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Management of eyelid retraction related to thyroid eye disease

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Abstract:

Eyelid retraction related to thyroid eye disease (TED) is a challenging condition. It is one of the main clinical signs and a major diagnostic criterion in TED. This condition may threaten vision due to exposure keratopathy, in addition to its esthetic alterations, which may lead to psychosocial implications and affect the patient's quality of life. Although it is more commonly observed in the upper eyelid, it may be present on both the upper and lower lids. Numerous surgical and nonsurgical treatment modalities have been described and will be reviewed in this article. Management should be based on an individual patient assessment, taking into consideration the disease stage, severity, and clinician experience.

Keywords:

Biological agents, blepharotomy, botulinum toxin, eyelid retraction, hyaluronic acid, levator recession, spacer grafts, thyroid eye disease, triamcinolone

Introduction

Thyroid eye disease (TED) is an autoimmune disease that can result in visual impairment and cosmetic disfigurement. It is often associated with Grave's disease.[1-3] Approximately 15%–30% of patients with Grave's disease will experience clinically significant TED.[4] The prevalence of TED among Asians was found to be higher when compared to Europeans. This higher prevalence of TED in Asians could be due to genetic predispositions, biochemical factors, or the higher prevalence of smokers in Asian countries.[2]

The European Group on Graves Orbitopathy classification system separates the severity of TED into three broad categories [Table 1].[5] Mild TED usually includes one or more of the following: Mild eyelid retraction (<2 mm), mild soft-tissue involvement, exophthalmos of <3 mm above normal, transient or no diplopia, and corneal exposure amenable with lubrication. Moderate-to-severe TED impacts daily life and usually includes one or more of the following: Eyelid retraction ≥2 mm, moderate or severe soft tissue involvement, exophthalmos 3 mm or more above average, and diplopia. Patients with dysthyroid optic neuropathy, severe corneal exposure, globe subluxation, choroidal folds, or transitory visual obscurations are categorized as having sight-threatening TED.[5]

Eyelid retraction is one of the main clinical signs and a major diagnostic criterion in TED. Upper eyelids resting at or above the limbus, while lower eyelids resting below the lower limbus are considered retracted.[2,6-8] Bartley found that eyelid retraction was the most common ophthalmic feature of autoimmune thyroid disease, being present either unilaterally or bilaterally in >90% of patients in Olmsted County, Minnesota; lower eyelid retraction (LER) was observed in 85% in a cohort of 120 patients at the time of diagnosis.[9,10] Eyelid retraction may threaten vision due to exposure keratopathy, in addition to its esthetic alterations, which may lead to psychosocial implications and affect the patient's quality of life.[6,11,12] Although it is more commonly

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Table 1: Severity of Grave's orbitopathy classification (adapted from the European Group on Graves Orbitopathy)

Stage	Features
Mild GO	Minor lid retraction <2 mm
	Exophthalmos <3 mm above normal
	No or intermittent diplopia and corneal exposure responsive to lubricants
Moderate-to-severe GO	Lid retraction ≥2 mm
	Exophthalmos ≥3 mm above normal
	Inconstant or constant diplopia
Sight-threatening GO	Dysthroid optic neuropathy and or/ corneal breakdown

GO=Grave's orbitopathy

observed in the upper eyelid, occurring in approximately 80% of TED patients, it may be present on both the upper and lower lids. Eyelid retraction can also be associated with lagophthalmos on downgaze and nighttime lagophthalmos.[1] In Asian individuals, LER can coexist with entropion due to the unique ethnic anatomical features.[13]

