Evidence Gap Analysis of the Burden of Illness and Treatment of Thyroid Eye Disease

Gildea L,[1] Heyes A,[1] Arvin-Berod C,[2] Heyerick A,[2] Urdaniz E,[2] Vainilovich Y,[2] Trainor L,[3] Densmore D[3]

[1] RTI Health Solutions, Manchester, United Kingdom; [2] argenx BV, Ghent, Belgium; [3] argenx Inc., Boston, MA, United States

BACKGROUND

- Thyroid eye disease (TED) is a rare autoimmune disease of the eye and surrounding tissues.[1]
- Between 25% and 70% of patients with TED have hyperthyroidism or a history of hyperthyroidism due to Graves' disease (GD).[1-3]
- TED is characterized as an autoimmune-mediated inflammation and remodeling of the orbital soft tissues and periorbital areas.[4,5]
- The most common features of TED are exophthalmos or proptosis (bulging eyes, stare), inflammation, blurred or double vision, and lacrimation.[1-3]
- The exact pathogenesis of TED is unclear.[6-8]
- TED has an initial active phase of inflammatory changes, after which the disease stabilizes when inflammation begins to subside (plateau or static phase) and then progressively improves as inflammation stabilizes (inactive phase) without returning to the pre-TED state.[1]

OBJECTIVE

- To identify evidence gaps in the literature on the burden of illness and treatment of TED to support the launch of efgartigimod to treat this rare autoimmune disease.

METHODS

- A structured literature review was conducted of articles published from 10 October 2013 through 10 October 2023 in PubMed, Embase, and Cochrane using a predefined search strategy.
- Articles on disease description, epidemiology, humanistic and economic burden, treatment guidelines, and treatment patterns were included.

RESULTS

Epidemiology: Key Findings and Evidence Gaps

- TED occurs predominantly in middle-aged people, with more severe disease in older individuals.
  - In the United States (US), prevalence of TED was 0.09% and highest in people aged 50-59 years (Table 1).[10] Globally, studies have estimated TED prevalence rates from 0.1% to 0.3%.[11]
- The incidence and prevalence of TED are higher in women, likely due to the association with GD, which is higher in females.[1] There is inconclusive evidence suggesting that more severe disease occurs in men.
  - US population-based incidence cohort of Olmsted County, Minnesota, residents reported 120 cases of TED diagnosed over a 15 year period (1976-1990). Incidence was higher in females, with 16.0 cases/100,000 population/year, compared with 2.9 cases/100,000 population/year in males (standardized rate ratio, 5.5; 95% confidence interval [CI], 3.3-9.3).[12]
- Risk factors for TED are multifaceted and are based on age, gender, environmental factors, and immune diseases.[3]
- Very few studies report the incidence of TED in the US, United Kingdom, France, Germany, Italy, and Spain. Data reported in 1994 from a representative county in the US (Olmstead County, Minnesota) are still widely referenced in the literature.[1,11,13]
- There is a paucity of evidence comparing the prevalence of TED among different ethnic groups; however, ethnicity may be an important factor.[14]
- TED does not have a specific International Statistical Classification of Diseases (ICD) code. Therefore, various ICD codes capturing the signs and symptoms are used to identify TED in the US.[15]
- It may be difficult to estimate the number of patients with TED due to the lack of recent information and the heterogeneity of methodology and results between different epidemiology studies in certain countries.

Table 1. Prevalence of TED in the United States

Characteristic	Total patients observed, N (%)	Patients with TED, n (%)	Percent prevalence (SE)
All patients	47,872,555 (100)	41,211 (100)	0.09 (0.0004)
Age, years			
18-29	4,208,063 (9)	1,441 (3)	0.03 (0.0009)
30-39	3,694,074 (8)	2,997 (7)	0.08 (0.0015)
40-49	5,117,054 (11)	5,403 (13)	0.11 (0.0014)
50-59	8,254,130 (17)	10,138 (25)	0.12 (0.0012)
60-69	11,648,079 (24)	12,076 (29)	0.10 (0.0009)
≥ 70	14,951,155 (31)	9,156 (22)	0.06 (0.0006)
Female	27,564,337 (58)	33,761 (82)	0.12 (0.0007)
Male	20,308,218 (42)	7,450 (18)	0.04 (0.0004)

SE = standard error.
Source: Ramesh et al.[10]

RESULTS *(continued)*

Key Findings and Evidence Gaps in Clinical, Humanistic, and Economic Burden

- TED is associated with significant clinical burden and has a negative impact on health-related quality of life (HRQOL).
- The Graves' Ophthalmopathy Quality of Life (GO-QOL), Graves' Ophthalmopathy Quality of Life Scale (GO-QLS), and Thyroid Eye Disease Quality of Life (TED-QOL) are disease-specific instruments that have been used to evaluate HRQOL in various TED studies.[16] The GO-QOL is the most extensively studied and is used in clinical research due to its robust reliability across populations.

