# Indirect treatment comparison of teprotumumab versus rituximab or tocilizumab in patients with moderate-to-severe active thyroid eye disease

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## BACKGROUND

- Thyroid eye disease (TED) is a serious and progressive autoimmune condition characterized by inflammation and orbital fat and tissue remodeling
- Teprotumumab, a monoclonal antibody targeting insulin-like growth factor I receptor, has been licensed for the treatment of TED in multiple countries. The approval was based on phase 2 (NCT01868997) and phase 3 OPTIC trial (NCT03298867) showing superior proptosis reduction and diplopia response (≥1 grade reduction from baseline) versus placebo
- The American and European Thyroid Association guidelines recommend teprotumumab for patients with significant diplopia and/or proptosis, while also noting that rituximab and tocilizumab may be considered for glucocorticoid-resistant TED

## OBJECTIVE

- In the absence of head-to-head trials, the objective of this study was to evaluate the relative efficacy of teprotumumab vs rituximab and tocilizumab with respect to change from baseline (CFB) in proptosis and diplopia response rate in patients with moderate-to-severe active TED via indirect treatment comparison (ITC)

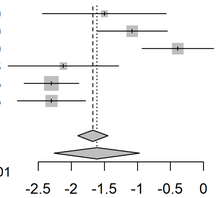
## METHODS

- Data for ITC included individual patient data from two teprotumumab randomized controlled trials (RCT), and aggregate data from one rituximab RCT and six tocilizumab studies (1 RCT and 5 observational), identified through systematic review and feasibility assessment
- For teprotumumab vs rituximab, an anchored matching-adjusted indirect comparison (MAIC) was employed, using data from each teprotumumab RCT and the rituximab RCT, adjusting for smoking, baseline proptosis, baseline diplopia, age, and sex. Estimates from the analysis using each trial were pooled via inverse variance-weighted meta-analysis
- For teprotumumab vs tocilizumab, an unanchored MAIC was performed adjusting for smoking, prior radioactive iodine therapy, baseline proptosis, baseline diplopia, age, and sex. Six tocilizumab studies were pooled for proptosis comparison
- Mean difference (MD) for proptosis CFB and odds ratio (OR) for diplopia response at 24 weeks were estimated using a weighted linear regression and weighted logistic regression respectively, with robust variance estimation for the 95% confidence intervals (CIs)

### Meta-analysis pooling of proptosis CFB for tocilizumab

| Study | Total | Mean | SD | MRAW | 95%-CI | Weight (common) | Weight (random) |
|---|---|---|---|---|---|---|---|
| Perez-Moreiras, 2018 | 15 | -1.50 | 1.8519 | -1.50 | [-2.44; -0.56] | 6.0% | 14.0% |
| Wang, 2024 | 45 | -1.08 | 1.8300 | -1.08 | [-1.61; -0.55] | 18.4% | 17.5% |
| Lee, 2024 | 19 | -0.39 | 1.2100 | -0.39 | [-0.93; 0.15] | 17.8% | 17.4% |
| Farde, 2025 | 22 | -2.12 | 2.0046 | -2.12 | [-2.96; -1.28] | 7.5% | 14.9% |
| Boutzios, 2023 | 12 | -2.30 | 0.7325 | -2.30 | [-2.71; -1.89] | 30.6% | 18.4% |
| Perez-Moreiras, 2021 | 54 | -2.30 | 1.9355 | -2.30 | [-2.82; -1.78] | 19.7% | 17.7% |
| **Common effect model** | **167** | | | **-1.67** | **[-1.90; -1.45]** | **100.0%** | . |
| **Random effects model** | | | | **-1.61** | **[-2.26; -0.97]** | . | **100.0%** |

Heterogeneity: $I^2$ = 88.0%, $\tau^2$ = 0.5495, $p$ < 0.0001




## KEY TAKEAWAYS

- **Teprotumumab demonstrated greater reductions in proptosis and improvements in diplopia compared with rituximab, and greater reductions in proptosis compared with tocilizumab**
- **These findings support teprotumumab as an effective treatment option for pre-treated patients with moderate-to-severe active TED**

