Course Title: Thyroid Eye Disease

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Financial Disclosures: Regarding treatment of TED, both speakers have been involved in clinical trials in TED and have received funding from Horizon Pharma, and were paid advisors for Horizon

Course Description:

This course will attempt to help the attendees learn the pathophysiology of Graves' disease and thyroid eye disease, the clinical phenotypes, the management options, new drug findings and how to treat thyroid related strabismus.

Course Objectives:

- Understand how to diagnose Thyroid Eye Disease
- Understand the pathophysiology of Thyroid Eye Disease
- Management options of Thyroid eye disease
- New Treatment Options for Thyroid eye disease

Lecture Outline

Diagnosis

- History
- Physical examination
- Signs
- Symptoms
- Clinical diagnosis
    - Strabismus can be confirmed with a comprehensive eye examination. The acute phase of TED results in variable strabismus and diplopia.
    - Proptosis is also a feature of the acute phase. As the disease progresses, the strabismus and proptosis worsens.
    - Assessment of the severity of strabismus in the setting of other ocular findings consistent with ythyroid eye disease (lid retraction, stare, lid lag, proptosis, periorbital edema) should prompt a work-up of thyroid function.
    - Because the ophthalmopathy associated with thyroid dysfunction may occur at any time during the course of the disease and may precede other systemic findings, it is important to begin the thyroid work-up and continue with routine follow-ups.
- Diagnostic procedures

    - CT/MRI orbit without contrast or Ultrasound: enlargement of the extraocular muscles without involvement of the tendons
- Laboratory test
    - Thyroid function tests: T3, T4, TSH. These may be low, normal, or high.
    - Thyrotropin receptor autoantibody (TSI). Circulating TSI levels correlate strongly with the clinical activity score of the eye disease.
    - Acetylcholine receptor antibody to exclude t co-existent myasthenia gravis (5% of patients).
- Differential diagnosis
    - Cranial nerve palsies
    - Inflammatory conditions like myositis and idiopathic orbital inflammation
    - Myasthenia gravis in patients with fluctuating double vision and ptosis
    - Chronic progressive external ophthalmoplegia
    - Space-occupying lesions of the orbit
    - Trauma to extraocular muscles (orbital fracture, orbital/intranasal surgeries, etc)

Immunology of TED from a Non-immunologist.

The active phase of TED is characterized by orbital and periorbital inflammation targeting connective tissue and fat. Electron and light microscopy suggest that the muscle cells remain intact early in the disease. However, intense infiltration of T lymphocytes, mast cells and occasional B cells often intercalate between extra-ocular muscle fibers and can be found in orbital fat, suggesting that connective tissue and represents the primary autoimmune target.

What is the antigen in the thyroid and eye?

One antigen associated with ophthalmopathy is the flavine adenine nucleotide (FAD) cofactor of several mitochondrial enzymes, including SDH.

What is the antibody against the thyroid and eye?

Antibodies against the flavoprotein (Fp) subunit of succinate dehydrogenase (SDH), the 64-kd protein, and G2s, a thyroid and eye muscle shared protein of unknown function, are good markers of eye muscle cell damage in patients with OM.

How is the antibody stimulatory?

The stimulatory TRAb M22 increases HA production in undifferentiated GO orbital fibroblasts via phosphoinositide 3-kinase/phosphorylated AKT/mammalian target of rapamycin activation. Blockade of IGF-IR inhibits both HA synthesis and Akt phosphorylation induced by M22 or IGF-I in these cells, suggesting that TSH receptor and IGF-IR signaling may be closely linked in the GO orbit.

The biologic reactions from autoimmune reaction that result in the phenotype of TED?

Orbital fibroblasts are integral to the pathogenesis of TED and may modulate immune responses by production of cytokines and hyaluronan in response to activation of shared autoantigens including thyrotropin receptor and insulin-like growth factor-1 receptor. Bone marrow-derived fibrocytes share many of these phenotypic and functional features, suggesting a link between systemic and site-specific disease.