	Key findings	Evidence gaps
Clinical burden	• Diagnosis of TED relies on clinical signs and symptoms.[17] • TED has an initial active phase of inflammatory changes, after which the disease stabilizes when inflammation begins to subside and then progressively improves as inflammation stabilizes without returning to the pre-TED state.[1] • Moderate to severe TED is associated with both physical and emotional symptoms; the emotional effects are due to the profound effect of TED on physical appearance.[18] Physical symptoms can include ocular dryness/grittiness, soft tissue edema, conjunctival redness, eyelid redness, proptosis, excessive tearing, conjunctival swelling, decreased vision, and pain with eye movement.[18] • TED is associated with excess morbidity and mortality.[19] • Due to its reliance on clinical features, which vary greatly, between ethnic populations, diagnosis of TED is subjective and burdensome. Studies have also shown that anatomical differences between Asian and White patients lead to a difference in risk for dysthyroid optic neuropathy.[14]	• The diagnosis of TED is based on clinical parameters and therefore has the potential to be subjective and inconsistent between different specialists. • There is currently no standardization of treatment outcomes for assessment in randomized clinical trials for active moderate to severe TED. This makes it difficult to compare results from different trials and draw sound conclusions on the efficacy of a given treatment.[20]
Humanistic burden	• TED has a severe effect on HRQOL, social functioning, and neuropsychiatric disorders (emotional, cognitive, and affective disorders).[21] • A US study reported that rates of all mental health issues were significantly higher in patients with TED compared with the general US population in 2019 (all $P \geq 0.003$).[18] • Regarding health status of patients with severe TED, the highest mean utility value, 0.60 (95% CI, 0.54-0.67), was observed for the least severe disease state (no diplopia/small proptosis); and the lowest mean utility value, 0.30 (95% CI, 0.24-0.36), was observed in the most severe disease state (constant diplopia/large proptosis).[22]	• No information was identified assessing HRQOL in carers of patients with TED. • TED reduces HRQOL to levels similar to or worse than those associated with classically disabling diseases, which may be out of proportion to the severity of TED-related physical changes defined by clinicians. • Changes in appearance and improved function with surgery have proven to be inconsistently associated with improvement in HRQOL.[16] • Given TED's impact on patients and a lack of longitudinal data on HRQOL in patients with TED, tracking the HRQOL of patients with TED over time would lead to an improved understanding of the long-term impact.[23]
Economic burden	• The major drivers of direct costs are hospitalizations, emergency visits, and treatment costs.[24,25] • Patient productivity is impacted by TED; indirect costs include the inability to return to work after sickness, work role limitations, unemployment, and the need for disability pensions.[25,26]	• Very few studies on the economic burden of TED were identified in the published literature. No evidence was found on the economic burden of the caregiver. • Information on direct costs, resource use, and indirect costs of TED were identified for only the US and Germany. Further studies are required to generate evidence of the economic burden of TED in the US and other countries to account for different costs, social systems, and clinical management. • Further research is required to better understand the natural history of TED to inform treatment pathways that may prevent complications needing surgery.[24] • Further research on social determinants of health should be undertaken to help understand economic burden in lower-resourced populations.

