INTRODUCTION

Thyroid ophthalmopathy (TO), also known as thyroid eye disease or Graves’ orbitopathy, is an autoimmune inflammatory disorder involving the orbit. Ninety percent of patients with TO are hyperthyroid, 5% are hypothyroid and another 5% are euthyroid [1]. In a few patients, TO precedes hyperthyroidism [2-5]. Rather than being a complication of Graves’ disease, TO seems to be a concomitant expression of the same underlying pathological autoimmune process directed against cross-reactive autoantigens in the thyroid and retrobulbar tissues [6-9].

In newly diagnosed Graves’ disease, 20% have mild and inactive TO, 5.8% present with moderate to severe, active TO and 0.3% develop compressive optic neuropathy [10]. The natural course of TO is typically characterized by an active phase followed by disease stabilization, as described by the “Rundle curve” [10-15]. An early diagnosis of the active disease phase is important since immunosuppressive and disease-modifying therapies exert their effects only on active TO, while subjects with burn-out TO may only benefit from rehabilitative surgery [16]. The general algorithm for the management of TO is summarized in Fig. 1.

One goal of TO treatment is to control the modifiable risk factors. Uncontrolled hypothyroidism and hyperthyroidism, radioactive iodine therapy and smoking with dose-dependent manner have been associated with development of TO [17-24]. Cessation of smoking, achievement of euthyroidism and prophylactic oral prednisolone prior to radioactive iodine therapy in at-risk patients form important preventive steps to control these modifiable risk factors for TO [24-26].

Although severe TO is rare, it can cause irreversible loss of vision related to corneal exposure and compressive optic neuropathy, and such patients should be urgently treated to avoid devastating sight loss. Despite the management of TO is improved over the decades, an efficient therapeutic strategy remains still elusive, as most patients experience deterioration of their quality of life. This review will describe current trends in the management of TO, from well-established therapies such as glucocorticoids, orbital irradiation and orbital decompression to more innovative therapies targeting immune system or specific molecules involved in TO pathogenesis.
CORTICOSTEROIDS

To date, corticosteroids are the treatment of choice for moderate to severe active TO. Numerous different oral and intravenous regimens are reported, with no clear consensus on the optimum dosage, dosing intervals, and duration of treatment that is undergoing continued refinement [27]. In 2005, Kahaly et al. [28] reported a cohort of 70 consecutive patients with severe active TO randomized to receive either intravenous methyl prednisolone (500 mg methylprednisolone once weekly for 6 weeks, then 250 mg once weekly for 6 weeks) or oral prednisolone (100 mg daily for a week with a gradual taper over 3 months). A positive clinical response was observed in 77% for the intravenous group compared with 51% of those receiving oral treatment. Subsequent studies have shown that pulsed intravenous methyl prednisolone is more effective [29-33] and has a better safety compared with oral prednisone [28,34-38]. More recently, a study on a retrospective series of patients has shown that responsive patients have inactivation of TO as early as 6-8 weeks from the beginning of intravenous methylprednisolone, or may be otherwise switched to other treatments, alone or in combination with steroids [42].

For prevention of radioactive iodine (RAI) induced exacerbation of TO, oral corticosteroids is widely used in daily practice, and prednisone at a dose of 0.2 mg/kg per body weight started 1 day after RAI and withdrawn after 6 weeks can be used [40]. A meta-analysis that evaluated oral prednisone treatment in the setting of RAI therapy suggested that oral prednisone (0.4-0.5 mg/kg) should be used for patients with mild to moderate TO, whereas low-dose prednisone (0.2-0.3 mg/kg) should be used for mild TO and for those patients without pre-existing TO, but with risk factors for developing it [41].

The limitation of intravenous methylprednisolone treatment is that 20-30% of patients are poorly responsive or unresponsive at all and that approximately 10-20% of patients present with disease relapse after drug withdrawal [38]. More recently, a study on a retrospective series of patients has shown that responsive patients have inactivation of TO as early as 6-8 weeks from the beginning of intravenous methylprednisolone, or may be otherwise switched to other treatments, alone or in combination with steroids [42].

