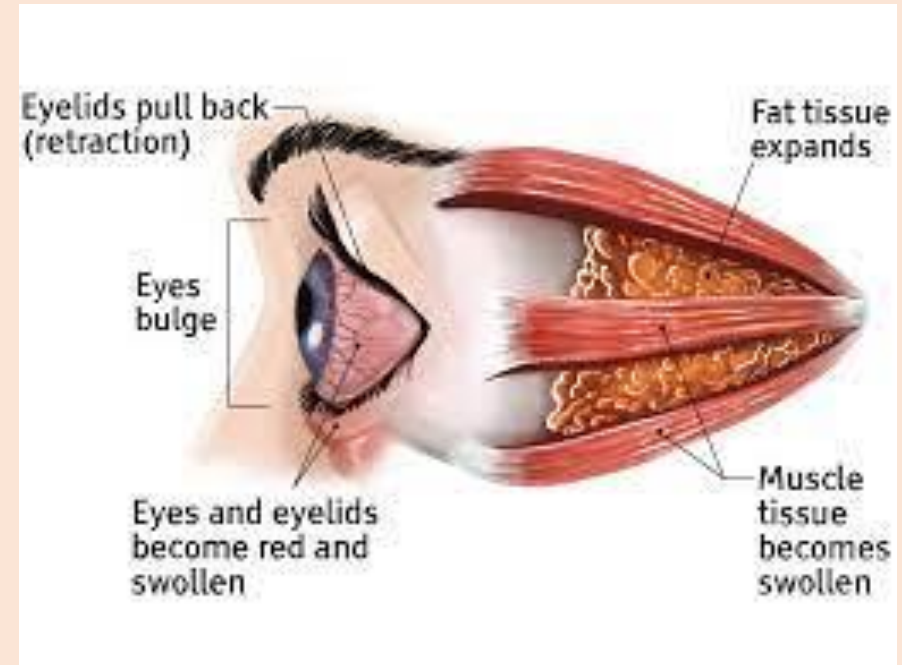
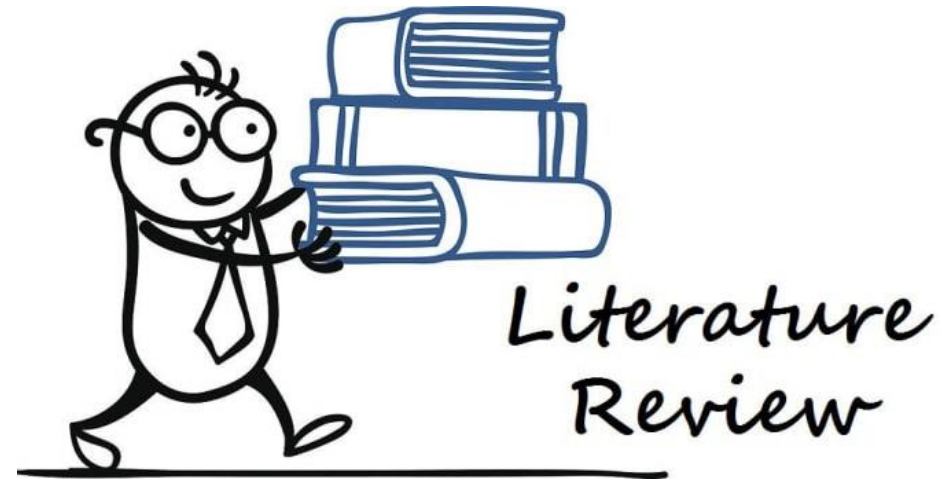


