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Teprotumumab vs. Intravenous Methylprednisolone Alone, and in Combination with Mycophenolate Mofetil, for Moderate-to-Severe Active Thyroid Eye Disease: A Matching-adjusted Indirect Comparison

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BACKGROUND

- Thyroid eye disease (TED) is a complex, autoimmune condition characterized by heterogeneous visual dysfunction and disfigurement (e.g., diplopia/double vision, proptosis/bulging eyes).[1]
- Treating moderate-to-severe TED is challenging, with limited response to off-label treatments.[2]
- The American Thyroid Association (ATA) and European Thyroid Association (ETA) guidelines recommend intravenous methylprednisolone (IVMP), teprotumumab, radiotherapy, and oral corticosteroids for the treatment of active TED.[3]
- Teprotumumab, a first-in-class, monoclonal antibody that targets the insulin-like growth factor-1 receptor, has demonstrated efficacy in phase 2 (NCT01868997[4]) and OPTIC phase 3 (NCT03298867[5]) trials for patients with TED.[6]
- Teprotumumab has been approved by the United States Food and Drug Administration[7] and European Medicines Agency to treat moderate-to-severe TED.[8]
- Due to the lack of head-to-head data for teprotumumab vs. IVMP alone, and in combination with mycophenolate mofetil (MMF), indirect treatment comparisons are required to evaluate the relative efficacy.

OBJECTIVE

- The objective of this study was to estimate the relative treatment effect of teprotumumab in comparison with IVMP and IVMP+MMF, with respect to change from baseline (CFB) in proptosis and diplopia response rate, in patients with moderate-to-severe active TED using matching-adjusted indirect comparisons (MAIC).

METHODS

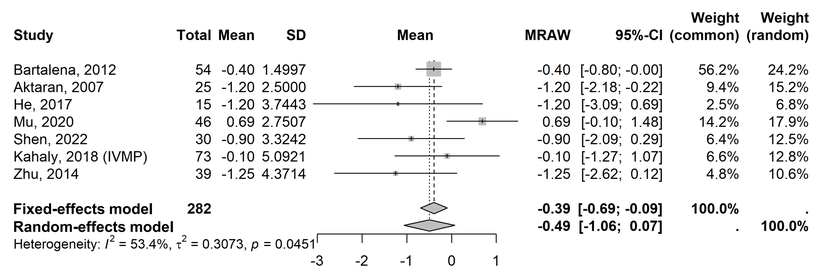
- Two systematic literature reviews (conducted in June 2023) identified randomized controlled trials (RCT) and real-world evidence (RWE) studies of teprotumumab and comparators reporting CFB in proptosis (mm) and diplopia response (≥1 grade reduction).
- A feasibility assessment (FA) was performed on studies identified through the systematic literature review (SLR) to evaluate heterogeneity in study design, patient populations, treatments, and outcomes.
- Inclusion in the FA was restricted to studies using IVMP 4.5 to 5.0 g, alone or with MMF 1 g daily for 24 weeks, in adults with moderate-to-severe active TED, consistent with European Group on Graves' orbitopathy and ATA/ETA guidelines.[2,3]
- Based on the FA, an unanchored MAIC was required due to the absence of a connected evidence network.
- The FA identified individual patient data from teprotumumab phase 2 (n=42) and OPTIC phase 3 (n=43) trials, which were pooled to increase sample size and robustness.
- Pooled treatment effects for IVMP were derived from seven studies on proptosis[9-15] and four on diplopia[13-16] and were calculated using random-effects meta-analyses.
- For IVMP+MMF, one study was identified for proptosis and none for diplopia.
- Full treatment duration was used in all analyses: 12 weeks for IVMP and 24 weeks for teprotumumab and IVMP+MMF, capturing maximum cumulative effects and ensuring fair comparison.
- In the base case, RCTs were prioritized as gold-standard evidence. A scenario analysis including RCTs and RWE for IVMP incorporated 10 studies for proptosis and six for diplopia.
- Potential treatment effect modifiers and prognostic factors were considered to address imbalances between groups. Covariates were identified by clinicians and the literature and selected based on availability in the trials.
- Propensity score weights were applied to the teprotumumab group to match covariate distributions with those of the comparators.
- Weighted linear regression estimated mean differences (MD) for proptosis CFB; weighted logistic regression estimated odds ratios (OR) for diplopia response.