The eyelid retraction mechanism is likely multifactorial.[7,14-16] In 1939, Pochin proposed that exaggerated sympathetic stimulation could be one of the mechanisms of eyelid retraction.[17] However, Noh *et al*. observed that there is sympathetic overactivity in extraocular muscles in healthy patients and patients with TED, suggesting that the cause of eyelid retraction was not related to sympathetic overactivity alone.[18] Some studies found evidence that inflammation and fibrosis of Muller's muscle may be present in TED.[19,20] Regarding the levator palpebrae superioris muscle, some authors point to the enlargement of this muscle and overactivity in TED patients due to a possible restriction of the inferior rectus muscle secondary to Hering's law.[15,21,22] In an analysis of 50 patients with unilateral TED-related upper eyelid retraction (UER), on tomographic analysis, in 85% of the cases, the levator palpebrae superioris muscle was enlarged when compared to the healthy side.[23] Another mechanism proposed takes into account the orbicularis oculi muscle. A study with rabbits with hyperthyroidism reported a reduction in myofibers in the preseptal portion of the orbicularis muscle when compared to normal controls. Thus, weakened tonus in the orbicularis muscle could lead to overaction of the levator muscle.[24] Regarding the lower eyelid, in TED, an increase of the inferior rectus muscle is often observed; this excessive tension on the margin could lead to LER.[25]

Without treatment, in the natural evolution of TED, there is usually an initial, progressive phase of inflammation that usually lasts from 6 to 24 months, reflecting the autoimmune process, followed by a plateau, and a final phase of remission that can last more than 12 months and is characterized by regression of the inflammatory process and the development of fibrosis.[26,27]

Eyelid edema is frequently observed in patients with TED. Its origin is still unknown. Histological analysis shows lymphatic dilatation and perivascular cellular infiltrates, mostly lymphocytes, in the dermis.[28]

When evaluating the ocular surface of patients with TED, instability of the tear film and varying degrees of dry eye syndrome are often present. Squamous conjunctival metaplasia associated with decreased Schirmer's test in graves patients has been reported. These damages have been attributed to inflammation of the ocular surface.[29,30]

Surgical Management

Surgical intervention in TED is usually indicated during the quiescent phase and in a stepwise approach because each of the procedures can influence the results of the other.[2,31] Orbital decompression is usually performed first if deemed necessary, followed by strabismus surgery, and finally, eyelid retraction surgery.[1] However, single-stage surgical approaches have also been demonstrated to be effective, especially if there is no clinical extraocular imbalance before surgery.[32,33] Ben Simon *et al*. compared simultaneous orbital decompression and correction of UER (97 patients) versus staged procedures (61 patients) and have shown no inferiority in final results regarding margin reflex distance (MRD1), lagophthalmos, and exophthalmos. Overcorrection and consecutive ptosis occurred less often after combined orbital decompression and eyelid retraction surgery than after isolated eyelid repositioning surgery.[32] Bernardini *et al*.[33] reported orbital decompression surgery associated with esthetic eyelid surgery in a single stage: Retraction correction was carried out using two different techniques based on the amount of eyelid retraction as determined preoperatively; for retraction of 3 mm or less, a posterior Muller's muscle recession was performed after orbital decompression with the patient under general anesthesia, and intraoperative adjustment was not required. For cases with more than 3 mm of retraction, an anterior blepharotomy was performed before the decompression, with the patient awake to allow for intraoperative adjustment. Upper blepharoplasty and transconjunctival lower blepharoplasty were also performed, and en-bloc lower eyelid retractor release immediately after completion of the transconjunctival lower blepharoplasty was performed to repair LER.[33]

Upper Eyelid Retraction

Numerous surgical techniques to treat TED-related UER have been described, aiming to obtain predictable and satisfactory postoperative eyelid contour and height,

including full-thickness blepharotomy, Mueller's muscle recession or excision, anterior or posterior levator recession with or without adjustable sutures, use of spacer grafts, levator lengthening by marginal myotomy, castellated levator aponeurotomy, orbital septal flap, and medial transposition of the lateral horn of the levator aponeurosis.[7,32-48]