# Medical Treatment of Thyroid Eye Disease (TED)

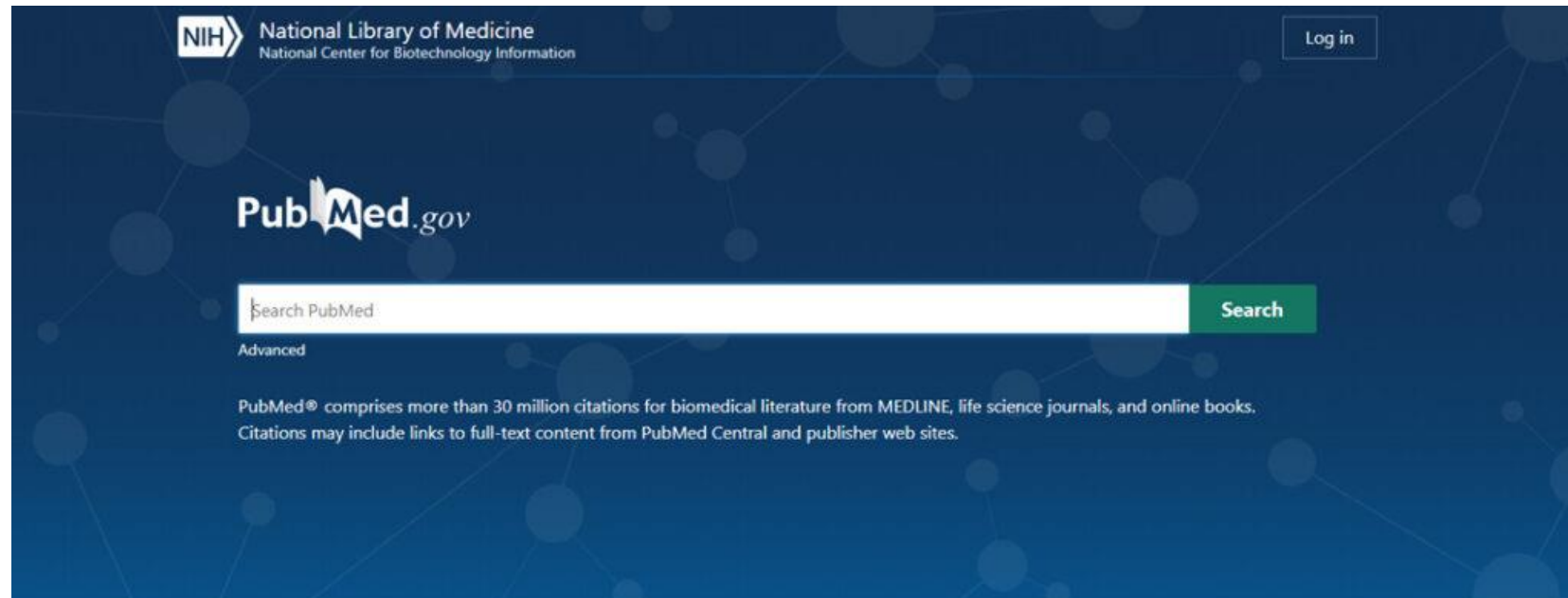


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Data has been retrieved from the literature searching on Pubmed



## Introduction

**Thyroid eye disease (TED)** or the **Graves' orbitopathy (GO)** is a complex inflammatory disease that can have a long clinical course with sight-threatening and debilitating ocular sequelae and the most common extra-thyroid symptom of Graves' disease (GD)

- Clinically visible manifestation of GO can be observed in approximately 25-50% of patients with Graves' disease
- Although the course of TED was identified over 60 years ago, effective treatment options have proved to be challenging

## Management

An appropriate approach should be performed by a multidisciplinary team of **ophthalmologists, endocrinologists, radiologists, and orbital surgeons**

**Protocols of Graves' Ophthalmopathy Treatment plan should be individually designed for each patient**

- Any patient with symptoms or signs of orbitopathy in the HR group (**elderly, male, diabetic, or smoker**), positive FH of orbitopathy, a recent history of progression, or any moderate inflammatory changes should be referred to the ophthalmologist within a few weeks

## Management

Approach in GO management includes **non-pharmacological, pharmacological, rehabilitative surgery, and radiotherapy**, based on the assessment of **clinical activity** and degree of **severity**

# Clinical activity assessment

**ACTIVE**

- Considering categories:
- ✓ Vision
  - ✓ Inflammation
  - ✓ Strabismus
  - ✓ Appearance

Management

Medical

**Surgical  
(urgent)**

**STABLE**

- Considering categories:
- ✓ Proptosis
  - ✓ Strabismus
  - ✓ Eyelid

Management

**Surgical  
(elective)**

Observe

# Nonspecific therapies



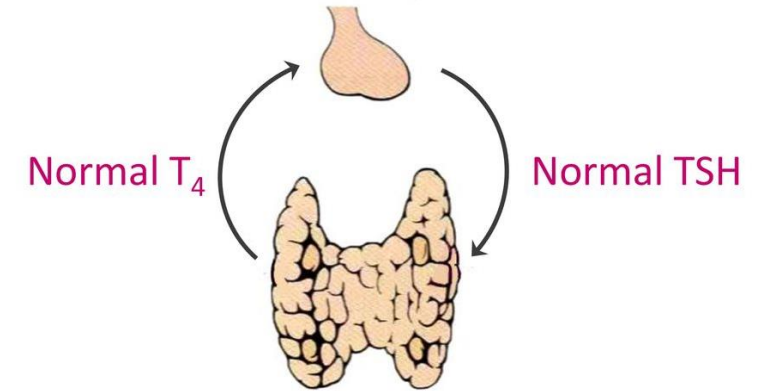
- Selenium, has also been found to be helpful in patients with mild disease
  - RCT: selenium given at 100 mcg twice a day for 6 months was found to be associated with improved quality of life, reduced soft tissue inflammation, and slowed progression in patients with TED



- However, the study drew patients from selenium deficient areas. It is unclear if the same beneficial effects would be found in areas without deficient selenium, such as the United States.

## Nonspecific therapies

- Restoration of euthyroidism
  - Patients with normal thyroid hormone levels had a better response
- Ocular surface optimization with preservative-free artificial tear eye drops
  - Gel or ointment can be used, especially at night
  - Closing the eyes using eye-tape at night can help prevent nocturnal corneal dryness





## Nonspecific therapies

### Stop smoking



- Recent studies have found that hypoxia caused by smoking can lead to an excessive proliferation of orbital fibroblasts, lipogenesis and production of glycosaminoglycans and pro-inflammatory cytokines, which can cause the occurrence and the development of TAO
- Smoking is related to an increased risk of Graves' hyperthyroidism (twofold), GO (three to four times), or relapse of GD or GO, and it is linked to a more severe GO.

## Nonspecific therapies

### Stop smoking

- Smoking can reduce the therapeutic effect of chemotherapy and radiotherapy
  - Even past smoking, was an independent risk factor associated with impaired response to intravenous corticosteroids in patients with GO
- Study: Never smokers with active moderate-to-severe GO, who were treated with cumulative doses of 4.5 g intravenous methylprednisolone within 3 months, responded better than both active smokers and past smokers.