RESULTS

Base-case meta-analysis – CFB in proptosis

- A meta-analysis of seven IVMP RCTs[9-15] showed a pooled CFB in proptosis of -0.49 mm (Figure 1).
- After matching, baseline characteristics between teprotumumab and IVMP were well balanced (Table 1).

Figure 1. Meta-analysis of CFB in proptosis for IVMP – random- and fixed-effects models



CI, confidence interval; IVMP, intravenous methylprednisolone; MRAW, raw mean; SD, standard deviation

KEY TAKEAWAYS

- **Teprotumumab provides a clinical benefit compared with both IVMP and IVMP+MMF for patients with moderate-to-severe active TED.**
- **These findings align with two previous indirect comparisons[17,18] and strengthen the evidence supporting the efficacy of teprotumumab in TED.**

RESULTS (CONT.)

Table 1. Baseline characteristics before and after matching – CFB in proptosis

Teprotumumab vs. IVMP			
Covariate	**Teprotumumab (pooled phase 2 and 3) baseline characteristics**		**IVMP baseline characteristics (pooled RCTs, n=7 studies)**
	Before matching (n=78.00)	**After matching (n=35.36)**	
Proportion of smokers (mean, %)	23.08	35.66	35.66
Baseline proptosis (mean, mm)	22.97	20.94	20.94
Baseline diplopia (mean, %)	79.49	61.30	61.30
RIT (mean, %)	10.26	16.31	16.31
Teprotumumab vs. IVMP+MMF			
Covariate	**Teprotumumab (pooled phase 2 and 3) baseline characteristics**		**IVMP+MMF baseline characteristics (n=1 study)**
	Before matching (n=75.00)	**After matching (n=38.90)**	
Proportion of smokers (mean, %)	23.08	53.01	53.01
Baseline diplopia (mean, %)	79.49	66.27	66.27
RIT (mean, %)	10.26	18.07	18.07
Age (years)	51.55	52.10	52.10
Sex (%, male)	29.49	26.51	26.51

IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; RCT, randomized controlled trial; RIT, radioiodine therapy

Base-case MAIC – CFB in proptosis

- The analyses adjusted for the following treatment effect modifiers and prognostic factors:
  - Teprotumumab vs. IVMP: smoking, baseline diplopia, baseline proptosis, radioiodine therapy (RIT)
  - Teprotumumab vs. IVMP+MMF: smoking, baseline diplopia, age, sex, RIT
- Baseline proptosis was excluded from the IVMP+MMF analysis since including it led to an ESS below an acceptable threshold.
- In the base case (RCTs only), teprotumumab was associated with a greater CFB in proptosis vs. IVMP (MD: -2.41 mm) and IVMP+MMF (MD: -3.06 mm) (Table 2).

Table 2. Base-case MAIC results – CFB proptosis

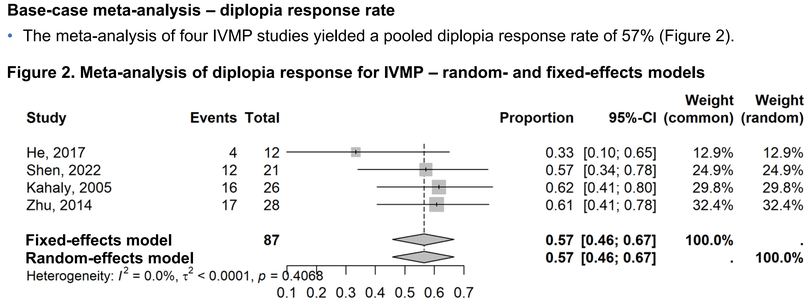
	ESS	**MD in CFB proptosis, mm (SE) [95% CI]**
Teprotumumab vs. IVMP (adjusted for proportion of smokers, baseline diplopia, baseline proptosis, RIT)		
Adjusted results	35.36	**-2.41** (0.41) [-3.22, -1.60]
Unadjusted results	NA	-2.70 (0.34) [-3.37, -2.03]
Teprotumumab vs. IVMP+MMF (adjusted for proportion of smokers, baseline diplopia, RIT, age, sex)		
Adjusted results	38.90	**-3.06** (0.66) [-4.35, -1.77]
Unadjusted results	NA	-2.94 (0.62) [-4.15, -1.73]

CFB, change from baseline; CI, confidence interval; ESS, effective sample size; IVMP, intravenous methylprednisolone; MD, mean difference; MMF, mycophenolate mofetil; NA, not applicable; RIT, radioiodine therapy; SE standard error

Base-case meta-analysis – diplopia response rate

- The meta-analysis of four IVMP studies yielded a pooled diplopia response rate of 57% (Figure 2).

