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Pharmacological Treatments for Thyroid Eye Disease

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Abstract

Thyroid eye disease (TED), which affects the majority of patients with Grave's disease, is associated with significant ophthalmic morbidity. In patients with mild disease, supportive treatment with lubricating medication can be sufficient. However, in patients with severe TED and disfiguring proptosis or sight-threatening neuropathy, more aggressive medical or surgical interventions are necessary. Corticosteroids remain the preferred pharmacological treatment modality in the majority of patients with an active inflammatory component. Other immunosuppressive drugs in combination with corticosteroids may be helpful in patients with corticosteroid-resistant TED. Newer agents such as somatostatin analogues have

not shown to be of significant clinical benefit; however, initial studies on the use of antioxidants and cytokine antagonists are encouraging.

Thyroid eye disease (TED) is a serious ophthalmological condition that affects approximately 50–70% of individuals with Graves' disease.[1] Symptoms include photophobia, foreign body sensation, proptosis and diplopia. Visual deterioration can be secondary to lagophthalmos, exposure keratitis, corneal ulceration or as a result of optic neuropathy.[2-4] Severity of TED is classified as mild, moderate or severe based on the degree of proptosis, constancy of diplopia and the effect of optic neuropathy on visual acuity.[3] There are varying levels of disease activity based on the amount of inflammation present and which correspond to four stages of TED: initial, active, partial regression and static.[3,4] The active phase is characterised by inflammation and dynamic orbital changes and can last from 18 to 36 months. The static phase follows where little improvement or change is noted. TED is associated with a dysthyroid state in 95% of patients and is worsened by smoking and radioactive iodine therapy.[5]

An understanding of the pathophysiology of TED is crucial in choosing the appropriate drug therapies. The exact pathophysiology of TED has yet to be elucidated, although it is known to be a combination of multiple autoimmune, cellular and mechanical processes that are likely to operate in a positive-feedback cycle.[6] Cross-reactivity between thyroid follicular stimulating autoantibodies and orbital tissue thyroid-stimulating hormone (TSH) receptors is probably an important factor in the pathogenesis.[6-9] Furthermore, cytokines, resident macrophages and fibroblasts triggered by either cellular or humoral immunity also play an essential role.[10-13] Orbital fibroblasts are particularly important as they produce glycosaminoglycans that are responsible for the build up of orbital tissue, that in turn create a host of problems – including muscle dysfunction, compressive optic neuropathy, proptosis and periorbital oedema.[6-17] Recently, insulin growth factor-1 has been identified as part of a pathway that activates fibroblasts in TED. Thus, theoretically a pharmacological agent that disrupts this pathway may be useful as a future treatment for TED.[18]

The main treatment modalities for TED are medical (pharmacological and radiotherapy) and surgical.[4] Management is tailored to the severity, activity and stage of disease.[3] While active disease may respond to pharmacotherapy and radiotherapy, treatment for patients with static disease is limited to surgical intervention. In this review we discuss the most common pharmacological options with an emphasis on new and novel pharmacological agents including immunosuppressive drugs, somatostatin analogues, antioxidants and cytokines.

We reviewed the relevant medical literature by searching MEDLINE (1970–2005), using the key phrase 'thyroid orbitopathy', and the combinations with the following keywords 'treatment', 'pharmacological', 'steroids', 'immunosuppressives', 'cytokines', 'somatostatin', 'radiation' and 'decompression'. Our search was mainly on human studies, as well as experimental models in animals, and preference was given to manuscripts published in English-language journals. Articles from peer-reviewed journals were included. From these studies and their references, 205 abstracts were reviewed, and those pertinent to our discussion were selected. Major ophthalmic and medical textbooks were also reviewed for content, as well as original references, and these were manually searched. Clinical studies were selected if they were randomised, controlled trials, single or double-blind, or interventions compared with placebo or other therapeutic agents. Case

series and single case reports were also included when reviewing experimental treatments. The commonly used terms used in this review are defined in table I.

1. Treatment Modalities in Thyroid Eye Disease

1.1 Nonpharmacological Management

The severity of TED is based on the evaluation of clinical signs and symptoms, and is the main criterion of whether treatment is indicated. Approximately 60–80% of patients with the disease show some improvement spontaneously.[5] These patients have a mild course of the disease that can be managed with supportive measures and by eliminating modifiable risk factors, such as smoking and controlling the underlying thyroid disease. Symptoms of dry eyes are controlled by using lubricating eye drops and punctal plugs. Transient diplopia may be corrected with corrective prisms. Patients with lagophthalmos should be instructed to tape their eyes shut at night to avoid corneal damage.