Elner *et al*.[35] presented the graded full-thickness anterior blepharotomy procedure, first communicated by Koornneef in 1999. The technique consists of a standard lid crease incision in the area of most significant lid retraction, followed by dissection through the orbicularis oculi muscle and septum. Then, levator, Muller's muscle, and conjunctiva are incised just superior to the tarsal plate, and the incision is extended in a full-thickness fashion, medially and temporally. A modified technique was described by Hintschich and Haritoglou[34] who advises preserving a central pedicle of the conjunctiva to prevent central ptosis. Since retraction is usually worse laterally, addressing the lateral horn is almost always necessary to obtain an adequate height and shape of the eyelid.[34] This technique provides significant advantages: It is simple, does not require great surgical skills or experience, and is applicable for any degree of UER. Postoperative complications related to this procedure include ptosis, wound dehiscence, full-thickness hole, and overcorrection of contour after suture removal.[34] Lee *et al*.[36] described a modified graded full-thickness blepharotomy in East Asian patients. Their technique is similar to that described by Hintschich and Haritoglou,[34] but the composition of the bridge described by Lee *et al*.[36] is variable depending on the severity of the retracted eyelid. The extent of the blepharotomy is determined by asking patients to cooperate intraoperatively to assess eyelid height and contour. Skin-tarsal plate-skin tight fixation suture is performed at the end to prevent the formation of multiple lid creases since the levator muscle is transected during the blepharotomy.[36]

The blepharotomy procedure permits to address possible fibrosis of the conjunctival substantia propria.[49] Nevertheless, Kikkawa[50] observed no significant difference in fibrosis or quantitative fibroblast count between palpebral conjunctival specimens obtained from patients who underwent recession of LPS and Muller's muscle for UER in the quiescent stage of TED and a control group.[50]

Numerous surgical techniques have been described aiming to debilitate the upper eyelid retractors (levator muscle and Muller's muscle) alone or in combination by an anterior or posterior approach.[7,32,40,41,51,52] Posterior-approach Müller's muscle recession avoids an external upper eyelid scar and leaves the anterior eyelid structures intact, thus facilitating, if necessary, revision by an external lid approach.[41] The need to increase/direct the debilitation of the retractors laterally to correct the lateral flare, and graded recession have been described as key surgical steps, as well as the use of local anesthesia to control the amount of correction intraoperatively.[7,51,52]

The use of spacers to lengthen the levator palpebrae superioris muscle has been reported.[43,44] Watanabe *et al*.[43] described a transcutaneous levator-lengthening technique using the reflected orbital septum as a spacer in TED patients. The orbital septum is dissected and sutured to the superior one-third of the tarsal plate using two or three 6-0 vicryl sutures to achieve the correct contour. Alternatively, a flap can be associated with a graded recession in the context of anterior blepharotomy. This technique may not be possible in all patients since the orbital septum may be attenuated and dehiscent in older patients.[43] Adjustable sutures have also been described; however, nowadays are not used by the majority of surgeons probably because the final results are seen only 4 or 6 weeks after surgery.[7]

For cases of retraction in both the upper and lower eyelids, there is a greater concern for exposure keratopathy from lagophthalmos. Lee *et al*.[53] described a technique of simultaneous transconjunctival repair of upper and LER in patients with TED without harvesting tissue from a third surgical site. An internal incision is made in the upper eyelid to allow for upper eyelid recession as well as the harvest of an autologous tarsoconjunctival graft. Initially, a line 4 mm superior to the inferior margin of the tarsus is delineated (at least 4 mm is left in the upper eyelid to maintain its structural integrity and prevent horizontal kink). A full-thickness tarsoconjunctival graft is harvested to include all of the tarsus from the 4 mm marking up to the superior margin of the tarsus. The graft is then placed in the lower lid as a posterior spacer graft after recessing the retractors at the inferior tarsal border. Attention is then returned to the harvest site in the everted upper eyelid: Sequential incisions are made through the exposed Muller's muscle and levator aponeurosis in a graded fashion until the upper eyelid has been recessed to the desired height. Finally, traction sutures are placed through the margins of both the upper and lower eyelids and are tied to each other as a temporary tarsorrhaphy for 5–7 days. They studied 22 eyes of 19 patients with TED, and the average change in MRD1 was 1.86 ± 1.34 mm, while the average change in the inferior scleral show was 1.3 ± 0.49 mm.[53]

