Immunotherapy of thyroid Eye Disease

Aliaa Mohamed Shohieb¹, Nashat Shawky ², Ashraf Shoma³

1: Final Year Medical Student, Mansoura Manchester Medical Programme, Faculty of Medicine, Mansoura University.  
2: Associate Professor of Ophthalmology, Mansoura University Hospital, Mansoura, Egypt.  
3: Department of surgery, Mansoura University Hospital, Mansoura, Egypt.

Abstract

Thyroid eye disease (TED) is a complex autoimmune disorder that may lead to fundamental morbidity. TED presents with wide range of manifestations originating radically from orbital inflammation which leading to exophthalmos, vision impairment, double vision, severe eye dryness and in advance cases vision loss may occur. On top of that, it has also series of negative impacts on the patient quality of life, psychological and emotional well-being. The full clinical picture of thyroid eye disease (TED) can be explained by the enlargement of the orbit. Corticosteroids are the gold stone of treatment in TED. However, in case of steroids withdrawal recurrence is common. Moreover, in the majority of the patients, the anatomy of the orbit is not replaced to the normal state, that’s why rehabilitative surgery may be necessary to correct the deformity, diplopia and to maintain vision. Available treatment options for moderate-to-severe TED include immunotherapy. The pathophysiology of TED has been reported to identify new effective therapeutic agents. Immunotherapies are on the top of the list as they have shown considerable benefit affecting the nature course of the disease and improve the quality of life of the patients. Options include Teprotumumab (anti-IGFR) that show efficacy in improving exophthalmos, Rituximab (anti-CD20) decrease the inflammation and Tocilizumab (anti-IL-6) with the capacity to benefit both of these manifestations.
INTRODUCTION

Thyroid eye disease (TED) is an autoimmune condition with many ophthalmic manifestations and psychosocial consequences. TED has been characterized to have an active inflammatory phase which followed by disease inactivity. In TED, the muscles and fatty tissues of the orbit become edematous and inflamed, pushing the eyeball forward and affecting the movements of the eye. Which lead to bulging eyes (exophthalmos or proptosis)[1,2].

Thyroid eye disease cases are mostly related to an overactive thyroid gland (hyperthyroidism state) and usually with one of the most common causes of an overactive thyroid gland, which is Graves' disease. Symptoms of Graves’ disease include dry eye and sometimes tearing, sense of eye irritation or grittiness, conjunctival inflammation and redness, edema of the eyelids, photophobia and diplopia. Lately eye movement may be affected, corneal ulceration, compression of the optic nerve and rarely, loss of vision[1,2,3].

Currently, treatment options included many courses of steroid therapy, orbital radiotherapy and the recent way which is the targeted monoclonal antibodies such as Rituximab and Teprotumumab, both are approved by the US Food and Drug Administration (FDA) for the medical treatment of TED[2,3].

Clinical picture of TED

Graves’ disease defined as autoimmune syndrome involving the thyroid, orbital connective tissues, also parts of the skin. One manifestation of Graves’ disease is thyroid-associated ophthalmopathy, or thyroid eye disease, which is characterized by orbital inflammation, tissue remodeling and fibrosis. TED is most commonly associated with hyperthyroidism, however patients may be hypothyroid or euthyroid[2,4].

Ophthalmic manifestations are reported in around half of cases with GD, and patients most commonly present in middle age and women are highly affected than men. TED may precede by endocrine manifestations. Symptoms include puffiness of the eyes, lid retraction, proptosis, squint, conjunctival inflammation, increased Intra ocular pressure, and rarely, vision may affected from keratitis or pressure on the optic nerve [2,4].

The stages of the disease divided to active and latent. The active stage lasting for around 6 months up to 2 years. The term “active disease” stands for activation of the immune system [4,5].

Effects of the active stage of grave’s disease on the back and front of the eye.

The muscles and fat tissue of the eye become edematous, this swelling exerts a force on the back of the eye causing it to protrude forward. The changes of the back of the eye also include thickening and scarring of connective tissue of the eye. However erythema, edema, proptosis and lid retraction commonly noted in the front of the eye.
**Immunotherapy of thyroid Eye Disease**

**Figure 1: Progressing (or “active”) Thyroid Eye Disease [5].**

**Effects of the Inactive stage of grave’s disease on the back and front of the eye.**
Over the time in the inactive stage some changes, like swelling may improve and other changes like protruding eyes, diplopia or strabismus may become permanent.