Table I. Definition of commonly used ophthalmological terms

Ophthalmic term	Definition
Chemosis	Subconjunctival oedema
Exophthalmos/proptosis	Forward displacement of the globe
Lagophthalmos	Incomplete closure of the eyelid
Compressive optic neuropathy	Compression of the optic nerve that results in vision loss
Exposure keratitis	Inflammation of the cornea secondary to dryness
Diplopia	Double vision
Retrobulbar	Area behind the eye
Peribulbar	Area around the eye
NOSPECS[a] classification	A method of grading thyroid eye disease based on 6 classes: class 0 (no signs or symptoms) to class 6 (sight loss)

a A common mnemonic for Graves' ophthalmopathy: N = no signs or symptoms; O = only signs (lid retraction/lag/edema); S = soft tissue swelling; P = proptosis; E = extraocular muscle involvement; C = corneal exposure; S = sight loss.

Patients with severe TED manifest the more serious symptoms such as disfiguring proptosis and optic neuropathy, and require more aggressive medical and surgical interventions.

1.2 Orbital Radiotherapy

Studies suggest that orbital irradiation is an effective treatment for TED.[19-23] Orbital irradiation has a nonspecific anti-inflammatory action and may also specifically target orbital lymphocytes and fibroblasts.[20,22] The effects of irradiation are first seen at 2–3 weeks, but gradual improvement can be evident for several months. The response seen is lessening of soft tissue signs, improved ocular motility and improved orbital compliance. However, recently the efficacy of orbital radiotherapy has been disputed.[21,24] A prospective, internally-controlled study, conducted by Gorman et al.,[24] showed little therapeutic benefit of orbital radiotherapy in patients with moderate disease. Furthermore, the majority of studies on radiotherapy show that proptosis tends not to significantly improve.[19,22] Despite these findings, orbital radiotherapy remains a standard treatment offered to patients.[21] The most common adverse effect of orbital irradiation is transient worsening of dry eye symptoms. Cataract formation, radiation retinopathy and optic neuropathy are possible adverse effects that can result in significant visual deterioration.[19,23] However, the protective shielding techniques and the low doses of irradiation that are used have reduced the risk of these potential adverse effects making orbital radiotherapy a relatively safe treatment option.[23,24]

1.3 Surgical Orbital Decompression

Orbital decompression is an option when there is vision loss secondary to optic nerve compression, disfiguring proptosis or severe exposure keratopathy.[25-28] Symptomatic diplopia is the most common complication associated with orbital decompression[29] and may require the use of corrective strabis-

mus surgery. Other complications that are usually transient are postoperative conjunctival chemosis and infraorbital nerve anaesthesia or hyperesthesia. Blindness and postoperative infection are rare complications.[25]

2. Pharmacological Management

2.1 Corticosteroids

Corticosteroids are the mainstay of anti-inflammatory and immunosuppressive therapy of TED and are usually the first choice for treatment. It is thought that corticosteroids act by modulating cytokines, resident macrophages and fibroblasts involved in the pathogenesis of TED. Because corticosteroid use is associated with morbidity, they are not indicated unless moderate to severe symptoms of active orbital inflammation (such as severe orbital congestion, corneal involvement and optic neuropathy) are present. Under these circumstances, treatment is directed at arresting disease activity with the objective of preventing further deterioration of visual function.

The response to corticosteroids is typically seen in 1–2 weeks and includes a reversal of soft tissue signs, increased orbital compliance, improved ocular motility and improvement in visual function as a result of decreased optic nerve compression.[4,30,31] Despite the established role of corticosteroids in relief of acute symptoms, no universally accepted standard of delivery exists. Corticosteroids can be administered locally by injection or systemically via the oral and intravenous routes.[4]

2.1.1 Systemic Corticosteroids

Oral corticosteroids are usually given as a starting daily dose of prednisone 1 mg/kg, followed by gradual dose tapering. In clinical studies, approximately 60% of patients respond to oral corticosteroids;[30] however, improvement is usually limited to a decrease in soft tissue swelling and optic neuropathy, without much improvement in disfiguring proptosis or diplopia.[31] This rate of response is particularly unimpressive when the rate of self-resolution of this syndrome is taken into account.[5] Also, oral corticosteroids require high doses that are not well tolerated and are virtually impossible to maintain without significant complications and an overall decrease in quality of life.[4,32] Discontinuation of oral corticosteroids is generally associated with a relapse of symptoms and signs, unless a slow tapering regimen is implemented.[33]