Surgical outcomes are variable with any type of technique, and there is no consensus about the best surgical correction for TED-related UER.[7]

Lower Eyelid Retraction

There are two main procedures to raise the lower lid in TED: Recession of the capsulopalpebral fascia with or without the use of spacers, by either a transcutaneous or transconjunctival approach.[25,54] A composite recession of the orbital septum and inferior retractor complex, combined with the release of the inferior retractor lateral horn, followed by the release of the orbitomalar ligament and advancement of the lower-eyelid skin, orbicularis, and conjunctiva, has also been described to elevate the lower lid.[55]

The posterior route is the preferred method to address the eyelid retractors.[25] If the retraction is severe (more than 3 mm), a spacer interposition between the recessed retractors and the inferior tarsal border is indicated to counteract gravitational effects and postsurgical scarring that tend to push the eyelid downward after surgery.[25] Around 2 mm of elevation is reported by most surgeons after the use of spacers to correct LER.[25]

A variety of autologous and alloplastic grafts have been described for the management of LER.[25,56,57] The ideal spacer graft should be biocompatible, easily accessible, have a low rate of contracture, some degree of stiffness to provide support, and finally, it should promote tissue integration with minimal inflammation and allow mucosalization on the conjunctival side.[56] Size, thickness, shape, pliability, and structural constraints, as well as donor site morbidity, may limit the use of autologous grafts. Although synthetic options are available, integration may be limited, and extrusion or foreign-body reactions may occur.[57]

The surgical technique for lower eyelid posterior graft implantation is similar across studies: Graft placement inferior to the tarsus. Adjunctive major procedures reported are variable and include canthoplasty, tarsorrhaphy, midface lift, orbit decompression.[56]

Eye banked sclera was the first posterior spacer graft used in the lower eyelid. However, its use may be limited due to degradation, shrinkage, and concern for rejection and transmission of pathogens, including prions.[57] The use of fascia allografts has also been described, but they lack the necessary rigidity for LER repair.[57] Other autogenous options include auricular cartilage,[58,59] transconjunctival grafts,[60,61] hard palate,[62-65] and dermis or fat, composite grafts.[59,66-68]

Hard palate mucosal grafts are considered by some to be the gold standard due to its stiffness, as well as its mucosal surface, which serves to replace the conjunctiva. These grafts are harvested from the area between the palatine raphe and the gingiva to avoid the neurovascular structures in this region. It should be placed in a low position in the eyelid to minimize contact with the cornea. This tissue is stiff enough to maintain eyelid contour but is much more flexible than cartilage. In addition, only minimal shrinkage has been reported in most cases.[56,69] However, it requires a second incision for harvest, is associated with increased operative time, postoperative discomfort, donor site hemorrhages, difficulty of access, and need of special material are reported as disadvantages.[25,61,63] The use of custom-molded dental plates has been shown to reduce donor site discomfort.[56]

Ear cartilage is easy to harvest with low donor site morbidity. However, it is almost too stiff to handle and does not easily conform to the globe, resulting in noticeable contour deformities. It is also limited in size and can be palpable for years after the procedure.[25,56,70]

Gardner *et al*. reported a mean elevation of 2 mm using autogenous tarsus in 38 patients.[60] Oestreicher *et al*.[61] assessed the outcomes of posterior lamellar grafting using sclera, tarsoconjunctival, and hard palate grafts in LER repair. Reduction in lagophthalmos, superficial punctate keratopathy, and the scleral show was demonstrated for all etiology groups and graft types included in the study.[61]