With regard to dose, it is recommended that the total cumulative dose of intravenous corticosteroid should not exceed 8 g in consideration of steroid-related adverse effects [36]. A recent prospective observation showed that a cumulative dose of less than 4.5 g had good tolerance and low morbidity [43]. However, in terms of treatment response, a recent multicenter double blind randomized study has shown that a cumulative dose of 7.5 g of methylprednisolone has a higher response rate in patients with moderate-severe TO, when compared with intermediate or lower doses (5 g or 2.25 g, respectively), although it is associated with more frequent adverse events [38].

The morbidity and mortality of corticosteroid therapy in TO patients have been estimated to 6.5 and 0.6%, respectively [36]. Corticosteroids treatment may be accompanied by adverse effects, including liver dysfunction, hypertension, peptic ulcer disease, diabetes, infection, psychosis, or glaucoma [28,44-46]. A marked increase of liver enzymes is the most common adverse event associated with intravenous methylprednisolone. In order to reduce complications, careful screening of risk factors is mandatory. Before the treatment, patients should be screened for hepatitis virus markers and autoantibodies related to autoimmune hepatitis, and clinical monitoring should be regularly performed in order to promptly identify and treat complications [36].

TARGETED TREATMENTS

The mainstay treatments for immunosuppression have been systemic corticosteroids, but which has significant adverse effects mentioned above. Therefore, novel immunomodulating agents targeting several antigens including B cells, tumor necrosis factor
(TNF), thyroid stimulating hormone receptor (TSHR), insulin like growth factor-1 (IGF-1) receptor, interleukin-6 (IL-6) receptor and various inflammatory cytokines has been studied with the purpose of modifying the natural course of disease and sparing corticosteroid [47,48].

1. Targeting B cell

Rituximab, an anti-CD20 monoclonal antibody that targets CD20 on B cells and its precursors is most actively researched immunosuppressive agent [49]. A systematic review of 43 TO cases treated with rituximab showed improvement in disease activity and severity in 91% [49]. A randomized controlled trial in Europe comparing rituximab to intravenous methylprednisolone in active moderate-severe TO supports effectiveness and disease-modifying effects with 100% response rate, no reactivation of TO at 24 weeks and less rehabilitative surgery required at 76 weeks [50]. However, a prospective randomized, double-blinded, placebo-controlled trial comparing rituximab to placebo did not show a significant difference in the improvement of disease activity at 24 and 52 weeks, and there were more moderate-to-severe adverse events in the rituximab group [51]. As so, the effect of rituximab remain conflicting in the treatment of TO.

2. Targeting TNF

There are small number of researches about anti-TNF monoclonal antibodies adalimumab and soluble TNF receptor etanercept in patients with active TO [52-54]. Adalimumab reduced inflammatory score in 6 of 10 patients, the greatest benefit being seen in active TO with severe inflammatory signs [54]. Etanercept was found to be effective in controlling activity of TO, leading marked improvement in mainly soft tissue changes reported at 60%, but up to 30% had recurrence of TO activity after treatment cessation [52].

3. Targeting TSHR

A recently developed drug-like small molecule antagonist of TSHR binds to TSHR and blocks basal and stimulated signal transduction [55]. Because cAMP, pAkt, and hyaluronan production are fibroblast functions that are activated via TSHR signaling and are important in the pathogenesis of TO, small molecule TSHR antagonists may prove to be effective in the treatment or prevention of the disease in the future [55].

4. Targeting IGF-1 receptor

The IGF-1 receptor is coexpressed on orbital fibroblasts along with the TSH-R and in vitro blocking of the IGF-1R attenuates TSH-dependent signaling [56]. In recent study, it was found that fibrocytes treated with teprotumumab, a human monoclonal antibody that blocks the IGF-1 receptor were found to have lower levels of expression of IGF-1 receptor and TSH receptor, suggesting teprotumumab could have a role in reducing or even preventing TO [56].

5. Targeting IL-6 receptor

Another important pathway in active TO is represented by the IL-6/soluble IL-6 receptor system. Elevated serum soluble IL-6R concentrations were in fact measured in patients with active TO [57]. Tocilizumab, a recombinant, humanised monoclonal antibody to IL-6 receptor, has been trialled in 18 patients with active TO refractory to intravenous steroids. After tocilizumab infusion, CAS improved in 100% patients, proptosis decreased in 72%, and ocular motility improved in 83%. In this cohort, one patient with compressive optic neuropathy improved, avoiding orbital decompression [58].

