selenium in Graves'hiperthyroidism. J Clin Endocrinol Metab 102:4333–4341
74. Strianese D (2017) Update of Graves' disease: advances in treatment of mild, moderate and severe thyroid eye disease. Curr Opin Ophthalmol 28:505–513
75. Stranges S, Navas-Acien A, Rayman M, Guallar E (2010) Selenium status and cardiometabolic health: state of evidence. Nutr Cardiovasc Dis 20:754–760
76. Rayman M (2012) Selenium and human health. Lancet 379:12561268
77. Rocourt C, Cheng W (2013) Selenium supranutrition: are the potential benefits of chemoprevention outweighed by the promotion of diabetes and insulin resistance? Nutrients 5:1349–1365
78. Heufelder A, Wenzel B, Bahn R (1993) Glucocorticoids modulate the synthesis and expression of a 72 kDa heat shock protein in cultured Graves' retroocular fibroblast. Acta Endocrinol (Copenh) 128:41–50
79. Krassas G, Heufelder A (2001) Immunosuppressive therapy in patients with thyroid eye disease: an overview of current concepts. Eur J Endocrinol 144:311–318
80. Zang S, Ponto K, Kahaly G (2011) Clinical review: intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. J Clin Endocrinol Metab 96:320–332
81. Ayabe R, Rootman D, Hwang C, Ben-Artzi A, Golberg R (2014) Adalimumab as steroid-sparing treatment of inflammatory-stage thyroid eye disease. Ophthal Plast Reconstr Surg 30:415–419

المنارة للاستشارات
www.manaraa.com

82. Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, Ezrachi D, Shimon I, Leibovici L (2009) Treatment modalities for Graves' ophthalmopathy: systematic review and metaanalysis. J Clin Endocrinol Metab 94:2708–2716
83. Mou P, Jiang L, Zhang Y, Li Y, Lou H, Zeng C et al (2015) Common immunosuppressive monotherapy for Graves' ophthalmopathy: a meta-analysis. PLoS ONE 10:e0139544
84. Kahaly G, Pitz S, Hommel G, Dittmar M (2005) Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab 90:5234–5240
85. Bartalena L, Pinchera A, Marcocci C (2000) Management of Graves' ophthalmopathy: reality and perspectives. Endocr Rev 21:168–199
86. Sisti E, Coco B, Menconi F, Leo M, Rocchi R et al (2015) Intravenous glucocorticoid therapy for Graves' ophthalmopathy and acute liver damage: an epidemiological study. Eur J Endocrinol 172:269–276
87. Bartalena L, Krassas G, Wiersinga W, Marcocci C, Salvi M et al (2012) Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopahty. J Clin Endocrinol Metab 97:4454–4463
88. Covelli D, Vannucchi G, Campi I, Currò N, D'Ambrosio R, Maggioni M et al (2015) Statins may increase the risk of liver dysfunction in patients treated with steroids for active Graves' orbitopathy. J Clin Endocrinol Metab 100:1731–1737
89. Sisti E, Menconi F, Leo M, Profilo M, Mautone T, Mazzi B et al (2015) Long-term outcome of Graves' orbitopathy following high-dose intravenous glucocorticoids and orbital radiotherapy. J Endocrinol Invest 38:661–668
90. Macchia P, Bagattini M, Lupoli G, Vitale G, Fenzi G (2001) High-dose intravenous corticosteroid therapy for Graves' ophthalmopathy. J Endocrinol Invest 24:152–158
91. Smith J, Rosenbaum J (2001) A role methotrexate in the management of non-infectious orbital inflammatory disease. Br J Ophthalmol 85:1200–1224
92. Emon M, Kodamullil A, Karki R, Younesi E, Hofmann-Apitius M (2017) Using drugs as molecular probes: a computational chemical biology approach in neurodegenerative disease. J Alzheimers Dis 56:677–686