2.1.2 Oral versus Intravenous Corticosteroids

High-dose intravenous corticosteroids are usually reserved for patients with severe orbitopathy as its use for milder TED is not well elucidated.[34] A study by Marcocci et al.[35] found that 88% (36 of 41) of patients treated with intravenous corticosteroids achieved successful clinical improvement, compared with 63% (26 of 41) treated with oral corticosteroids. However, this and other studies are difficult to interpret because they report composite findings, are frequently not randomised or controlled, and employ multiple strategies and drugs including combinations of oral and intravenous corticosteroids, orbital irradiation or the addition of NSAIDs.[31,35-40]

A recent study by Kahaly et al.[41] compared intravenous and oral corticosteroids for 70 patients in a randomised trial that did not include other treatment modalities. In this study, intravenous methylprednisolone (0.5 g/week for 6 weeks and then 0.25 g/week for 6 weeks) was compared with oral prednisolone (0.1 g/day for the first week and then tapering the dose by 0.01 g/week) in patients with severe untreated TED in the active phase. At 3 months, more patients in the intravenous corticosteroid group had a better clinical response per clinical exam to treatment than in the oral corticosteroid group ($p < 0.01$). Consistent with previous studies, the patients in the intravenous group experienced significantly fewer adverse effects, such as hyper-

tension and depression, than those in the oral corticosteroid group. It was also demonstrated that patients in the intravenous group required fewer additional future treatments such as surgical decompression. However, this study did not include a control group. Macchia et al.,[42] obtained similar results in a similarly designed study with 51 patients divided into two groups (25 patients were treated with intravenous corticosteroids and 26 patients treated with oral corticosteroids). All patients showed improvement in ocular symptoms, but patients in the intravenous group reported fewer adverse events. Interestingly, Kahaly et al.[41] and Macchia et al.[42] showed that the cumulative dose of intravenous corticosteroids used was two to three times lower than in previous studies (4.5g vs 9–12g). This is an important point, as higher doses of corticosteroids are associated with more morbidity.

In a noncontrolled case series of 18 patients, Hart et al.[43] found that high-dose pulsed intravenous methylprednisolone (0.5g) given daily for 3 days effectively treated TED. The authors used a Modified Ophthalmopathy Index Score based on the physical exam as the main outcome measure. Response to treatment was progressively better in patients with shorter time course of disease. Wakelkamp et al.[44] investigated whether surgical decompression or treatment with corticosteroids was the best method for first-line treatment of TED in 15 patients. Treating patients (6 of 15) with surgery initially was not found to yield superior results compared with the traditional method of utilising corticosteroids as first-line therapy (9 of 15). The authors recommended methylprednisolone pulse therapy as the initial treatment for patients with TED, although they noted that intravenous corticosteroids have many potential serious adverse effects, including severe liver damage in susceptible patients.

While the association of fatal liver failure and intravenous corticosteroids has not been proven, the association has been reported,[35,41,45] and should be considered when choosing treatment modalities. High-risk patients, such as those predisposed to liver disease, should be closely monitored for evidence of liver damage when intravenous corticosteroids are used.[41] Interestingly, in the study by Kahaly et al.[41] where a lower total cumulative dose of intravenous corticosteroids was used, no patient had an increase in liver enzyme levels.

2.1.3 Local Corticosteroids

The delivery of corticosteroids locally via orbital injections is another method of treatment for TED, as well as provocative testing for active orbitopathy. The corticosteroid is injected inside the septum near the orbital rim and is usually tolerated well. A number of studies have found varying levels of success with the use of such therapy.[46-53] Potential risks include depigmentation,[54] globe perforation,[55-57] corneoscleral or conjunctival melting,[58-60] occlusion from embolisation or pressure-induced optic nerve compression,[61-68] methyl cellulose initiated granuloma,[54] proptosis, fat atrophy[58-71] and intractable elevated intraocular pressure.[72] Furthermore, placing corticosteroids in an orbit where space is already limited as a result of disease processes may only exacerbate symptoms of TED.[45]

Poonyathalang et al.[47] examined the efficacy of triamcinolone administered by retrobulbar injections in 19 previously untreated patients (27 eyes). They injected triamcinolone once weekly for 4 weeks and found a significant reduction in proptosis after 3 months by approximately 1mm. After 3 months, a reduction of ≥1mm in proptosis was seen in 56% of the eyes, no change in 37% and a worsening in 7%. At 6 months' follow-up, reduction of proptosis was seen in 52% of eyes, whereas a worsening was seen in 11% of eyes. Results for extraocular muscle (EOM) function were less impressive,

with improvement at 3 months in only 41% of patients, no change in 47%, and a worsening of EOM function noted in 12% of patients, and results all static at 6 months' follow-up. Visual field testing did not change during this study. The only significant complication was increase in intraocular pressure in eight eyes that responded to topical glaucoma medications.