Autogenous dermis grafts are relatively easy to harvest, often from the postauricular region. The grafts are pliable, conform well to the eyelid and globe, are not overly rigid or stiff, and are typically very difficult to visualize once healing has occurred after implantation, as opposed to cartilage or hard palate grafts. However, they can shrink.[67,70]

The use of porous polyethylene has been reported as a posterior lamella spacer. However, it was associated with more complications when used in the lower eyelid.[71]

Regarding bioengineered materials, bioengineered acellular dermal matrix grafts, purported advantages include the ability to customize to the desired size, they do not require a donor site, are easy to handle, have low complication rates, and with its use, the wound-healing response could be enhanced because they retain connective tissue components that offer structural support.[56,57,72,73] In addition, these bioengineered materials are processed to remove cellular components from human, porcine, and bovine dermis, and therefore are associated with less risk of rejection and disease transmission.[57,72] However, they tend to contract more and may be associated with a higher resorption rate.[56] When comparing the human acellular dermal matrix, like Allo Derm, to the

porcine dermis, the latter is stiffer and can provide a similar amount of support as ear cartilage with more ease of handling and contouring.[56] Reported complications included cyst formation, chemosis, infection, pyogenic granuloma, aberrant nerve regeneration, and corneal abrasion. No serious complication such as blindness, anaphylactic reaction, or untreatable disease transmission was identified. Reoperation was needed in 5% of cases.[57]

Most reports in the literature addressed human-derived grafts (AlloDerm, DermaMatrix, Belladerm, and ReDerm). Studies that addressed porcine bioengineered derived materials (ENDURAGen, TarSys, Permacol) were less often, and bovine-derived graft (SurgiMend) use was reported in a single study.[57]

Kim *et al*. retrospectively assessed the surgical outcome of lower eyelid retractor recession with and without AlloDerm (LifeCell Corporation, Woodlands, TX, USA). Patients undergoing orbital decompression were divided into three groups: Group 1 underwent lengthening using human AlloDerm (36 eyes), Group 2 underwent inferior retractor recession (33 eyes), and Group 3 underwent decompression only (26 eyes). Mean improvements in MRD2, as well as postoperative improvement in the inferior scleral show, were significantly higher with the use of the AlloDerm.[74]

Liao and Wei[75] retrospectively reviewed 32 patients with TED who underwent LER surgery using a xenograft (TarSys, IOP Ophthalmics, Costa Mesa, CA, USA). Significant differences between preoperative and postoperative lagophthalmos and MRD2 were observed. No implant rejection was reported, although it was observed that resorption and a certain extent of an allergic reaction might occur in some patients. The allergic inflammation may be the cause of more prolonged swelling and puffy appearance in some cases.[75]

Despite its ease of use, a prospective comparative study has shown a higher retraction rate with acellular dermis allografts (57%) compared to autologous hard palate mucosal grafts (16%).[76]

The literature overall showed good success rates regardless of the spacer graft used, except for Medpor, which had a high complication and failure rate.[71] The majority of patients in the published studies achieved a significant level of lower eyelid elevation, with a small minority of patients developing complications. An analysis of comparative studies also did not reveal one graft material superior to the rest in terms of efficacy.[56] Bioengineered acellular dermal matrix implants seem to provide a convenient off-the-shelf alternative that obviates second surgical site morbidity. Nevertheless, further studies are warranted, especially those with long-term follow-up data.[57]

Nonsurgical Management

Minimally invasive procedures for the management of eyelid retraction, especially UER, in TED have gained relevance due to rapid administration, security, and potential reversibility.[77] In addition, a number of biological agents have been reported for the management of TED.[78]

Neuromodulators

Chemodenervation is a good alternative for patients who cannot undergo or do not desire surgical treatment for UER or for those with severe retraction who are awaiting surgery. It can also be used as a transient treatment for exposure keratitis and conjunctivitis during the active phase of the disease. Its use is safe; however, the results can be unpredictable.[7,49,77]