## Treatment modalities for thyroid eye disease

Basis of treatment is on interruption of the autoimmunity with immunosuppressive therapy and focus on reducing orbital inflammation

### **Nonspecific suppression**

Treatments for TED have largely been non-specific and involved immunosuppression targeting the adaptive immune system

### **Specific suppression**

Recent new insights into the molecular basis of thyroid eye disease have led to the use of more specific therapies such as monoclonal antibodies

## Glucocorticoids

Glucocorticoids are still the mainstay of TED therapy

- Administration of high-dose IV steroids can halt lymphocyte recirculation and interfere with inflammation and with the release of autoantigen
  - Unfortunately, because some of these mechanisms are also involved in **physiologic signaling** rather than **inflammatory signaling**, the therapeutic effects of glucocorticoids might be accompanied by clinically significant side effects

## Glucocorticoids

Administration route:

- Oral, IV, retrobulbar , SC

Current literature favors high dose systemic administration for severe active TED

- Studies: A greater positive clinical response in patients receiving IV methylprednisolone treatment vs. of patients treated with oral prednisolone (77% vs 49%) / retrobulbar (60 % vs 30%) injection
  - IV steroids are most effective in reducing inflammatory soft tissue findings and ocular motility dysfunction
    - It did not improve proptosis or diplopia significantly

## Glucocorticoids

The recent consensus statement of EUGOGO recommended high-dose IV GC as the first-line treatment for patients with a **CAS  $\geq 3/7$**

- Study: ivGC therapy was more effective when the CAS was  $> 2.5$  ???
- the CAS of Asian patients might be  $< 3$ 
  - This is because of the differences in orbital anatomy between Caucasians and Asians
  - Asian eyelids tend to have more subcutaneous and suborbicularis fat
    - The thicker eyelid might lead to reduced orbital inflammation

If IV glucocorticoid administration is not possible, oral prednisone can be given for 12 weeks, with initial dose of 0.1- 0.2 gram/day, gradually tapered down to and 0.01 gram/week (cumulative dose of 4 grams).

## Glucocorticoids

The recent consensus statement of EUGOGO recommended high-dose IV GC as the first-line treatment for patients with a **CAS  $\geq 3/7$**

### Different Doses and Protocols

- Monthly: 0.5g daily for 3 consecutive days in weeks 1, 5, 9, and 13 for a total dose of 6.0g over 3 months
- Weekly: 0.5g weekly for 6 weeks, followed by 0.25g weekly for 6 weeks for a total dose of 4.5g over 12 weeks
- Daily: 0.5g daily for 3 consecutive days per week for 2 weeks, followed by 0.25g daily for 3 consecutive days per week for another 2 weeks and by tapering oral prednisone.

## **Glucocorticoids**

### **Different Doses and Protocols**

- Weekly protocol was more effective than daily protocol and showed less adverse events than the other two protocols
- After completion of treatment: relapses account for about 20% and compressive optic neuropathy (ON) can develop in 7.5% of patients
- Treatment response of pulse IV steroid therapy may be seen within 1–2 weeks



## Glucocorticoids

### Different Doses and Protocols

**Clinical Study:** comparing different cumulative dosages of GCs

- A cumulative dose of **4.5 g** was recommended because it does not result in suppression of the hypothalamus–pituitary–adrenal axis

## **Glucocorticoids**

Identified risk factors for adverse effects from IV methylprednisolone are:

- Dose
- Age older than 53 years
- Daily pulses
- Pre-existing hepatitis , Significant liver dysfunction , history of viral hepatitis
- Severe cardiovascular morbidity
- Uncontrolled hypertension
- Psychiatric disorders
- Uncontrolled diabetes

## **Glucocorticoids**

## **Clinical points:**

- The shorter the duration of eye symptoms, the more favorable the effects of IVGC therapy
  - Thus, prompt diagnosis and treatment (within 13 months) is important
- Restoration of euthyroidism could have affected the effects of IVGC therapy

## Glucocorticoids

### Weak points of steroid therapy:

- A part of GO patients was not responsive to GCs treatment or relapsed after the withdrawal of GCs
- Its side effects
- GCs did not alleviate the **proptosis** more obviously compared with the placebos or other nonsurgical therapies

## Glucocorticoids

## Radioiodine (RAI) ablative treatment for Graves' hyperthyroidism (GD)

- It has been associated with de novo occurrence or worsening of GO
  - The development or progression of GO after RAI is thought to be the consequence of radiation damage to the thyrocytes, resulting in release of thyroid antigens and activation of autoimmune reactions directed to the orbit
- Evidences exist that radioiodine worsens the active ocular disease in 15% of cases within the 6 months after the treatment

## Glucocorticoids

## Radioiodine (RAI) ablative treatment for Graves' hyperthyroidism (GD)

### Risk factors:

- Pre-existing GO
- GD duration (less than 5 years)
- Active smokers
- Severely hyperthyroid prior to therapy
- Elevated serum levels of TSH-receptor Ab
- If post-RAI hypothyroidism is not promptly corrected
- Ablation technique: thyroidectomy compared with RAI