## RESULTS

- After MAIC weighting, the baseline characteristics between teprotumumab and comparator populations were well balanced, with effective sample sizes (ESS) of approximately 40–60% across all primary analyses
- Teprotumumab was associated with a greater reduction in proptosis compared to rituximab (MD [95% CI]: -3.65 mm [-5.07, -2.23]), and tocilizumab (-1.20 mm [-2.07, -0.32]).
- Diplopia response rates were higher for teprotumumab vs rituximab (OR [95% CI]: 38.95 [3.24, 468.28]); the large OR and wide CI reflected the substantial variance due to no diplopia responses in the rituximab arm (continuity correction applied)
- For diplopia, evidence for tocilizumab was limited to a small observational study from Asia and considered exploratory due to geographic differences and poor baseline overlap with teprotumumab trials. Teprotumumab showed numerically higher odds of response versus tocilizumab (OR 2.55 [0.52, 12.43]), though interpretation was constrained by geographic differences and small ESS

### Baseline characteristics and outcomes

| Author, year | Treatment | N | Age (mean) | Male (%) | Smoker (%) | RIT (%) | Proptosis BL, mm (mean) | Diplopia BL (%) | Proptosis CFB, mm (Mean, SD) | Diplopia response (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Index trials (teprotumumab)** | | | | | | | | | | |
| Phase 2: Smith, 2017 | Placebo | 45 | 54.1 | 20.0% | 40.0% | 11.1% | 23.1 | 68.9% | -0.38 (1.78) | 37.0% |
| | Teprotumumab | 42 | 51.7 | 33.3% | 26.2% | 9.5% | 23.4 | 90.5% | -3.14 (1.54) | 74.3% |
| Phase 3: Douglas, 2020 | Placebo | 42 | 48.9 | 26.2% | 19.0% | 9.5% | 23.2 | 66.7% | -0.44 (1.14) | 28.6% |
| | Teprotumumab | 41 | 51.6 | 29.3% | 22.0% | 9.8% | 22.6 | 68.3% | -3.24 (1.62) | 67.9% |
| **Rituximab study** | | | | | | | | | | |
| Stan, 2015 | Placebo | 12 | 61.8 | 33.3% | 16.7% | 75.0% | 23.3 | 83.3% | -0.38 (2.49) | 20.0% |
| | Rituximab | 13 | 57.6 | 30.8% | 15.4% | 61.5% | 24.6 | 92.3% | 0.25 (1.91) | 0.0% |
| **Tocilizumab studies** | | | | | | | | | | |
| Perez-Moreiras, 2018 | Placebo | 17 | 47.5[a] | 23.5% | 0.0% | 0.0% | 22.0 | NR | 0.00 (1.11)[a] | NR |
| | Tocilizumab | 15 | 45.1[a] | 26.7% | 0.0% | 0.0% | 21.0 | NR | -1.50 (1.11)[a] | NR |
| Farde, 2025 | Tocilizumab | 23 | 63.8 | 17.4% | 39.1% | 17.4% | 21.5 | NR | -2.12 (2.00) | NR |
| Lee, 2024 | Tocilizumab | 19 | 46.4 | 31.6% | 21.1% | NR | 19.1 | 78.9% | -0.39 (1.21) | 66.7% |
| Wang, 2024 | Tocilizumab | 64 | 46.4 | 36.0% | 4.7% | NR | 18.2 | NR | -1.08 (1.83) | NR |
| Boutzios, 2023 | Tocilizumab | 12 | 58.4 | 50.0% | 66.7% | NR | 22.0 | 33.3% | -2.30 (0.73) | NR |
| Perez-Moreiras, 2021 | Tocilizumab | 54 | 53.8 | 24.1% | 38.9% | 18.9% | 21.8 | NR | -2.30 (1.94) | NR |
| **Tocilizumab pooled**[b] | Tocilizumab | 167 | 51.8 | 29.4% | 26.2% | 15.4% | 20.4 | 61.3% | -1.61 (4.27) | -- |