In a randomised, controlled study, Ebner et al.[46] examined the effectiveness of orbital corticosteroid injection in 41 patients with early stage TED, 24 in the treatment group and 17 in the non-treatment group. The treatment group received weekly peribulbar injections (triamcinolone 20mg) over 4 consecutive weeks, while the control group received no injections. Diplopia and muscle thickness were used as the parameters for measuring outcome. There was a statistically significant increase in the area of binocular vision without diplopia in the treatment group. In addition, the superior rectus muscle-levator complex significantly decreased in size at 24 weeks. Intraocular pressure and best corrected visual acuity did not differ between the treatment populations at weeks 10 or 24. The authors did not note any adverse effects as a result of the procedure or use of corticosteroids.

Marcocci et al.[48] compared the difference between local retrobulbar corticosteroids versus systemically administered corticosteroids in patients with TED, all of whom also received irradiation (total dose 2000 rads). Forty-four patients were given 14 retrobulbar injections every 20–30 days for 9 months, while 30 patients received systemic corticosteroids tapered over 6 months. Patients were followed for 1–2 years. The authors found that favourable results with local administration of corticosteroids occurred 25% of the time compared with 60% favourable result rate when utilising systemic corticosteroid administration. While the authors did not find local administration to be of equal value to systemic treatment, they did note adverse effects to be milder than with systemic corticosteroids.

Corticosteroids have been the mainstay of treatment for patients with moderate to severe TED and often produce rapid improvement in clinical symptoms. However, whether this leads to an improvement of the final outcome of the disease is yet to be answered.[54] The studies discussed provide evidence that intravenous and local administration of corticosteroids may be safe and efficacious. Furthermore, while some patients may be wary of an injection to the eye, studies suggest that injected corticosteroids have a better adverse-effect profile than oral corticosteroids.[54]

Interestingly, controlled studies have demonstrated that the combination of radiotherapy and high-dose corticosteroids is more effective than radiotherapy alone.[73] Similarly, it has been shown that the combination of orbital irradiation and systemic corticosteroids is more effective than corticosteroids alone.[74] This demonstrates that corticosteroids, used in combination with other treatment plans, may be the ideal method of treating TED.

Clinicians are also using prophylactic corticosteroids in patients with Graves' disease who are treated with radioiodine therapy to prevent the development of TED, as some studies have linked radioiodine therapy with an activation of TED.[75] Worsening of TED after radioiodine therapy is often transient and mild, but studies suggest it can be prevented by concurrent administration of prednisone to selected, high-risk patients.[75] While a deeper exploration of this subject is beyond the scope of this review, it does highlight another use for corticosteroids in the management of Graves' disease; not only are corticosteroids indicated for moderate to severe TED, but for patients with mild TED who will receive radioactive iodine ablation.

2.2 Other Immunosuppressive Drugs

By its very nature as an autoimmune disease, TED would be expected to respond to immunosuppressive therapy.[32] Studies of immunosuppressive drugs have been largely limited to ciclosporin (cyclosporine) and, to a lesser extent, methotrexate.[2,32,76,77] Other possible immunosuppressive drugs are considered unsatisfactory for the treatment of TED.[2,32,76] Most studies on immunosuppressive agents have been uncontrolled and included patients who had received prior treatments.[77,78]

Kahaly et al.[77] conducted a randomised, controlled, prospective study comparing prednisone to a combination of prednisone and ciclosporin in two groups of 20 patients with moderate to severe TED. The first group consisted of patients receiving a tapering dose of prednisone for 10 weeks and the second group consisted of patients receiving 10 weeks of prednisone combined with 12 months of ciclosporin. Severity of symptoms was measured with an activity score which was calculated using subjective and objective symptoms, as well as imaging findings. While the activity score statistically significantly decreased in both treatment groups after 10 weeks, the fall in the activity score was steeper in the combined treatment group at 10 weeks. Furthermore, at 10 weeks the ciclosporin group had a greater reduction in proptosis by an average of 2mm. After the discontinuation of prednisone at 10 weeks, there were fewer patients with rebound inflammatory signs in the ciclosporin group than the prednisone group. In addition, over a 1-year period there were fewer relapses in the ciclosporin group. The authors concluded that the use of ciclosporin with prednisone significantly decreases acute inflammatory symptoms and prevents future flares. However, it is important to note that the activity scale gives disproportionate weight to soft tissue involvement.