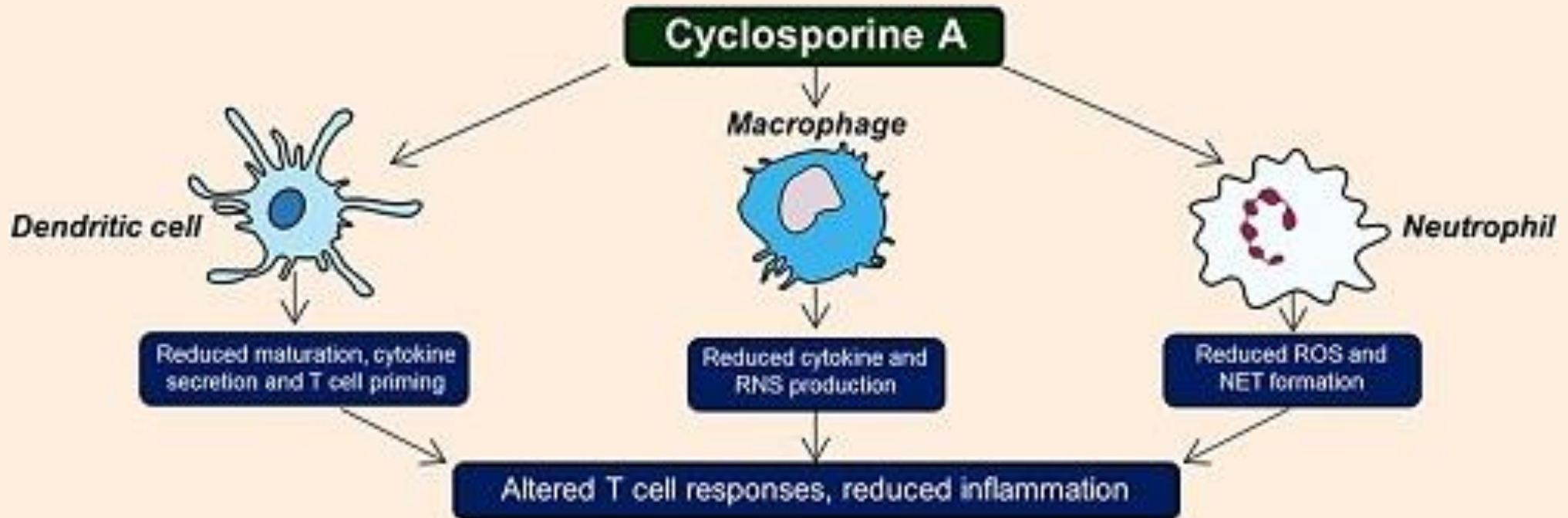
## Glucocorticoids

## Radioiodine (RAI) ablative treatment for Graves' hyperthyroidism (GD)

- In addition, corticosteroid prophylaxis (either oral prednisone at cumulative dose of 1.54 g or IV methylprednisolone at 1.5 g) is effective at reducing the risk of RAI-induced TED
- A lower dose of oral prednisone (0.2 mg/kg body weight) has also been found to be equally effective

## Cyclosporine

CysA preventing the secretion of interleukin-2 by CD4+ T-lymphocytes , and thereby interfering with the expansion of lymphocyte clones.