Two major approaches using neuromodulators to manage UER have been described in the literature: transcutaneous and transconjunctival injections.[79-86] Transcutaneous and transconjunctival approaches showed similar effects and complications.[77] Morgenstern *et al*.[82] postulated that the eyelid-lowering effect might be primarily due to alteration in Muller's muscle rather than levator muscle and that the transconjunctival approach reduced any undesirable weakening orbicularis muscle and risk of lagophthalmos.[82]

Morgenstern *et al*.[82] reported the use of botulinum toxin-A (BTX-A) in inactive TED, observing an improvement in UER in 94.4% of patients (decrease range: 1–8 mm).[82] Costa *et al*. compared the use of BTX-A in patients with active and inactive TED. The improvement was significant in both groups, with the height of the palpebral fissure decreasing by 3.05 mm in the active group and 3.81 mm in the inactive group; a beneficial effect on lateral flare was also observed. The longest-lasting effect was seen in the inactive TED group (up to 3 months compared to 1 month in the active TED group).[83] Salour *et al*. studied the use of BTX-A injection in 25 lids in patients with stable disease, finding an average reduction in lid height of 4.24 mm and an effect that persisted for 4 months.[87] In Ozturk Karabulut *et al*. series, the mean duration of treatment was 5.1 months, and normal MRD1 was achieved in 81% of patients.[86]

Transitory ptosis was the most common complication, regressing spontaneously in 1–8.5 weeks.[77] The risk of this complication may be reduced by injecting low

volume and high concentration of botulinum toxin in two points, at the medial and lateral one-third of the superior tarsal border into the horns of the levator aponeurosis, via a transconjunctival approach, thereby preserving the central levator fibers.[86]

Hyaluronic Acid

Hyaluronic acid (HA) has been used as a minimally invasive option to manage UER in TED patients. The effect can last from 6 to 12 months in the periocular region and, if reversal is necessary, it can be performed using hyaluronidase.[88-90] Its use in the UER aims to deposit the material in the eyelid retractor muscles to add weight to the upper eyelid. In the lower eyelid, the goal is to lengthen the retractors and provide scaffolding support to elevate the lid against the lower orbital rim. The result is immediate, and the route of administration can be transcutaneous and transconjunctival.[88,89] Although effective in mild cases, this modality of treatment may not be enough in the majority of patients with TED. However, it may be an option for those deferring surgery within minor asymmetries,[49] or an alternative to treat residual flare after surgery. Figure 1 shows a TED patient who received HA injection to treat residual lateral flare after a full-thickness blepharotomy.

Mancini *et al*.[89] treated mild upper lid retraction with HA filler. Of the eight patients treated, three had TED. The main outcome measure was a reduction in vertical fissure height asymmetry. The mean pretreatment asymmetry was 1.53 mm, and after the injection of filler was 0.70 mm. The mean pretreatment asymmetry within the TED group was1.7 mm, and was reduced to 0.5 mm after treatment. The average most extended follow-up on the TED patients was 6 months.[89]

In a prospective and dynamic ultrasound study, HA subconjunctival injections in the levator aponeurosis plane for UER secondary to TED were applied on eight patients either in the inactive or active stage of TED. An average volume of 0.45 mL was injected subconjunctivally. Patients in the active TED group had the best results. The mean MRD1 was 5.6 mm preprocedure, while the mean postprocedure MRD1, 1 month following injections, was 4.6 mm. The effect persisted for a mean of 15 months. Duration of the effect of HA on eyelid position was longer in patients injected during the active stage of TED.[90]

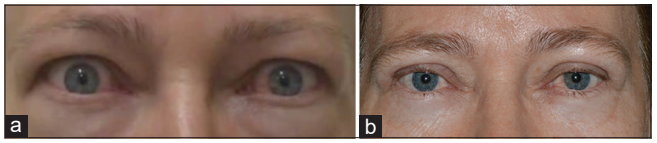

Figure 1: This female patient presented with thyroid eye disease in the quiescent phase. (a) Before and (b) after photographs after full-thickness blepharotomy, transconjunctival lower blepharoplasty and hyaluronic acid injection to treat residual lateral flare. Patient from Figure 1 gave permission to be included in the manuscript

