**Question 1:** What factors predispose a TED patient for reoccurrence of disease

**Response 1:**

**Factors Predisposing TED Patients to Disease Recurrence** **-**

### **Risk Factors for TED Recurrence**

* Men, older patients, smokers, and those with rapid onset of orbitopathy are more likely to have severe TED requiring surgical intervention [${1}].
* Smoking is the strongest modifiable risk factor for TED development and progression, associated with poorer treatment outcomes and increased risk of reactivation [${1}].
* Radioactive iodine (RAI) therapy, while effective for hyperthyroidism, can increase the risk of de novo TED development and worsening of ophthalmopathy, especially in smokers [${1}].

### **Impact of Smoking and RAI on TED Recurrence**

* Smoking is strongly associated with disease progression, poorer treatment outcomes, and increased risk of future reactivation in TED patients [${1}].
* RAI therapy has been shown to increase the risk of developing de novo TED and worsening ophthalmopathy, particularly in certain patients, such as smokers [${1}].

### **Role of Smoking and RAI in TED Pathogenesis**

* Smoking is a significant risk factor for TED development and progression, with a greater association with the amount of cigarettes smoked post-Graves' disease diagnosis [${3}].
* RAI therapy is a known risk factor for both the development and progression of TED, with glucocorticoid usage potentially mitigating the associated risks [${3}].

-------------------------------------------------------------------------------------------------------------------------------

**User Comment:** The answer provides some relevancy. Needs more information about Recurrence of TED. Should be using reference on 'Recurrent Thyroid Eye Disease'.

​**Details Required:** Need specific document and the content being referred here for Recurrent Thyroid Eye Disease

**Question 2:** What are the complications caused by glucocorticoids in TED

**Response 2:**

## **Complications Caused by Glucocorticoids in Thyroid Eye Disease (TED)**

Glucocorticoids are commonly used in the management of Thyroid Eye Disease (TED) to reduce inflammation and symptoms associated with the condition [${8}].

### **Impact on Disease Course**

* High-dose glucocorticoids have been evaluated in numerous trials for TED but have not shown success in modifying the disease endpoints or preventing long-term sequelae [${2}].
* Glucocorticoids are typically administered during the active phase of moderate to severe TED to lessen inflammation-related signs and symptoms [${8}].

### **Quality of Life and Socioeconomic Impact**

* TED can severely impact quality of life and socioeconomic status, with proptosis and diplopia significantly affecting daily activities and self-confidence [${2}].
* Patients with TED may experience limitations in driving, working, watching television, reading, and social interactions due to the physical changes caused by the disease [${2}].
* These drastic quality-of-life changes have been associated with higher rates of suicide in the TED patient population [${2}].

Overall, glucocorticoids play a role in managing inflammation in TED but do not prevent long-term complications or modify the disease course significantly [${8}].

-------------------------------------------------------------------------------------------------------------------------------

**User Comment:** The response does not provide details of the complications caused by steroid use in TED. ​

**Details Required:** Reference needed about the effects of steroid on TED

Is the highlighted yellow part of the response is relevant or not?

**Question 3:** What are the adverse events associated with TEPEZZA

**Response 3:**

## **Adverse Events Associated with TEPEZZA**

### **Adverse Events from Clinical Trials of Teprotumumab**

Adverse events associated with teprotumumab in clinical trials were primarily mild (grade 1 or 2), with the most common being muscle spasms (30%), alopecia (20%), hyperglycemia (10%), diarrhea (10%), and fatigue, headache, and hearing impairment (10%) [${1}].

### **Recommendations for Mitigation of Side Effects**

* Laboratory Panels: Baseline comprehensive metabolic panel, vitamin D, B12, and multivitamins including folic acid [${1}].
* Supplement Considerations: Start magnesium supplements, vitamins D and B, and day to follow [${1}].
* Other Considerations: Oral hydration before infusion, Epsom salt bath on the day of infusion and day to follow, IGF-1R ear drops, continuous glucose monitoring, diabetic diet, biotin supplement, artificial tears, and topical cyclosporine [${1}].