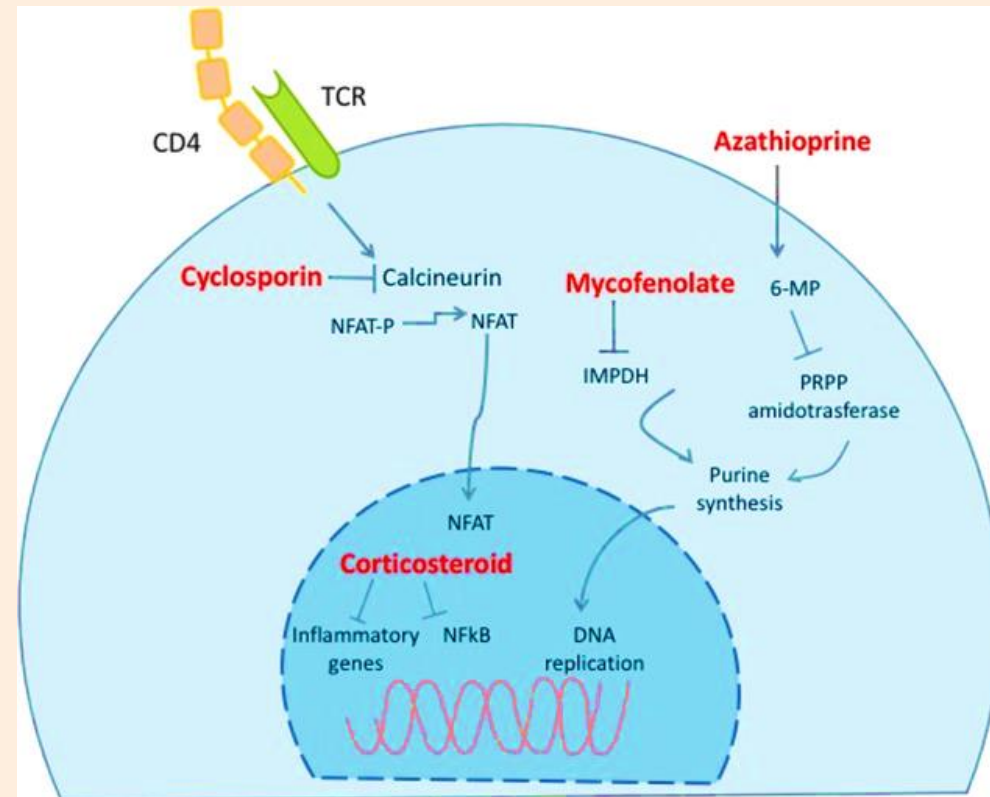


## Cyclosporine

- Acting on the amplification phase of the immune response, cyclosporine may prevent the reactivation of the cycle of autoimmunity
  - Being an ideal agent to maintain remission of TED
- TNF-alpha release from either source is inhibited by CysA making these also ideal agents to induce inhibition of the cicatricial phase of thyroid eye disease

# Cyclosporine

- Studies: Results with cyclosporine as a single agent were rather conflicting but mostly non-satisfactory



## Cyclosporine

Study, RCT: Cyclosporine, alone or in combination with glucocorticoid

- A greater improvement in CAS and visual acuity were observed with combination therapy when compared with prednisone monotherapy at 10w
  - After 10w, there were no significant improvements in proptosis, CAS, or visual acuity
- Relapses occurred in 40% (8/20) of patients in the prednisone group during the following 6 months and in 5% (1/20) in the combined treatment group at 9 months

## Azathioprine/ AZA

- AZA is a cytostatic agent and The site of action is direct on DNA
- AZA has not been shown to be of benefit as a single agent but exhibits effectiveness when combined with radiation therapy or steroid
- Its major toxicity: bone marrow suppression , Nausea and vomiting

In a multicenter, double-blind, randomized controlled trial :

- Improved clinical outcome at 48 weeks with Azathioprine treatment, associated to steroid