These findings are in general agreement with a case series by Leovey et al.[78] that found 9 of 12 patients previously treated with corticosteroids without improvement demonstrated slight or moderately favourable effect when treated with a combination of ciclosporin (250–400 ng/mL) and methylprednisolone (8–12 mg/kg day). Progress was measured with ophthalmic examinations. The authors infer that ciclosporin enhanced the effectiveness of methylprednisolone even in those individuals who were previously glucocorticoid resistant. This study is difficult to interpret; it was not controlled and it is also possible that patients' improvement was entirely due to the intravenous methylprednisolone. However, the authors conclude that since the patients were previously resistant to glucocorticoid monotherapy, ciclosporin was likely to have played a part in their improvement found in the study.

Prummel et al.[79] directly compared prednisone with ciclosporin in treating severe TED. The study was a randomised, single-blind, clinical trial where two groups of 18 patients were either given ciclosporin (initial dose of 7.5 mg/kg bodyweight per day) or prednisone (20–60 mg/day) for 12 weeks. Response to treatment was based on the NOSPECS numerical classification system (table I). After 12 weeks, nine patients in the prednisone group and five patients in the ciclosporin group responded adequately to therapy. Those patients who did not respond to therapy in either treatment group then received both ciclosporin and low-dose prednisone for another 12 weeks. The majority of the subjects who did not respond to a single agent responded to the combination regimen. The authors concluded that single-drug therapy with ciclosporin is less effective than prednisone; however, the combination may be effective in patients who do not respond to either drug alone. Prednisone treatment alone was tolerated less well than combination therapy and ciclosporin alone. Ciclosporin therapy was associated with hypertension (six patients), irreversible rise in serum creatinine levels (one patient) and diverticulitis (one patient).

TED and rheumatoid arthritis may result from a similar pathogenic mechanism. Therefore, some of the commonly used treatments for rheumatoid arthritis can be beneficial in patients with TED.[76,80] Methotrexate is an established treatment for rheumatoid arthritis;[76] however, data on the effects of methotrexate on TED remain limited. Heufelder et al.[81] examined methotrexate as a treatment for refractory TED. The majority of patients with previously unsuccessful orbital radiotherapy or corticosteroid treatment demonstrated improvement with methotrexate therapy. Smith and Rosenbaum[82] examined the effect of methotrexate on several noninfectious inflammatory diseases. Three of the subjects examined had TED in both eyes. All three subjects had undergone treatment with prednisone, irradiation and decompression prior to this study. All subjects experienced clinical benefit with two being able to cease prednisone use. One of the two subjects who ceased prednisone use did have a flare up of the TED that required temporary re-administration of prednisone. Visual acuity improved in one or both eyes in two subjects, while the other subject experienced a slight decrease in visual acuity in one eye.

Adverse effects noted in those with patients with TED who were treated with methotrexate were fatigue, elevated serum liver enzymes, arthralgia, gastrointestinal disturbance and hair thinning.[81] Generally, hepatic toxicity is a serious concern with methotrexate, although it is usually associated with long-term use that would not be likely in the treatment of orbital inflammation.[81,82] The studies using methotrexate are not controlled and so further studies need to be conducted to draw any definitive conclusions about the effectiveness of methotrexate in the treatment of TED.

The studies reviewed show that the use of immunosuppressive therapy for the treatment of TED has potential, especially in treating patients with disease that is resistant to traditional therapies. Whether immunosuppressive agents have a place in the initial treatment of TED is yet to be proven and their benefit should be weighted against their possible serious adverse-effect profile.

2.3 Somatostatin Analogues

The possibility of somatostatin analogues being used for the treatment of TED gained popularity after *in vitro* and *in vivo* studies demonstrated that somatostatin receptors were differentially expressed in the orbits of patients with TED.[83] Two common formulations of somatostatin analogues have been employed: octreotide (available in the traditional and long acting release [LAR] formulations) and lanreotide.[4] Traditional octreotide has a half-life too short to be of significant long-term therapeutic value[4,31] and, therefore, lanreotide and octreotide LAR are the preferred somatostatins.