**Figure 1: Inactive Stage Of Thyroid Eye Disease [5].**

**Other symptoms of Thyroid Eye Disease [6,7].**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drawn back eyelid, (lid retraction)</td>
<td>Eyelids are drawn back or retracted</td>
</tr>
<tr>
<td></td>
<td>This may lead to constant gaze</td>
</tr>
<tr>
<td></td>
<td>Difficulty in eye closure</td>
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<tr>
<td>Foreign body sensation and dryness</td>
<td>Eyes feel dry</td>
</tr>
<tr>
<td></td>
<td>It feel like sand in the eyes</td>
</tr>
<tr>
<td>Watery, teary eyes</td>
<td>Extra fluid lead to blurred vision</td>
</tr>
<tr>
<td>Painful eyes</td>
<td>Pain may be felt all around the eyes and</td>
</tr>
<tr>
<td></td>
<td>exaggerated in moving</td>
</tr>
<tr>
<td></td>
<td>Pressure around the eyes, result in headaches</td>
</tr>
<tr>
<td>Color vision loss</td>
<td>Colors look dull or washed out</td>
</tr>
<tr>
<td></td>
<td>In rare cases, all color vision may be lost</td>
</tr>
<tr>
<td>Vision loss</td>
<td>In advance cases, blindness may occur</td>
</tr>
</tbody>
</table>
**Table 1:** Signs and symptoms of Thyroid Eye Disease [8].

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
<th>Clinical Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild: Early-stage TED</td>
<td>Gritty sensation; dry eye; excessive watery eyes; chemosis or eyelid erythema and swelling; unclear vision; retro-orbital pain</td>
<td>Mild, soft tissue inflammation; Focal dilations of the conjunctival vessels; keratoconjunctivitis; corneal staining</td>
</tr>
<tr>
<td>Moderate: Progression of orbital inflammation</td>
<td>Pulling sensation around the eye; eyelid erythema and swelling; lid retraction and protruding eyes</td>
<td>Edema of extraocular muscles; conjunctival inflammation; eyelid swelling; exophthalmos; extraocular muscles may be visible</td>
</tr>
<tr>
<td>Severe: Advanced TED</td>
<td>Advanced strabismus with diplopia; progressing unclear vision; fading color vision in one or both eyes; diminution in visual acuity, visual field, and color vision (signs of optic neuropathy)</td>
<td>Progressive exophthalmos with eyelid retraction, posterior blepharitis, keratitis and inflammation of extraocular muscles and fibrosis leading to strabismus and increased IOP.</td>
</tr>
</tbody>
</table>

**Table 2:** CAS, clinical activity score of Thyroid Eye Disease [9].

<table>
<thead>
<tr>
<th>CAS</th>
<th>For initial assessment, only score items 1-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spontaneous orbital pain</td>
</tr>
<tr>
<td>2</td>
<td>Gaze evoked orbital pain</td>
</tr>
<tr>
<td>3</td>
<td>Eyelid swelling</td>
</tr>
<tr>
<td>4</td>
<td>Eyelid erythema</td>
</tr>
<tr>
<td>5</td>
<td>Conjunctival injection</td>
</tr>
<tr>
<td>6</td>
<td>Chemosis</td>
</tr>
<tr>
<td>7</td>
<td>Inflammation of caruncle or plica</td>
</tr>
<tr>
<td>8</td>
<td>Increase of &gt;2mm in proptosis</td>
</tr>
<tr>
<td>9</td>
<td>Decrease in uniocular excursion in any way direction of &gt; 8 degree</td>
</tr>
<tr>
<td>10</td>
<td>Decreased acuity equivalent to 1 Snellen line</td>
</tr>
</tbody>
</table>

**Figure 2:** An approximation of a curve depicting severity of thyroid eye disease over time that is based on a concept by Rundle [9].
**Pathophysiology of Thyroid Eye Disease**

The Pathophysiology of active TED is described by orbital tissues infiltration by immune cells (e.g., by T lymphocytes, mast cells and B lymphocytes). Orbital Fibroblasts groups can be further differentiate into myofibroblasts. Thus lead to deposition of extracellular matrix and hyaluronan in the orbital tissue. Expansion of the orbit by the deposition exaggerate exophthalamos and affect eye motility. However the full detailed thyroid eye disease pathology remain unclear, (TSH-R) intolerance and IGF-1R; IGF-1R overexpression demonstrated to be the main cause in the disease pathogenesis [1,10].