Figure 2. Meta-analysis of diplopia response for IVMP – random- and fixed-effects models



CI, confidence interval

RESULTS (CONT.)

Base-case meta-analysis – diplopia response rate (cont.)

- After matching, baseline characteristics between teprotumumab and IVMP were well balanced (Table 3).

Table 3. Baseline characteristics before and after matching – diplopia response rate

Covariate	**Teprotumumab (pooled phase 2 and 3) baseline characteristics**		**IVMP baseline characteristics (pooled RCTs, n=4 studies)**
	Before matching (n=63.00)	**After matching (n=38.95)**	
Proportion of smokers (mean, %)	23.81	25.34	25.34
Baseline proptosis (mean, mm)	23.18	21.19	21.19
RIT (mean, %)	12.70	12.73	12.73
Age (years)	51.20	47.03	47.03
Sex (% male)	31.75	34.29	34.29

IVMP, intravenous methylprednisolone; RCT, randomized controlled trial; RIT, radioiodine therapy

Base-case MAIC – diplopia response rate

- The analysis of teprotumumab vs. IVMP adjusted for the following treatment effect modifiers and prognostic factors: proportion of smokers, baseline proptosis, RIT, age, and sex.
  - Baseline diplopia was not included as an adjustment variable because the analysis was restricted to patients who presented with diplopia at baseline.
- Patients treated with teprotumumab had twice the odds of diplopia response compared with IVMP (OR: 2.09) (Table 4).
- No studies were identified for this outcome for the IVMP+MMF comparison.

Table 4. Base-case MAIC results – diplopia response rate

	ESS	**OR [95% CI]**
Teprotumumab vs. IVMP (adjusted for proportion of smokers, baseline proptosis, RIT, age, sex)		
Adjusted results	38.95	**2.09** [0.93, 4.68]
Unadjusted results	NA	1.92 [0.96, 3.86]

CI, confidence interval; ESS, effective sample size; IVMP, intravenous methylprednisolone; NA, not applicable; OR, odds ratio; RIT, radioiodine therapy

Scenario analysis (RCTs and RWE)

- In the RCT+RWE scenario, meta-analysis of six IVMP studies yielded a pooled mean CFB in proptosis of -0.62 mm and a diplopia response rate of 47%.
- Compared with IVMP, teprotumumab showed a greater CFB in proptosis (MD: -2.20 mm) and almost three times the odds of diplopia response (OR: 2.88). (Table 5)

Table 5. Scenario analysis results – RCTs and RWE (teprotumumab vs. IVMP)

	ESS	**MD in CFB proptosis, mm (SE) [95% CI]**
CFB in proptosis (adjusted for proportion of smokers, baseline diplopia, baseline proptosis, RIT)		
Adjusted results	27.42	**-2.20** (0.43) [-3.04, -1.36]
Unadjusted results	NA	-2.58 (0.32) [-3.20, -1.96]
	ESS	**OR [95% CI]**
Diplopia response rate (adjusted for proportion of smokers, baseline proptosis, RIT, age, sex)		
Adjusted results	34.83	**2.88** [1.17, 7.10]
Unadjusted results	NA	2.84 [1.33, 6.09]

CFB, change from baseline; CI, confidence interval; ESS, effective sample size; MD, mean difference; NA, not applicable; OR, odds ratio; RIT, radioiodine therapy; SE standard error

LIMITATIONS

- Unanchored MAIC assumes all relevant effect modifiers and prognostic factors are controlled for. Some key baseline covariates (e.g., TED duration) were not reported or were inconsistently reported in comparator trials, limiting adjustment.
- A risk of bias may exist due to residual or unmeasured confounding.
- Outcomes were compared at 12 weeks for IVMP and 24 weeks for teprotumumab and IVMP+MMF to reflect peak efficacy; however, differing assessment timepoints may introduce bias.

DISCLOSURES

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- Galin Spicer was an Amgen employee and stockholder at the time of this work.

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