ORBITAL IRRADIATION

Orbital lymphocytes and fibroblasts are sensitive to ionizing radiation [59] which is particularly effective in improving muscle motility during active disease [60]. Although a typical radiotherapy dose is 20 Gy, given in 10 fractions of 2 Gy, lower doses may be equally as effective [61]. A cumulative doses between 10 and 20 Gy may be effective [61]. Orbital irradiation is best effective in patients in whom irradiation was given shortly after the onset of symptoms and relatively ineffective against fibrotic extraocular muscle restriction or strabismus and has no effect on chronic proptosis [62]. Orbital irradiation is found to be effective for tapering off corticosteroid [63] and more effective when a combination of oral glucocorticoids and orbital irradiation is used rather than either treatment alone [59]. Orbital irradiation combined with long-term azathioprine has been found to be effective in thyroid-related restrictive myopathy [64].

Orbital irradiation should be used with caution in diabetic patients due to the risk of new or deteriorating diabetic retinopathy and preferably restricted to patients older than 35 years of age due to the long latency of radiotherapy-induced tumors [65].
ORBITAL DECOMPRESSION

Orbital decompression is a surgical procedure in that bone and fat removal may be performed separately or combined to maximize decompression. The choice of surgery is dependent on a combination of individual surgeon’s preference and intersubject variability in orbital morphology [66,67]. Immediate decompression surgery has no advantage over intravenous steroid therapy for improvement of visual acuity in the short term and surgical manipulation may worsen orbital inflammation if performed during the active phase [68]. However, in compressive optic neuropathy, when a prompt and adequate response is not seen with high dose systemic steroid, surgical decompression should be considered. In compressive optic neuropathy, the goal of orbital decompression is to relieve the hydrostatic pressure at the orbital apex, therefore reduce orbital congestion and improve vascular perfusion and axonal flow within the optic nerve [69]. The retrocaruncular transconjunctival approach is useful for removing the bony medial wall as far posteriorly as the annulus of Zinn allowing wide visualization of the entire medial orbital wall for effective decompression of the orbital apex with no visible scar and minimal tissue injury [69]. For two wall decompression, the conjunctival incision can be extended into the inferomedical conjunctival fornix to allow adequate exposure to decompress the anterior orbital floor medial to the infra-orbital nerve [69]. In more severe cases, the full three wall including lateral wall can also be decompressed through a lower lid swinging flap alone [69]. The balanced orbital decompression including simultaneous medial and lateral wall decompressions is thought to reduce the risk of postoperative diplopia by ‘balancing’ the amount of decompression on both sides of the orbit, thus reducing horizontal globe shifts [70]. In patients with compressive optic neuropathy who fail three-wall decompressions, the addition of transcranial orbital roof decompression can be performed [71]. The previous report about transcranial approach, showed improved visual acuity and visual field and reduced proptosis with no change in diplopia after 5 years of follow-up [71].

Diplopia after decompression surgery is not uncommon that is why orbital decompression is performed prior to strabismus surgery in the management of TO. A recent study reported that opening the periorbita was associated with an increased incidence of new-onset diplopia [72]. Opening the periorbita allows orbital soft-tissue content herniation, but may have an undesired effect of increased diplopia. In that report, when 123 patients undergoing medial wall and strut sparing floor decompression surgery were reviewed, in cases with periorbita opening, the incidence of new diplopia was 26.8% compared to 10.8% in cases in which periorbita remained intact [72].

As for the normalization of visual function after decompression surgery, almost half of patients have persistent visual field defects [73]. However, recently reported case series of patients with no-light perception vision from dysthyroid optic neuropathy with onset of 5 days to 3 months showed a return of vision following orbital decompression suggesting that axonal death may be delayed by months after total nerve function loss and that decompression may still be effective in reversing compressive optic neuropathy in patients with no-light perception vision of up to 3 months [74].

CONCLUSION

Despite extensive research, TO continues to be a difficult condition for the patient to cope with and for the clinician to treat. Patients with TO should be treated according to the severity of their eye disease, keeping in mind that TO has a broad spectrum of clinical manifestations and a highly variable natural course. Current treatments consist of systemic immunosuppression, orbital irradiation, and surgery. Along with these treatments, achieving euthyroidism and smoking cessation should be emphasized. It is promising for patient refractory to conventional therapy that pathogenesis of TO at molecular level which advance development of new therapies targeting cellular immunity are now better understood. Future therapies targeting immune system or specific molecules are under investigation and show promise for the future.

REFERENCES