The immune realization of both TSH-R and IGF-1R become evident to be merging with orbital tissue reactivity through recruitment of proinflammatory cytokine release and hyaluronan build up. Type 1 T helper (Th1) cells, B lymphocytes, mast cells and macrophages infuse the orbit, and Th1 cells therefore produce cytokines such as [IL-2]. Inflammatory cytokines induce fibroblasts to produce glycosaminoglycans, including hyaluronan, that expand the intraorbital tissue through adipose and muscle enlargement (Figure 3)[11,12].

![Figure 3 A](image)

**Figure 3 A:** Shows progression of the disease. An autoimmune process initiates an inflammatory response that results in active phase TED. After the initial inflammation quiets, TED becomes inactive, **Figure B** and enters a post-inflammatory, stable, fibrotic phase. Clinical picture include redness, pain, and edema. Histopathologic studies show inflammatory cell infiltration during active TED with muscle fibers remaining intact or becoming fibrotic, and a lack of inflammation as the disease progresses[8,11,12].
Figure 4: Pathophysiology of thyroid eye disease (TED)[11].

The APCs incorporate TSHR and IGF-1R then present them to helper T cells, in order to this T cells are activated leading to 2 separate ways either stimulating B cells to release auto-antibodies (GD-IgGs), or become auto-reactive T cells. GD-IgGs react with TSHR on thyroid follicular epithelial cells, causing follicular hyperplasia and hypertrophy. However, in response to the chemo-attractants that released by T cells, auto-reactive CD4 T cells take its own pathway to the tissues of the orbit and react with T cells and B cells and Orbital Fibroblasts release a wide range of inflammatory cytokines. IGF-1R and TSHR forming a complex on the OFs surface that reacts with GD-IgGs. OFs in TED derived from bone marrow cells. Activated OFs can be differentiated into either adipocytes or myofibroblasts and hyaluronan synthesis has been identified. This share in the expansion of orbital soft tissues in TED [11,13].

Pathogenesis of Orbital Fibroblasts

The main cell type involved in the pathophysiology of the TED and expanding of orbital soft tissues appears to be the orbital fibroblast (OF). OFs are found between muscle fibers in the interstitial space and inside orbital fat. OFs strains divided depending on the presence of Thy1 / CD90. In the extraocular muscles, Thy1-expressing (Thy1 +) OFs live. When triggered, myofibroblasts can be differentiated into the contractile factor [14].

Th1-deficient (Thy1-) OFs are orbit-wide pre-adipocytes that can differentiate into mature adipocytes. The adipogenesis and fibrosis cycles decide the relative proportion of activated Thy1 + and Thy1− OFs. When OFs are activated, hyaluronan build up and soft tissue enlargement leads to proliferation, [14].
Figure 5: Orbital fibroblast stimulation induce pro-inflammatory genes, contributing to glycosaminoglycans (GAGs) and hyaluronic acid synthesis. [14,15].

Pathogenesis of IGF-1R
Although, one of the auto-antigen in TED is the IGF-1R. This receptor and its waving mechanism have many roles in development of the tissue and may be elaborate in basis of immunological disorders. IGF-I exerts immune function regulatory activities and is expressed by skilled immune cells and stromal cells of the bone marrow. In several cell types in TED, including fibrocytes and orbital fibroblasts (OFs), IGF-1R is over-expressed and forms a functional complex with TSHR, and its activity is fundamental for mediating TSHR downstream signaling components [13,16].

Figure 6: IGF-I exerts regulatory actions on immune function by stimulating B cells, T cells and neutrophils[13].

IGF-1 immuno-reactivity was demonstrated in patients with TED on the surface of extraocular muscle and orbital fat cells. Furthermore, the rise in IGF-R1 expression in the tissue around the eye plays a major role in the disease. When attached to the IGF-R1 receptors, antibodies against these receptors are released in patients with TED. IGF-1-R activation induces orbital fibroblasts to synthesize GAGs and secrete chemoattractants, exaggerate orbital inflammation and congestion. GAG deposition induces excessive fibrosis (scar tissue formation) in orbital tissues around the eye, this lead to increase the pressure on nerves, blood vessels and eye tissue[13,15,16].
Figure 7: IGF-1-R and TSH-R are activated by TSI (GD-IgG). Orbital cytokines are produced by the activation of these receptors, leading to GAG deposition and orbital inflammation and congestion. [15].