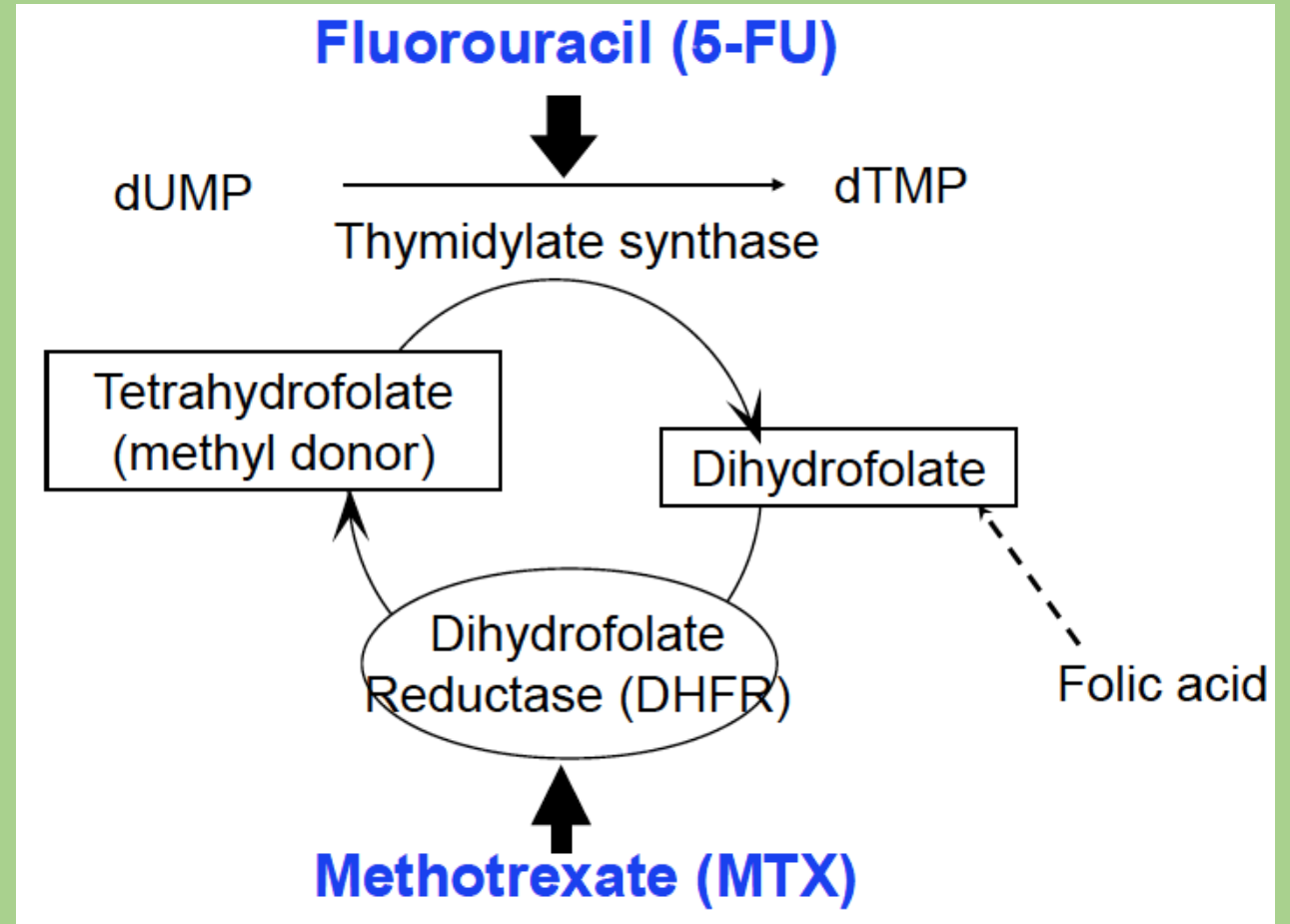


## Mycophenolate mofetil/MMF

- MMF is an immune modulatory drug which inhibits the proliferation of lymphocytes
- In a study of 74 patients with active moderate-to-severe TED who were randomized to receive either MMF or glucocorticoids
  - MMF group therapy showed a **better CAS** response than glucocorticoid (92.5% vs. 70.5% improved,  $P < 0.05$ )
  - a significantly **improved rate of diplopia and proptosis** at the 24th week (90.4% and 68.8% improved, respectively).
  - **Disease reactivation** was not observed in the patients treated with MMF but was observed in patients after glucocorticoid therapy
  - Adverse events occurred in 5% of patients treated with MMF which were mild to moderate due to increased risk of infection

## Methotrexate

Methotrexate is an immunosuppressive drug that **inhibits dihydrofolate reductase enzyme**, leading to the inhibition of the DNA, RNA, and protein synthesis



- It has been shown to be effective as a sole treatment in patients who failed steroids or became steroid dependent

## Methotrexate

Two recent studies have confirmed that methotrexate provides steroid sparing effect in a subset of patients with TED.

14 patients with TED who were unable to discontinue prednisone therapy without disease recurrence received methotrexate, from 15 mg/week orally to 20 mg/week subcutaneously

- of the 9 patients who remained on methotrexate, all were able to discontinue prednisone completely after an average duration of 7.5 months.
- Improved visual acuity and partial improvement in ocular motility was achieved in 7 and 5 patients, respectively.

## Methotrexate

Two recent studies have confirmed that methotrexate provides steroid sparing effect in a subset of patients with TED.

36 consecutive patients with recurrent active TED, previously treated with corticosteroids then stopped due to the occurrence of side effects

- 7.5 mg or 10 mg/week
- There was a statistically significant improvement in CAS at 12 months after treatment ( $P < 0.0001$ ).
- Ocular motility disturbances improved significantly at 12 months ( $P < 0.001$ ).
- There was no significant change in exophthalmos or eyelid position or vision.



**Nonspecific immunosuppressant**

**Others**

**Combined Therapy vs. Monotherapy.....**

## Others

- Studies have shown that high dose **IV immunoglobulin** is as effective as high doses of oral glucocorticoids
  - However, this is not routinely used today for the treatment of TED
- Other immunosuppressive medications, such as **somatostatin analogues**, and **ciamexone** have, in aggregate, been found ineffective in the treatment of TED

## **Others**

- Methimazole is a common drug indicated for thyroid dysfunction
  - According to studies, it is also an immunosuppressant
  - It could alleviate inflammation of the orbital tissue and improve the overall efficacy of glucocorticoids.

## **Others**

### Chloroquine and Hydroxychloroquine

- The cytostatic and antiadipogenic and anti-inflammatory effects

### Prostaglandin Analogue Bimatoprost

- long-term use of prostaglandin (PG) analogues has been shown to lead to PG-associated periorbitopathy (PAP), which is characterized by reversible atrophy of periorbital tissues, including orbital adipocytes

## **Others**

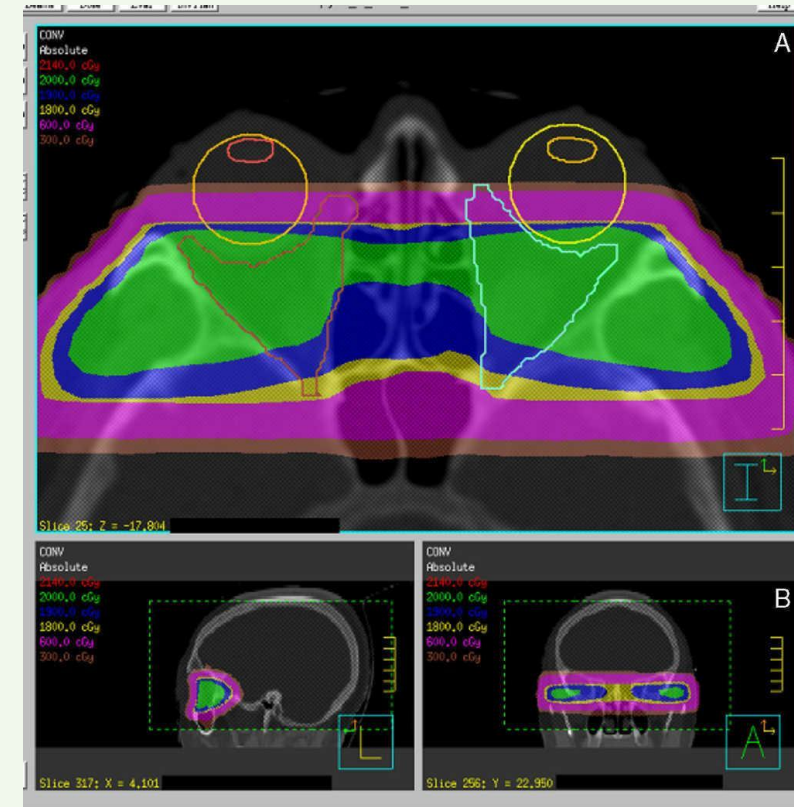
- Allopurinol
- Vitamin nicotinamide
- Pentoxifyllin
- Enalapril
- Vitamin D