93. Prummel M, Mourits M, Berghout A, Krenning E, van der Gaag R, Koornneef L et al (1989) Prednisone and cyclosporine in treatment of severe Graves' ophthalmopathy. N Engl J Med 321:1353–1359
94. Kahaly G, Schrezenmeir J, Krause U, Schweikert B, Meuer S, Muller W et al (1986) Ciclosporin and prednisone v. prednisone in treatment of Graves' ophthalmopathy: a controlled, randomized and prospective study. Eur J Clin Invest 16:415–422
95. Engel P, Gómez-Puerta J, Ramos-Casals M, Lozano F, Bosch X (2011) Therapeutic targeting of B cells for rheumatic autoimmune disease. Pharmacol Rev 63:127–156
96. Salvi M, Vannucchi G, Currò N, Introna M, Rossi S, Bonara P et al (2012) Small dose of Rituximab for Graves' orbitopathy: new insights into the mechanism of action. Arch Ophthalmol 130:122–124
97. Salvi M, Vannucchi G, Beck-Peccoz P (2013) Potential utility of rituximab for Graves' orbitopathy. J Clin Endocrinol Metab 98:4291–4299
98. Salvi M, Vannucchi G, Currò N, Campi I, Covell D, Dazzi D et al (2015) 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 100:422–431
99. Stan M, Garrity J, Carraza Leon B, Prabin T, Bradley E, Bahn R (2015) Randomized controlled trial of rituximab in patients with Graves' orbitopathy. J Clin Endocrinol Metab 100:432–441
100. Stan M, Salvi M (2017) Management of endocrine disease: rituximab therapy for Graves' orbitopathy—lessons from randomized control trials. Eur J Endocrinol 176:101–109
101. van Vollenhoven R, Emery P, Bingham CO, Keystone E, Fleischmann R, Furst D et al (2013) Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis 72:1496–1502
102. Descotes J (2009) Immunotoxicity of monoclonal antibodies. MAbs 1:104–111
103. Chen H, Shan S, Mester T, Wei Y, Douglas R (2015) TSH-Mediated TNFα production in human fibrocytes is inhibited by teprotumumab, an IGF-1R antagonist. PLoS ONE 10:e0130322
104. Donahue K, Gartlehner G, Jonas D, Lux L, Thieda P, Jonas B et al (2008) Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med 148:124–134
105. Komorowski J, Jankiewicz-Wika J, Siejka A, Lawnicka H, Kłysik A, Goś R et al (2007) Monoclonal anti-TNFalpha antibody (infliximab) in the treatment of patient with thyroid associated ophthalmopathy. Klin Oczna 109:457–460
106. Paridaens D, van den Bosch W, van der Loos T, Krenning E, van Hagen P (2005) The effect of etanercept on Graves' ophthalmopathy: a pilot study. Eye (Lond) 19:1286–1289
107. de-Pablo-Gómez-de-Liaño L, Fernández-Vigo J, Troyano-Rivas J, Niño-Rueda C, Romo-López Á, Gómez de Liaño R (2018) Response to tocilizumab treatment in Graves' ophthalmopathy by measuring rectus muscle thickness and chemosis using optical coherence tomography. Arch Soc Esp Oftalmol 93:386–391
108. Pérez-Moreiras J, Alvarez-López A, Gómez E (2014) Treatment of active corticosteroid-resistant graves' orbitopathy. Plast Reconstr Surg 30:162–167
109. Pérez-Moreiras J, Gomez-Reino J, Maneiro J, Perez-Pampin E, Romo Lopez A, Rodríguez Alvarez F et al (2018) Efficacy of tocilizumab in patients with moderate to severe corticosteroid resistant graves orbitopathy: a randomized clinical trial. Am J Ophthalmol 195:181–190
110. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T et al (2014) Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol 41:15–23
111. Chen H, Mester T, Raychaudhuri N, Kauh C, Gupta S, Smith T et al (2014) Teprotumumab, an IGF-1R blocking monoclonal antibody inhibits TSH and IGF-1 action in fibrocytes. J Clin Endocrinol Metab 99:1635–1640