Management of TED
Recently many lines of treatment have been updated to delay the progression of the thyroid eye disease in a non-surgical way. Immunotherapy (mostly glucocorticosteroids), orbital radiotherapy and decompression surgery are the latest choices that effective for moderate to severe thyroid eye disease. Glucocorticosteroids are the first-line agents associated with high incidence of adverse effects such as diabetes mellitus, hypertension, acute heart disease, weight gain, osteoporosis and acute liver failure. However, the latest biological therapy will alter the normal course of the...
disease and reduce the occurrence of late complications that might arise as a result of inflammation fibrosis. [17,18],

**Role of Teprotumumab in the management of TED**

Teprotumumab is a fully human monoclonal IgG1 antibody that targets human insulin-like growth factor-1 receptor receptors. After a clinical trial assessing its effectiveness in the treatment of thyroid eye disease (TED), it was approved by the FDA in January 2020 for the treatment of TED. Thyroid eye disease is a potentially crippling complication of inflammation and tissue remodeling of Graves’disease behind the eye. Teprotumumab is the first pharmaceutical product to be licensed for TED treatment and is thus a major step forward in the treatment of TED. In patients with quiescent TED, Teprotumumab plays an important role in reducing proptosis and the extraocular muscle size which altering the course of disease[19,20,21].

**Mechanism of action of Teprotumumab**

It has been shown that insulin-like growth factor-1 receptors (IGF-1R) in case of TED are over-expressed by orbital fibroblasts, in addition to being over-expressed in these patients by T-cells and B-cells. Graves’ disease IgG molecules have been found to mimic IGF-1R’s key ligand, insulin-like growth factor-1 (IGF-1), and their IGF-1R binding induces the expression of chemokines that play roles in tissue repair and inflammation. Teprotumumab is an IgG1 monoclonal antibody which is entirely human and directed against IGF-1R. It binds to and allows these receptors to be internalized and degraded, thereby preventing their downstream effects and alleviating symptoms of thyroid eye disease. [22,23,24].

Figure9: Left column: external preoperative and computed tomography of the orbit showing asymmetric left exophthalmos before treatment. Right column: external photograph and computed tomography of the orbit showing correction in exophthalmos and reduction in extraocular muscle size after three infusions of teprotumumab[23].
Role of Rituximab in the management of TED

The medical care strategy has concentrated on symptom regulation and reduction of thyroid hormone production, not immunosuppression, despite the role of autoimmunity in the pathogenesis of GD. However, biologic immunosuppressive therapy has recently become a promising alternative for GD treatment with the use of rituximab. Rituximab is a monoclonal antibody of high affinity consisting of an antigen binding region of murine origin and a constant human immunoglobulin (Ig) region of G1 [25,26].

Its target is CD20 (differentiation cluster), a surface marker of B cells that is present on pre-B and B cells, but generally not on stem cells or plasma cells. Rituximab acts by depleting CD20+ cells via both antibody-and supplement-mediated pathways, along with apoptosis induction. It also has a direct impact on reducing inflammation and enhancing the duration of the illness. [26,27,28].

Figure 10: pathogenic auto-antibodies stimulating the orbital fibroblast resulting in production of hyaluronan and giving rise to symptoms of thyroid eye disease[23].

Figure 10: Teprotumumab (IGF-1R) blocks the stimulatory effects of the pathogenic auto-antibodies on the orbital fibroblasts. TSI (thyroid stimulating immuno-globulins)[23].
Role of Tocilizumab in the management of TED

Tocilizumab is an immunoglobulin G1 subclass recombinant humanised antihuman monoclonal antibody directed against the interleukin-6 receptor (IL-6R) developed by recombinant DNA technology. Tocilizumab binds uniquely to both the soluble and membrane-bound forms (IL-6RM) of IL-6R. IL-6 is a proinflammatory cytokine formed by different types of cells, including lymphocytes T and B, monocytes and fibroblasts. In the early stages of TED, immune cells such as B and T lymphocytes play a major role in the pathophysiology [30,31].

However, high levels of IL-6 released by differentiated adipocytes and fibroblasts stimulate B lymphocytes and generate thyroid-stimulating immunoglobulin (TSI) in addition to an immunomodulatory role, leading to development of glycosaminoglycan, adipogenesis and inflammation or fibrosis. Reducing IL-6’s influence by blocking its receptors can play a role in reducing blood levels of TSI and improving proptosis and extraocular motility. [32,33,34].

Conclusion

TED is a progressive autoimmune disorder with many aggressive consequences and impacts. TED's pathophysiology become clearer and better tailored treatments upgraded to affect the course of the disease.

Immunotherapy, such as teprotumumab, rituximab and tocilizumab, are aimed at various stages of the disease and significantly affects the pathology of the disease, enhances major disease sequelae, including proptosis and diplopia, and has demonstrated substantial changes in the quality of life of TED patients.

REFERENCES


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