### **Infusion Details and Reactions**

Infusions of teprotumumab should be administered 3 weeks apart with varying dosages [${1}]. Infusion reactions tend to be mild or moderate and are managed with corticosteroids and/or antihistamines [${1}].

### **Authorization Process**

Insurance authorization is often required before teprotumumab administration, necessitating a provider's description of the patient's condition to justify treatment [${1}].

-------------------------------------------------------------------------------------------------------------------------------

**User Comment:** References should include phase3/4 publications to elaborate on the AE's from both acute and chronic studies.​

**Details Required**:

* Reference of additional info required to be displayed
* User should mention in query

**Question 4:** How does TED prognosis vary among patients?

**Response 4:**

## **Variability in TED Prognosis Among Patients**

Thyroid Eye Disease (TED) presents with a spectrum of clinical manifestations that can vary significantly among patients. Common symptoms of active TED include eye pain, excessive lacrimation, diplopia, photophobia, and blurry vision, with eyelid retraction being the most prevalent clinical finding in a cohort of patients in Minnesota [${1}].

### **Factors Contributing to Prognostic Variability**

* The onset, activity, and severity of TED can vary, leading to delays in accurate diagnosis, with an average time to diagnosis from symptom onset being 9 months [${2}].
* Patients with TED may experience an acute inflammatory phase lasting 6 to 36 months, followed by a chronic phase characterized by fibrosis, which can result in permanent disfigurement and functional vision loss [${2}].
* The disease course of TED can be unpredictable, with some patients experiencing mild, self-limited TED, while others may develop moderate/severe or sight-threatening disease [${2}].

Overall, the heterogeneous presentation of TED, including the timing of onset, activity, and severity, contributes to the variability in prognosis among patients, with some requiring no therapy or only supportive measures, while others may need medical or surgical intervention [${3}].

-------------------------------------------------------------------------------------------------------------------------------

**User Comment:** Noticed it mentioned Minnesota- I understand why it was mentioned, but it can be distracting- what about patient outside Minnesota? - Also not comprehensive in its description

**Details Required:** Response also seems good

"Minnesota" seems to appear, probably due to the research outcomes conducted in the place? reference to the document could help understand better to find the root cause behind appearance of a particular region

Is the response incorrect?

The last 2 paragraphs are general in nature not for Minnesota specific. Could you provide more context.

**Question 5:** Summarize the results of TEPEZZA on chronic TED.

**Response 5:**

**TEPEZZA Impact on Chronic Thyroid Eye Disease (TED)**

### **Study Findings:**

• Teprotumumab, known as TEPEZZA, has shown efficacy in patients with chronic TED, with significant proptosis reduction and improvements in diplopia and other symptoms [${2}]. • In a retrospective study of 31 patients with chronic, stable TED, TEPEZZA led to a mean proptosis reduction of 3.5 mm, similar to results in patients with active disease [${2}]. • Patients with diplopia experienced complete resolution or improvement on the Gorman scale after TEPEZZA treatment [${2}]. • Radiographic imaging showed a decrease in orbital fat volume and extraocular muscle volume, indicating positive outcomes [${2}].

### **Longitudinal Impact:**

• TEPEZZA has been found to reduce lacrimal gland size and increase tear production in patients with TED, showing efficacy in chronic cases as well [${3}]. • The study's longitudinal design allowed for a robust comparison within patients, highlighting the sustained impact of TEPEZZA on chronic TED [${5}].

### **Future Implications:**

• TEPEZZA's approval in 2020 by the FDA marked a significant advancement in TED treatment, with potential to change evaluation and management guidelines [${4}]. • Despite the high cost barrier, TEPEZZA's efficacy in chronic TED patients suggests a promising future for the management of the disease [${4}].

------------------------------------------------------------------------------------------------------------------

**User Comment:** Picked information from Chronic Case study from Ugradar but not from Phase 4 trial (perhaps not picked up due to terminology used in that paper- can we "broaden" that?). The information from Ugradar was picked from the Discussion of the Phase 4 trial paper. Also picked text from discussion of another paper, and did not summarize data

**Details Required:** One of the Phase 4 chunk appeared in sources; but didn't found much details regarding the chronic disease; Need specific content/document which need to be present in the response