Few studies assessed the use of HA to correct LER. Improvement in the scleral show, eyelid positioning, and eye exposure symptoms have been reported. However, undesired changes in the eyelid contour have been observed in some patients.[91,92] Goldberg *et al*.[93] reported the use of HA for correction of LER in 31 patients, 8 with TED, with a mean decrease of 0.52 mm in the inferior scleral show after 4 months.[93]

Triamcinolone Acetonide Injection

The administration of injectable glucocorticoid is an option for the management of UER in TED due to its anti-inflammatory and immunosuppressive actions.[94] Triamcinolone is an intermediate-acting glucocorticoid and is five times more potent than an equal weight of hydrocortisone. Triamcinolone acetonide (TA) is relatively insoluble and is absorbed slowly, along weeks. The proposed mechanisms of action of TA injection on TED-related UER include anti-inflammatory effect on the levator and Müller's muscle, steroid-induced ptosis, degenerative alterations in the levator muscle, detachment of the levator aponeurosis from the tarsal plate, and steroid-induced atrophy of the Müller's muscle.[95,96] Young *et al*. recommend that TA injection is aimed at the Müller's and levator palpebrae superioris.[94]

Previous studies on subconjunctival and percutaneous TA injection have shown effectiveness in reducing UER, especially in patients in the congestive phase of TED.[97-102] Besides reduction in MRD1, significant reduction in eyelid edema, erythema, conjunctival injection, chemosis, and CAS score were observed. Young *et al*.[94] found that TA injection was effective both as a primary treatment in patients receiving TA injection alone and as an adjunctive treatment for patients who previously had received systemic immunosuppressive therapy. Repeated injections may be necessary for optimal control.[94]

In a clinical trial, 95 patients were randomly divided into two groups. One group received subconjunctival TA in the upper eyelid, and patients in the control group were only observed. The treatment group presented normalization of the UER in 75% of the patients, while normalization was observed in 57% of the control group. The best response was obtained in the inflammatory TED group.[99] Xu *et al*.[98] evaluated 35 eyes treated with subconjunctival TA in the upper eyelid. All patients showed improvement in UER, and those who had the best results had eyelid symptoms for at least 6 months. A thinning of the levator/rectus muscle complex evaluated by ultrasound and MRI was observed as a sequel. As a side effect, half of the

patients had increased intraocular pressure.[98] Chee and Chee[97] reported four cases in which subconjunctival TA injections were administered in the upper eyelid. The mean improvement in MRD1 was 1.4 mm. Patients with more acute eyelid manifestations had a better response.[97]

Complications include IOP elevation, superior sulcus defect, high crease, and transient ptosis, and care should be taken in patients with thin eyelids without much inflammation.[94]

Biologic Agents

Recently, advances in our understanding of the immunological pathogenesis of TED have shifted the focus of management to novel biological agents, and multiple immune-modulators have been investigated in clinical trials. These treatments have the advantage of targeting key receptors implicated in the pathogenesis and immune dysregulation involved in TED, with potentially better safety profile and greater efficacy compared to traditional approaches.[103] Table 2 summarizes the main therapies.

Rituximab, a monoclonal antibody directed against the CD20 antigen on B-cells, interferes with antigen presentation and reduces inflammatory cytokine production. Two randomized, prospective clinical trials of rituximab for TED showed disparate results.[104,105] A subsequent *post hoc* analysis concluded that differences in the study populations might explain the different outcomes. The European study included younger patients, lower TRAb, and shorter duration of disease, all elements favoring a better response. The adverse events of concern relate mainly to the risk of dysthroid optic neuropathy, which seems to be increased by using rituximab in a certain subset of patients.[106] These studies suggest that rituximab therapy carried out earlier in the active phase of the disease may provide better results;[78] nevertheless further studies are needed to define the role of this drug in TED therapy.