- Vitamin C
- N-acetyl-l-cysteine
- Melatonin
- $\beta$ -carotene, Retinol,
- Vitamin E

## Orbital radiotherapy (ORT)

Two RCTs comparing ORT to sham irradiation in moderately severe TED showed a response rate of 50–60%,

- ORT has also been used as an adjunctive or, less commonly, as primary therapy for active TED for decades due to its effectiveness in reducing inflammation and the radio-sensitivity of orbital lymphocytes
- Contraindications: diabetic retinopathy, severe hypertension, and age less than 35 years
- Potential side effects: cataract formation and radiation retinopathy

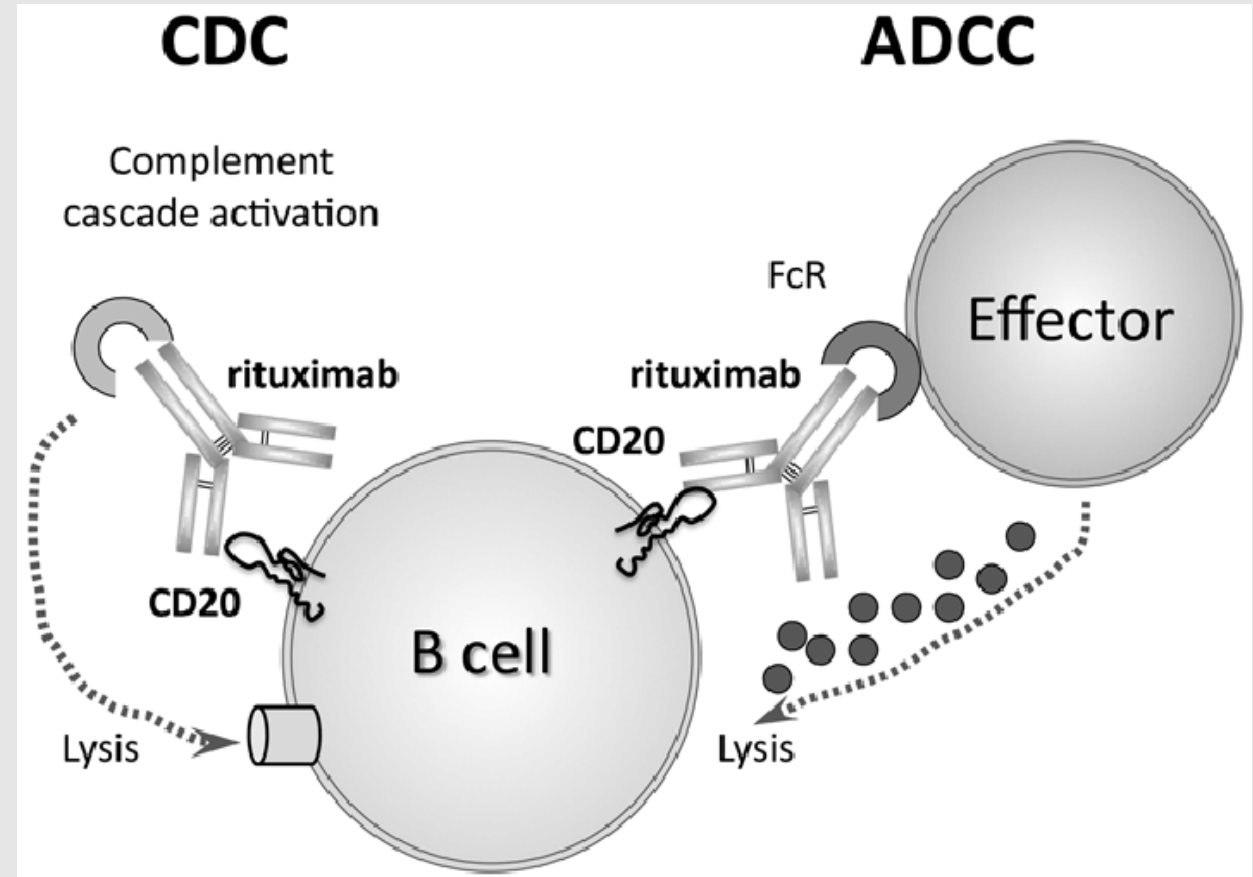




**Targeted Therapies**

## Rituximab

- It is an humanized anti-CD20 monoclonal antibody that targets CD20 on B cells and its precursors



- Rituximab targets B cells, which leads to B cell depletion and therefore may affect autoantibodies to the TSH receptor.



## Rituximab

Study/RCT:

- 21 patients randomized to two 1000 mg rituximab infusions or two saline infusions two weeks apart
  - no significant benefit of rituximab compared to placebo

Study: improved outcomes with rituximab compared to IV methylprednisolone

- 32 patients were randomized to receive rituximab (1000 mg twice or 500 mg once) or IV methylprednisolone (7.5 g)
- At 24 weeks, all rituximab patients had improved, compared with 69% of the methylprednisolone patients



## Rituximab

- Rituximab is typically well tolerated
- The most common side effects are hypotension, transient fevers, and pruritus.