In a recent review by Krassas,[84] beneficial effects were found in 67% of those given octreotide (70% of those given octreotide LAR [16 of 23] and 80% of those given lanreotide [8 of 10]). However, the studies used to create this aggregate were largely uncontrolled and failed to meet necessary scientific standards.[4,31] There have been several recent studies that have since demonstrated the value of somatostatin analogues to be more modest than originally thought.

Wemeau et al.[85] examined efficacy of octreotide LAR (30mg) in a randomised, double-blind, placebo-controlled study of 51 patients with mildly active TED. Octreotide LAR treatment was administered monthly for 4 consecutive months, while the progress of patients was followed for 6 months after initial treatment. Treatment success or failure was determined by dual observation of NOSPECS and Clinical Activity Score (CAS) criteria.[86,87] At the conclusion of the treatment period (4 months) and the study (6 months), no statistically significant difference in success rates existed between the study groups. Therefore, somatostatin analogue treatment

was not found to confer any significant therapeutic effect. Interestingly, the authors did note a statistically significant change in proptosis at the end of the treatment period. In the treatment group, the mean of bilateral Hertel measurements was decreased by 0.4mm at 4 months, compared with a reduction of 0.2mm in the placebo group. The decrease in proptosis was attributed to the changes in both adipose and muscular tissue. It is noteworthy that at the end of the study period (6 months after initial treatment and 2 months after the final treatment) the difference in proptosis no longer attained statistical significance between the two groups. One limitation was the possible selection bias that existed in this study. Adverse effects were generally mild and involved the gastrointestinal system, although one patient developed gallstones.

Dickinson et al.[88] conducted a randomised, double-blind, placebo-controlled study of octreotide LAR in patients with moderately severe TED. Fifty subjects were divided into two groups (25 patients in each group), with the first receiving intramuscular octreotide LAR 30mg at 4-week intervals for 32 weeks and the second receiving placebo for 16 weeks followed by intramuscular octreotide LAR 30mg at 4-week intervals for an additional 16 weeks. An ophthalmopathy index based on physical examination was used to measure treatment success. The authors found no clinically significant benefit to administration of octreotide LAR. Improvements in the group receiving treatment were generally mirrored by the placebo group indicating that improvement was probably a result of self-resolution of the disease. Proptosis was significantly decreased at 54 weeks for those receiving treatment with octreotide LAR for 8 months compared with those who received the drug for 4 months (preceded by 4 months of placebo). However, the actual change seen was not deemed to be of clinical importance (<1mm). At the initiation of this study, proptosis was higher in the treatment group, which may have influenced the results. The authors noted adverse gastrointestinal events in 65% of those who received treatment for all 8 months and 75% of the placebo group. Five patients in the latter group described these adverse effects as severe, while one patient developed inflammation of the gall bladder. Glycosylated haemoglobin showed a significant, albeit small, increase at 32 weeks in both groups (placebo-LAR 0.4 ± 0.48%; LAR-LAR 0.21 ± 0.20). At 32 weeks, biliary sludge was noted to increase upon ultrasound analysis in both groups (13 in the LAR-LAR group and 7 in the LAR-placebo group).

Despite the initial enthusiasm for somatostatin analogues, it appears that early results must be viewed in light of the tendency of TED to resolve within the natural course of the disease. Thus far, double-blind, placebo-controlled studies have demonstrated only a modest improvement in proptosis. However, it is encouraging that some benefit may be derived from somatostatin analogues. The current range of somatostatin analogue drugs target only two of four somatostatin receptors present in orbital fibroblasts and two of the five receptors found in the lymphocytes of TED patients.[83,89-91] Therefore, there is reason to believe that newer generation somatostatin analogues that target a wider range of somatostatin receptors may show markedly superior results in the treatment of TED. Pasireotide (SOM230) is a somatostatin analogue still undergoing development, which targets the greater range of somatostatin receptors that are seen in TED patients.[92,93]

Currently, the available assortment of somatostatin analogues should be considered in those patients with persistent proptosis that is unresponsive to other therapies. The generally mild adverse effects that somatostatin analogues elicit indicate that concurrent use with other therapies may be palatable from the patient's perspective, even though current benefits are small.