Tocilizumab, a monoclonal antibody against the interleukin-6 receptor, has been studied in several reports for the treatment of TED. In an interventional, nonrandomized study, improvement in proptosis and extraocular motility was seen in 72% and 83% of patients, respectively.[107] This medication has also been reported to be effective when administered subcutaneously in four biweekly doses over 8 weeks.[108]

Insulin-like growth factor-1 (IGF-1) is a widely expressed cell surface protein found in most tissues in the human body. IGF-1 pathways are implicated in several autoimmune diseases, including TED.[109] Studies have shown that anti-IGF-1 receptor (IGF-1R) antibodies are found in patients with Graves' disease but absent in healthy patients. The IGF-1Rs have been found to be upregulated in TED patients and to colocalize with the thyroid-stimulating hormone receptor (TSHR), forming a signaling complex.[103,110] Teprotumumab is a recombinant, human immunoglobulin G1 κ monoclonal antibody, targeted against the IGF-1 receptor, generated in genetically engineered Chinese hamster ovary cells.[78] By inhibiting the IGF-1R/TSHR signaling pathway, teprotumumab may reduce the production of proinflammatory cytokines, hyaluronan secretion, and orbital fibroblast activation in patients with TED.[103]

Teprotumumab was approved for the treatment of TED, without stipulations regarding disease activity or clinical activity score (CAS), by the United States Food and Drug Administration in January 2020.[78,111] Inhibition of the IGF-1 receptor is considered a new milestone in the treatment of TED since teprotumumab decreases orbital inflammation associated with TED and seems to reverse extraocular muscle fat hypertrophy resulting in proptosis reduction and improvement in diplopia. The reduction in proptosis was similar to that of patients undergoing surgical decompression. The phase 2 and 3 clinical trials included patients with the recent disease, active TED as determined by a CAS higher or equal to four. In addition, it comes with a low-risk side-effect profile, the most common being muscle spasm (13%).[110,112]

Although further studies are needed to determine whether teprotumumab will be helpful in chronic disease, studies showing notable improvement in proptosis and reduction in extraocular muscle volume have recently been reported in patients with chronic TED and low CAS, suggesting that teprotumumab may alter disease course even in patients with inactive or quiescent TED.[111,113,114]

Table 2: Biologic therapies for thyroid eye disease

Therapy	Target	Dosing	Findings
Rituximab	CD20	2 infusions (1000 mg) 2 weeks apart	Improvement of proptosis and motility
Tocilizumab	IL-6	3 infusions (8 mg/kg) every 4 weeks Or subctaneously in 4 biweekly doses over 8 weeks	Proptosis reduction
Teprotumumab	IGF-1R	Initial infusion (10 mg/kg) Followed by 7 infusions (20 mg/kg) every 3 weeks	Reduced proptosis and reduced diplopia

IGF-1=Insulin-like growth factor-1, IL-6=Interleukin 6

In a prospective study involving 23 consecutive patients treated with teprotumumab, all euthyroid at the time of treatment and with a mean CAS of 3.4, a significant reduction in upper and lower lid retraction was observed after teprotumumab therapy: Mean MRD1 was 5 mm before treatment and 4.3 mm following therapy ($P < 0.01$), whereas mean MRD2 was 6.3 mm before therapy and 5.9 mm posttherapy ($P < 0.05$).[115]

Conclusion

Eyelid retraction related to TED is a challenging condition. Several surgical and nonsurgical treatment modalities have been described. Management should be based on an individual patient assessment, taking into consideration the disease stage, severity, and clinician experience. Further research is needed to confirm the long-term effects of the novel biologics and whether the therapies will minimize the need for surgical intervention in future.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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