Serious adverse events including dysthyroid optic neuropathy have been reported

- Study: 6 cases of optic neuropathy, treated with RTX
  - failure of RTX was reported in one patient whose GO progressed to acute CON
  - in one with CON failed to improve on RTX despite achieving peripheral B cell depletion

## Tocilizumab/TCZ

- Tocilizumab (TCZ), a recombinant humanized monoclonal antibody against the IL-6 receptor, that binds both soluble and membrane-bound forms of the receptor.
  - It plays an important role in B cell activation and the development of antibody-producing plasma cells
- Tocilizumab is approved for the treatment of active, moderate-to-severe RA and GCA and is under consideration as a potential treatment for TED

## Tocilizumab/TCZ

1. Study : in 18 patients with active TED refractory to intravenous steroids
  - TCZ significantly improved CAS , proptosis, extraocular motility, and diplopia
2. A double-masked RCT, in patients with moderate-to-severe corticosteroid-resistant TED :
  - TCZ VS placebo:
    - A significant difference in the proportion of patients achieving a CAS < 3 and exophthalmos size change from baseline in patients treated with tocilizumab
3. Clinical trial: 93.3% of patients treated with tocilizumab vs 58.8% receiving placebo met the primary endpoint of reduction of CAS by  $\geq 2$  points at week 16
  - Did not significantly improve diplopia or proptosis

## Etanercept

- TNF-alpha receptor blocker
  - Study: working more in terms of activity than severity of disease

## Adalimumab

- A fully human monoclonal antibody against TNF
  - A case series: improvement in an inflammatory score in 50% patients

## Infliximab

- It has been successfully used in one steroid and orbital decompression resistant patient with severe TED and compression of the optic nerve

## **Teprotumumab**

- Teprotumumab, an IGF-1R inhibitory antibody, binds with high affinity and specificity to IGF-1R inducing internalization and degradation of the antibody-receptor complex
- The drug has been approved recently by the US Food and Drug Administration as the first medical therapy for this disfiguring and potentially blinding disease

## Teprotumumab

**2 RCT:** In patients with active moderate-to-severe TED

- Teprotumumab rapidly achieved improvement in clinical endpoints defining TED, including improved proptosis and diplopia
- Comparable only to surgical therapies achieved during the inactive phase of TED

## Emerging therapies



### **IMVT-1401**

- Recently, a monoclonal antibody targeting the neonatal Fc receptor (FcRn) has been proposed for the treatment of autoimmune diseases, including TED

### **TSHR antagonist**

- These antagonists selectively inhibit TSH-stimulated signaling. They have been found to reduce serum free T4 levels by 44% and lower mRNAs for thyroperoxidase by 83%



## Disease severity classification adapted from the European Group on Graves Orbitopathy (EUGOGO)

### Stage

### Symptoms and findings

**MILD**



**Mild eyelid retraction (<2mm), mild soft tissue involvement, mild exophthalmos (<3mm above normal), transient or no diplopia, corneal exposure responsive to lubricants**

- In the majority of studies which have investigated the natural history of GO in untreated patients, the orbitopathy improved in about a half of the patients, remained stable in about 35%, and worsened in approximately 15%

## Mild TED

- The mainstay of treatment is:
  - Control thyroid function
  - To cease smoking
  - Supportive ocular lubrication
  - Twice-daily selenium 100 mg for 6 months
  - Control of the risk factors

## Mild TED

- When the impact of GO on quality of life exceeds the risk of therapy, intravenous glucocorticoids can be given to active GO and rehabilitative surgery for inactive GO
- Botulinum toxin injection may be considered to reduce upper lid retraction and is a valuable therapeutic option in active disease where definitive surgery remains contraindicated

## Disease severity classification adapted from the European Group on Graves Orbitopathy (EUGOGO)

### Stage

### Symptoms and findings

Moderate to severe



Mild eyelid retraction ( $\geq 2\text{mm}$ ), moderate or severe soft tissue involvement, mild exophthalmos ( $\geq 3\text{mm}$  above normal), inconstant or constant diplopia, impact on daily functions of life

### Active GO

- High-dose systemic glucocorticoids are the first line of moderate-to-severe active GO
- Combination of oral glucocorticoids and orbital radiotherapy or other drugs
- Targeted therapy

## Disease severity classification adapted from the European Group on Graves Orbitopathy (EUGOGO)

### Stage

### Symptoms and findings

**Moderate to severe**



**Mild eyelid retraction ( $\geq 2\text{mm}$ ), moderate or severe soft tissue involvement, mild exophthalmos ( $\geq 3\text{mm}$  above normal), inconstant or constant diplopia, impact on daily functions of life**

Inactive GO

- Rehabilitative surgery
  - in patients with GO who have significant altered visual function or quality of life after GO become inactive for at least 6 months

## Disease severity classification adapted from the European Group on Graves Orbitopathy (EUGOGO)

### Stage

### Symtoms and findings

**Sight-threatening**

**Dysthyroid optic neuropathy  
, corneal breakdown**



- First-line therapy is intravenous glucocorticoids
- Protection of globe
- If the response is not good or there is deterioration in visual function, decompression surgery needs to be performed

غبار غم برود  
حال خوش شود  
حافظ