What is the phenotype of TED?

Six phenotypes of TED are observed: 1) congestive (active inflammatory), 2) "white eye" expansion, 3) "hydraulic" apex, 4) "white eye" apex, 5) cicatricial active, and 6) cicatricial passive.

The different scoring types that have been used to describe the findings of TED

VISA versus EUGOGO Classification, Assessment, and Management

Lid retraction may not mean TED

How to measure with the CAS score

1. Spontaneous retrobulbar pain
2. Pain on eye movements
3. Eyelid erythema
4. Conjunctival injection
5. Chemosis
6. Swelling of the caruncle
7. Eyelid edema or fullness

What muscles are most involved?

In TED, the inferior rectus and medial rectus muscles are most commonly involved, leading to hypotropia and esotropia. The superior and lateral rectus muscles are the next most commonly

involved, though isolated enlargement of the superior or lateral recti is highly atypical of TED. The oblique muscles are rarely involved.

What are the strabismic consequences most likely seen and why?

Strabismus in thyroid eye disease is a result of swelling and thickening of the extraocular muscles, which restricts eye movement and causes the eyes to move out of alignment. The resulting asymmetry between the two eyes can cause double vision (diplopia).

Medical Therapies

- Vitamins
    - Selenium
    - Vitamin D supplementation
    - Life style recommendations
- Topical medicines
    - Low-dose topical steroid such as loteprednol or fluorometholone
    - Lubrication—a regimen of artificial tears, gel and nighttime ointment
- Steroids
    - Intravenous steroids
    - Risks of steroid treatment
- Orbital radiation
    - Number of sessions
    - Synergistic with steroid
    - Side Effects
- Biologic therapy
    - Adalimumab (Humira)
    - Infliximab (Remicade)
    - Etanercept (Enbrel)
    - Rituximab
    - Tocilizumab
    - Teprotumumab

Mechanism of Action of Teprotumumab

- Teprotumumab - R1507 (formerly called Roche 1) is a fully human antibody which targets the Insulin-like Growth factor-1 Receptor (IGF-1R).
- The IGF-1R molecule has been shown to be important in tumor growth and protecting tumor cells from being killed.

- IGF-1R is over-expressed on a variety of tumors including breast, colon, prostate, lung, skin and pancreatic cancers and is a well validated target for an antibody therapeutic approach.
- IGF-1R overexpression is a factor in thyroid eye disease; IGF-1R inhibition attenuates downstream signaling of cytokine and hyaluronan production.
- Teprotumumab decreases TSHR and IGF-1R display by fibrocytes and attenuates TSH-dependent IL-6 and IL-8 expression and Akt phosphorylation

Results of the Teprotumumab Clinical Trials.

Teprotumumab is an investigational medicine and its safety and efficacy have not been established. The Phase 3 OPTIC confirmatory clinical study was conducted at leading centers in the U.S., Germany and Italy, with co-principal investigators Raymond Douglas, M.D., Ph.D., Cedars-Sinai Medical Center; and George Kahaly, M.D., Johannes Gutenberg University Medical Center.

In addition to the Phase 3 OPTIC trial, Horizon is conducting the OPTIC-X extension trial to gather further insight into the long-term efficacy and safety of teprotumumab. The robust clinical development program for teprotumumab in the treatment of TED includes positive Phase 2 results published in *The New England Journal of Medicine*.

- Teprotumumab, a monoclonal IGF-1R antagonist, has demonstrated to produce significant changes in composite outcomes of proptosis and clinical activity score as compared with placebo.
- The level of proptosis reduction with teprotumumab reported here is similar to that seen with decompression surgery. If these results are confirmed in the ongoing Phase 3 trial, teprotumumab will offer an alternative to surgery and its associated complications.
- https://www.nejm.org/doi/full/10.1056/NEJMoa1614949

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