2.4 Antioxidants

Oxygen free radicals have been implicated for a number of years as part of the pathogenesis of TED. One immediate link between TED and oxygen free radicals can be made by the high rate of smokers who contract this condition.[94-97] Lu et al.[98] found that oxygen free radicals were involved in the cytokine interleukin-1β-induced accumulation of glycosaminoglycans. Furthermore, these authors' findings indicated that orbital tissue in TED contained stress-related oxygen free radicals.[98] Heufelder et al.[99] examined the role of oxygen free radicals, oxygen radical scavengers and antithyroid drugs on the expression of a heat shock protein noted to be differentially expressed in the fibroblasts of individuals with TED. Hydrogen peroxide and heat were found to increase the baseline expression of the protein in orbital fibroblasts seen in Graves' disease; with oxygen free radicals partially enacting influence on the heat-induced heat shock protein expression. However, thiamazole (methimazole) and propylthiouracil (antithyroid agents that have oxygen free radical scavenging properties) along with oxygen radical scavengers diminished the hydrogen peroxide expression of the heat shock protein.[99] Burch et al.[100] further added to the belief that orbital fibroblast proliferation seen in TED patients was at least in part caused by oxygen free radicals. Superoxide-induced fibroblast proliferation was inhibited by thiamazole, allupurinol and nicotinamide.[100] The effect of propylthiouracil was small.[100]

Clinical studies of antioxidants in TED are limited. Bouzas et al.[97] conducted a prospective, nonrandomised, comparative study on antioxidants in the treatment of TED in 11 patients using NOSPECS as the outcome measure. Subjects had mild to moderate TED with active disease duration of <6 months, and all persisted in smoking during the study. The antioxidants allopurinol (300 mg/day) and nicotinamide (300 mg/day) for 3 months were compared with placebo.[97] More patients in the treatment group showed a statistically significant overall improvement than patients in the placebo group. In terms of proptosis, the effect of the antioxidants appeared to be limited, resulting in <1mm reduction. Ocular motility increased in 11 of 13 eyes initially affected with limited motility in patients in the treatment group. Decreased visual acuity secondary to punctate epithelial keratopathy were improved in nine of ten eyes. There were significant decreases in soft tissue swelling in the treatment group. Furthermore, no adverse effects of antioxidants were reported. What is particularly interesting about this study is that all patients were cigarette smokers; whether that makes them more prone to benefit from antioxidant treatment, or whether nonsmokers would also benefit from antioxidant treatment, is yet to be determined.

The current data indicate that antioxidants may have a promising role in the control or treatment of TED. However, more controlled studies need to be conducted before any definitive conclusions can be drawn.

2.5 Cytokine Antagonists

Cytokines play an important role in the pathogenesis of TED and, therefore, they are an attractive therapeutic target. There appears to be some level of interplay between antioxidants and cytokines, as suggested in the previously mentioned study by Lu et al.[98] Nicotinamide played a cytokine antagonistic role in a study of orbital fibroblasts of patients with TED.[99] Pentoxifylline is probably the most studied cytokine antagonist with regards to TED and has also been characterised as an antioxidant.[101]

While *in vitro* studies have shown that cytokine antagonists could play a role in TED therapy, clinical investigations of this possibility remain scant. Balazs et al.[102] examined the effect of a combination of intravenous and oral pentoxifylline on ten individuals with moderately severe TED in a

prospective and noncontrolled study. Patients received intravenous pentoxifylline 200 mg/day (10 days), and then oral 1800 mg/day (4 weeks), and then oral 1200 mg/day.[102] NOSPECS was used the measure clinical outcome. All ten patients had contraindications to corticosteroid use because of other medical conditions. Eight patients demonstrated soft tissue improvement. Interestingly, the same eight patients had decreased serum glycosaminoglycans and tumour necrosis factor (TNF)-α levels.[102] However, pentoxifylline treatment did not result in improvement in extraocular muscle motility or proptosis. Two patients experienced persistent nausea during the course of treatment. Given that this study did not include a control population, the results are difficult to interpret; however, it is hopeful that pentoxifylline may be useful in patients who are not able to tolerate corticosteroids.

Finamor et al.[103] preformed a randomised trial using pentoxifylline (1200 mg/day) in 18 women who had inactive TED. It is worth noting that the lack of men presents a potential shortcoming in this paper. Subjects were divided into two groups: one received pentoxifylline for 6 months (group A) and the other received placebo for 6 months followed by pentoxifylline for 6 months (group B). Results were measured by a 10-point subjective health-related quality-of-life questionnaire and objective proptosis measurements. There was a significant decrease in the median questionnaire score in group A after 6 months of treatment. For group B, after 6 months of placebo treatment there was no change in the median treatment score; however after 6 months of pentoxifylline there was a significant decrease in the score. Proptosis was measured every 3 months for both populations; in group A, proptosis was seen to improve significantly at 3 and 6 months. Proptosis remained stable during the placebo portion of group B's regimen, but was seen to decrease in a statistically significant manner every 3 months once pentoxifylline was administered. A portion of subjects (3 of 18) experienced adverse effects with pentoxifylline limited to the gastrointestinal system that improved with symptomatic therapy. The authors concluded that pentoxifylline seems to improve the quality of life and proptosis in patients with inactive TED. Most pharmacological treatment is aimed at helping those patients in the active stages of disease. These findings are promising as they may offer a nonsurgical treatment for inactive TED.