**Abbreviations**: BL, baseline; CFB, change from baseline; NR, not reported; RIT, radioactive iodine therapy; SD, standard deviation. **Footnotes**: a) Median was reported and was considered as mean in this table, the SD was calculated based on interquartile range; b) Baseline characteristics were pooled using weighted average based on studies with data available for each characteristics, and proptosis CFB was pooled via meta-analysis

### MAIC results for proptosis CFB

| Analysis | Treatment | ESS | ITC - MD (95% CI) |
|---|---|---|---|
| **Teprotumumab vs Rituximab**[a] | | | |
| Primary analysis | Teprotumumab (phase 2)[b] | 46.4 (60.2%) | -3.78 (-5.79, -1.77) |
| | Teprotumumab (phase 3)[b] | 37.5 (46.9%) | -3.52 (-5.53, -1.50) |
| | Teprotumumab (MA pooled) | -- | **-3.65 (-5.07, -2.23)** |
| | Rituximab (Stan, 2015) | 25 | Reference |
| **Teprotumumab vs Tocilizumab**[c] | | | |
| Primary analysis | Teprotumumab (phase 2 & 3) | 31.6 (40.5%) | **-1.20 (-2.07, -0.32)** |
| | Tocilizumab (6 studies pooled) | 167 | Reference |

**Abbreviations**: CFB, change from baseline; ESS, effective sample size; ITC, indirect treatment comparison; MA, meta-analysis; MD, mean difference. **Footnotes**: a) In an anchored MAIC, both intervention and placebo arms were included in the analysis, and therefore, were counted in the sample size; b) Phase 2 and Phase 3 teprotumumab trials were analyzed separately in order to maintain the randomization within the trial for anchored comparison; c) In the unanchored MAIC, only the intervention arms from each study were included

### MAIC results for diplopia response

| Analysis[a] | Treatment | ESS | ITC - OR (95% CI) |
|---|---|---|---|
| **Teprotumumab vs Rituximab** | | | |
| Primary analysis | Teprotumumab (phase 2) | 42.3 (68.2%) | 32.70 (1.03, 1035.17) |
| | Teprotumumab (phase 3) | 30.5 (54.4%) | 47.01 (1.31, 1689.93) |
| | Teprotumumab (MA pooled) | -- | **38.95 (3.24, 468.28)** |
| | Rituximab (Stan, 2015)[b] | 24 | Reference |
| **Teprotumumab vs Tocilizumab** | | | |
| Exploratory analysis | Teprotumumab (phase 2 & 3) | 13.6 (21.5%) | **2.55 (0.52, 12.43)** |
| | Tocilizumab (Lee, 2024) | 15 | Reference |

**Abbreviations**: ESS, effective sample size; ITC, indirect treatment comparison; MA, meta-analysis; OR, odds ratio. **Footnotes**: a) Only patients with baseline diplopia were included in the analysis; b) Continuity correction was performed for Stan, 2015 since its rituximab arm had zero events. Constant to all cells approach was used by adding 0.5 to all cells in both treatment arms

## LIMITATIONS

- The unanchored MAIC requires strong assumptions of fully adjusting for all relevant prognostic factors and effect modifiers; incomplete covariate reporting and reduced ESS contributed to uncertainty
- The evidence for comparators was limited and heterogeneous, particularly for diplopia outcome, with small sample sizes and limited overlap in key baseline characteristics, restricting the extent of adjustment and precision of the results
- Results from 1L teprotumumab trials were extrapolated to pre-treated populations, which may differ in disease severity and treatment response, introducing potential bias despite adjustment for reported baseline characteristics

## DISCLOSURES

This study was funded by Amgen, Inc. Alex Eddy and Christina Giannopoulou are employees of Amgen and hold stock/options. Zhiyi Lan, Yu Wang, and Yuting Kuang are employees of IQVIA, which has received consulting fees from Amgen Inc. for the conduct of this research.

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