المنارة للاستشارات
www.manaraa.com

112. Ye X, Bo X, Hu X, Cui H, Lu B, Shao J et al (2017) Efficacy and safety of mycophenolate mofetil in patients with active moderate-severe Graves' orbitopathy. Clin Endocrinol (Oxf) 86:247–255
113. Kahaly G, Riedl M, König J, Pitz S, Ponto K, Diana T et al (2018) Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. Lancet Diabetes Endocrinol 6:287–298
114. Seitz M (1999) Molecular and cellular effects of methotrexate. Curr Opin Rheumatol 11:226–232
115. Bartalena L, Tanda M, Medea A, Marcocci C, Pinchera A (2002) Novel approaches to the management of graves' ophthalmopathy. Hormones (Athens) 1:76–90
116. Sipkova Z, Insull E, David J, Turner H, Keren S, Norris J (2018) Early use of steroid-sparing agents in the inactivation of moderate-to-severe active thyroid eye disease: a step-down approach. Clin Endocrinol (Oxf) 89:834–839
117. Pasquali D, Vassallo P, Esposito D, Bonavolontà G, Bellastella A, Sinisi A (2000) Somatostatin receptor gene expression and inhibitory effects of octreotide on primary cultures of orbital fibroblasts from Graves' ophthalmopathy. J Mol Endocrinol 25:63–71
118. Stan M, Garrity J, Bradley E, Woog J, Bahn M, Brennan M et al (2006) Randomized, double-blind, placebo-controlled trial of long-acting release octreotide for treatment of Graves' ophthalmopathy. J Clin Endocrinol Metab 91:4817–4824
119. Tanda L, Bartalena L (2006) Currently available somatostatin analogs are not good for Graves' orbitopathy. J Endocrinol Invest 29:389–390
120. Chang T, Liao S (2006) Slow-release lanreotide in Graves' ophthalmopathy: a double-blind randomized, placebo-controlled clinical trial. J Endocrinol Invest 29:413–422
121. Bruns C, Lewis I, Briner U, Meno-Tetang G, Weckbecker G (2002) SOM 230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and unique antisecretory profile. Eur J Endocrinol 146:707–716
122. Tahara S, Murakami M, Kaneko T, Shimatsu A (2017) Efficacy and safety of long-acting pasireotide in Japanese patients with acromegaly or pituitary gigantism: results from a multicenter, open-label, randomized, phase 2 study. Endocrinol J 64:735–747
123. Gerding M, van der Zant F, van Royen E, Koornneef L, Krenning E, Wiersinga W et al (1999) Octreotide-scintigraphy is a disease-activity parameter in Graves' ophthalmopathy. Clin Endocrinol (Oxf) 50:373–379
124. Tang F, Chen X, Mao Y, Wan S, Ai S, Yang H et al (2017) Orbital fibroblast of Graves' orbitopathy stimulated with proinflammatory cytokines promote B cell survival by secreting BAFF. Mol Cell Endocrinol 446:1–11
125. Shen S, Chan A, Sfikakis P, Hsiu Ling A, Detorakis E, Boboridis K et al (2013) B-cell targeted therapy with rituximab for thyroid eye disease: closer to the clinic. Surv Ophthalmol 58:252–265
126. McCoy A, Kim D, Gillespie E, Atkins S, Smith T, Douglas R (2014) Rituximab (Rituxan) therapy for severe thyroid-associated ophthalmopathy diminishes IGF-1R (+) T cells. Clin Endocrinol Metab 99:1294–1299
127. van Vollenhoven R, Wax S, Li Y, Tak P (2015) Safety and efficacy of atacicept in combination with rituximab for reducing the signs and symptoms of rheumatoid arthritis: a phase II, randomized, double-blind, placebo-controlled pilot trial. Arthritis Reumatol 67:2828–2836
128. Lenert A, Lenert P (2015) Current and emerging treatment options for ANCA-associated vasculitis: potential role of belimumab and other BAFF/APRIL targeting agents. Drug Des Dev Ther 9:333–347
129. Hewett K, Sanders D, Grove R, Broderick C, Rudo T, Bassiri A et al (2018) Randomized study of adjunctive belimumab in participants with generalized myasthenia gravis. Neurology 90:1425–1434
130. van Steensel L, Paridaens D, van Meurs M, van Hagen P, van den Bosch W, Kuijpers R et al (2012) Orbit-infiltrating mast cells, monocytes and macrophages produce PDGF isoforms that orchestrate orbital fibroblast activation in Graves' ophthalmopathy. J Clin Endocrinol Metab 97:400–408
131. van Steensel L, Paridaens D, Schrijver B, Dingjan G, van Daele P, van Hagen P et al (2009) Imatinib mesylate and AMN107 inhibit PDGF-signaling in orbital fibroblasts: a potential treatment for Graves' ophthalmopathy. Invest Ophthalmol Vis Sci 50:3091–3098
132. Kim T, Rea D, Schwarz M, Grille P, Nicolini F, Rosti G et al (2013) Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. Leukemia 27:1316–1321
133. Li H, Fitchett C, Kozdon K, Jayaram H, Rose G, Bailly M et al (2014) Independent adipogenic and contractile properties of fibroblasts in Graves' orbitopathy: an in vitro model for the evaluation of treatments. PLoS ONE 9:e95586
134. Borriello A, Caldarelli I, Basile M, Bencivenga D, Tramontano A, Perrotta S et al (2011) The tyrosine kinase inhibitor dasatinib induces a marked adipogenic differentiation of human multipotent mesenchymal stromal cells. PLoS ONE 6:e28555
135. Virakul S, Dalm V, Paridaens D, van den Bosch W, Hirankarn N, van Hagen P et al (2014) The tyrosine kinase inhibitor dasatinib effectively blocks PDGF-induced orbital fibroblast activation. Graefes Arch Clin Exp Ophthalmol 252:1101–1109
136. Zhang L, Grennan-Jones F, Draman M, Lane C, Morris D, Dayan C et al (2014) Possible targets for nonimmunosuppressive therapy of Graves' orbitopathy. J Clin Endocrinol Metab 99:1183–1190
137. Kurtz J, Ray-Coquard I (2012) PI3 kinase inhibitors in the clinic: an update. Anticancer Res 32:2463–2470
138. Gershengorn M, Neumann S (2012) Update in TSH receptor agonists and antagonists. J Clin Endocrinol Metab 97:4287–4292
139. Fleischmann R, Schechtman J, Bennett R, Handel M, Burmester G, Tesser J et al (2003) Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. Arthritis Rheum 48:927–934
140. Daifotis A, Koenig S, Chatenoud L, Herold K (2013) Anti-CD3 clinical trials in type 1 diabetes mellitus. Clin Immunol 149:268–278

المنارة للاستشارات
www.manaraa.com

141. Rhiu S, Chae M, Lee E, Lee J, Yoon J (2014) Effect of tanshinone IIA in an in vitro model of Graves' orbitopathy. Invest Ophthalmol Vis Sci 55:5900–5910
142. Estcourt S, Hickey J, Perros P, Dayan C, Vaidya B (2009) The patient experience of services for thyroid eye disease in the United Kingdom: results of a nationwide survey. Eur J Endocrinol 16:483–487

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

المنارة للاستشارات
www.manaraa.com

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.

www.manaraa.com