TNFα is a cytokine that is of known importance in TED and has recently become a target of therapy.[80,104,105] Durrani et al.[106] successfully treated a patient with sight-threatening TED with the anti-TNFα antibody infliximab. Etanercept is another anti-TNF agent that blocks TNF from binding to its receptors by binding TNFα itself.[105,107,108] In a recent, prospective, noncontrolled study by Paridaens et al.[105] ten patients with active mild to moderate TED were treated with subcutaneous etanercept 25mg twice weekly.[105] Results were measured using a CAS, ophthalmopathy index (OI), proptosis measurements and patient-self assessment. CAS and OI scores decreased after treatment by 60% and 24%, respectively, with the majority of improvement being a decrease of soft-tissue changes, such as chemosis and erythema. However, periocular inflammatory signs re-emerged in three of the subjects only 2–6 weeks after the end of treatment. Diplopia was present in six of the patients in this study and etanercept provided improvement in three of these patients.[106] No major adverse effects were noted by the authors in this study.

Cytokine antagonists may become part of the treatment of TED in a subset of patients in the future, mainly those who cannot tolerate corticosteroids and patients with inactive disease. However, the long-term effects of cytokine antagonists on malignancies, infections and autoimmune diseases remain to be fully elucidated.[105] In general, cytokine-targeting therapy remains largely in its early stages making it difficult to ascertain the long-

term benefits, risks and costs of this new treatment modality in patients with TED.

3. Conclusion

Approximately 50% of all patients with Graves' disease have no ocular symptoms[31] and, therefore, the best intervention is risk-factor modification to prevent the development of symptoms. Smoking cessation is particularly important, as studies have shown that smoking worsens ocular symptoms.[41] Approximately 45% of patients with Graves' disease have a mild form of eye disease,[31] and for these individuals, assurance and supportive treatments such as lubricating eye drops and protective sunglasses are necessary. Furthermore, studies have supported the prophylactic administration of corticosteroids before radioiodine ablation in patients with mild TED and risk factors for developing the severe form of the ophthalmic disease in the future (tobacco use, high TSH levels and pre-existing eye disease).[31]

The minority of patients (3–5%), have evidence of moderate to severe TED and require more aggressive management.[31] If severe TED is in the static phase, with minimal evidence of active inflammation, then surgical decompression to correct diplopia, exposure keratopathy or disfiguring proptosis may be necessary.[25-28] If severe TED is in the active phase, then current treatment supports the use of corticosteroids with or without orbital irradiation.[109] While intravenous corticosteroids have been associated with liver toxicity,[35,41,45] multiple studies have shown that they are more effective and associated with fewer overall adverse effects than oral corticosteroids.[35-42,100] Furthermore, studies have also supported the use of orbital corticosteroid injections, although some may be weary of injections around the eye.[46-53]

Other pharmacological treatments for severe TED are the subject of ongoing research. While ciclosporin, used as a single agent, was not shown to be as beneficial as prednisone,[79] ciclosporin used in conjunction with prednisone seems to significantly decrease acute inflammatory symptoms and prevents future flares compared with prednisone alone.[77,78] Methotrexate may also be another treatment possibility for patients whose conventional treatment measures have been unsuccessful, although reports of success are minimal and from uncontrolled trials.[81,82] In a study of patients with TED who smoked cigarettes, allopurinol and nicotinamide were shown to improve ocular motility, visual acuity and orbital swelling.[97] This may be significant in patients with Graves' disease who are unable to stop smoking. Cytokine antagonists may be promising for patients who are unable to tolerate corticosteroids because of pre-existing medical conditions, or who have an inactive form of the disease but do not wish to undergo decompression.[103,105]

Unfortunately, as yet, studies on somatostatin analogues have not shown any significant improvement in TED symptoms.[85,88]

Investigation of newer drug treatments for TED is crucial; not only are the mainstay therapies not as effective as desired, but they are associated with adverse effects and morbidity that can potentially be avoided by newer drug therapies. The therapies discussed in this review show promise; however further research needs to be conducted before the full therapeutic benefits of these drug classes are conceptualised.

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