Key Findings in Guidelines and Treatment Patterns

- It is recommended that treatment for TED commence immediately after diagnosis to target the active phase of the disease.
- Management of TED depends on both the activity and the severity of the disease and can include pharmaceutical agents and procedures.
  - Mild TED:
    - Local treatments, wait-and-see strategy, oral selenium supplementation (in patients living in selenium-deficient areas); if quality of life is markedly impaired, low-dose immunomodulation (if TED is active) or rehabilitative surgery (if TED is inactive) and extensive counseling.
  - Moderate to severe TED:
    - First line: intravenous glucocorticoid or oral glucocorticoid or as a combination with mycophenolate mofetil.
    - Second line: intravenous glucocorticoid or oral glucocorticoid or as a combination with an immunosuppressant/radiotherapy.
- Treatments are recommended for different disease severities, but patients relapse or may not respond, and teprotumumab has been reported to be associated with relapse rates up to 37%.[5]
- Teprotumumab (Tepezza) is the only pharmaceutical treatment licensed for the treatment of TED and available only in the US and Brazil. Additionally, it is available via a Named Patient Use program in countries where it is not approved by the country's local regulatory authority.[27,28]
- Pharmaceutical TED treatments can be administered by mouth, intravenous injection, subcutaneous injection, periorbital injection, and sub-Tenon injection.
- Procedures for TED include orbital radiotherapy, orbital decompression surgery, eyelid surgery, and strabismus surgery.

CONCLUSIONS

- The incidence of TED is not well reported, and there are no specific ICD codes.
- It may be difficult to estimate the number of patients with TED due to the lack of recent information and the heterogeneity of methodology and results between different epidemiology studies.
- The diagnosis of TED is based on clinical parameters, and there is a lack of harmonized standard criteria or classification for establishing the diagnosis or severity of TED, which may cause inherent variations in the diagnosis, leading to potential bias in reporting and classification.
- With no standardization of treatment outcomes for assessment in randomized clinical trials, it is difficult to compare results from different trials and draw sound conclusions on the efficacy of a given treatment for TED.
- There is a lack of longitudinal data on HRQOL and the economic burden of TED.
- The reliance on clinical symptoms for the diagnosis, anatomical differences among different ethnic populations, and the lack of diversification in the diagnostic criteria make it challenging for clinicians to diagnose TED efficiently.[14,29]
- Very few studies compare the prevalence of TED among different ethnic groups.[14]
- There is still a lack of evidence on the importance of early TED treatment on long-term outcomes and disease progression.[5,30-33]
- There is limited understanding of optimal management strategies and no consensus on treatment approaches for TED:
  - There is a lack of head-to-head comparison studies for novel therapies with intravenous glucocorticoids.[20,34]
  - Oral glucocorticoids are less effective and more poorly tolerated than intravenous glucocorticoids, and topical glucocorticoid drops and intraocular depot injections are not efficacious compared with systemic therapy.[4,9,31]
  - Tocilizumab is recommended for TED inactivation but is less relevant for proptosis.[35] However, further studies are needed to identify the optimal duration and to verify the efficacy of tocilizumab treatment for moderate to severe TED.[31,33]
- There is an unmet need for a product with proven efficacy and safety in the treatment of TED. Teprotumumab is the only product licensed for this indication, but it is associated with hyperglycemia and hearing impairments (mild ear pressure to hearing loss), nausea, diarrhea, muscle spasms, dysgeusia, headaches, alopecia, and paresthesia[36,37] and is not available outside the US, Brazil, or Named Patient Use program.

DISCLOSURES

Arvin-Berod C, Heyerick A, Urdaniz E, Vainilovich Y, Trainor L, and Densmore D are employees of argenx. Gildea L and Heyes A are employees of RTI Health Solutions.

FUNDING

argenx provided funding to RTI Health Solutions to conduct this study and was involved in reviewing this poster.

REFERENCES

1. Bartalena L, et al. Front Endocrinol (Lausanne). 2020;11:615993. **2.** Bahn RS. New Engl J Med. 2010;362(8):726-38. **3.** Bartalena L, et al. J Intern Med. 2022;292(5):692-716. **4.** Men CJ, et al. Ther Adv Ophthalmol. 2021;13:25158414211027760. **5.** Burch HB, et al. Thyroid. 2022;32(12):1439-70. **6.** Hennein L, et al. J Binocul Vis Ocul Motil. 2022;72(1):32-46. **7.** Huang Y, et al. Eye (Lond). 2019;33(2):176-82. **8.** Douglas RS, et al. J Clin Endocrinol Metabol. 2010;95(1):430-8. **9.** Wang Y, et al. Ther Clin Risk Manag. 2019;15:1305-18. **10.** Ramesh S, et al. Am J Ophthalmol. 2023;253:74-85. **11.** Hiromatsu Y, et al. Intern Med. 2014;53(5):353-60. **12.** Bartley GB. Transactions Amer Ophthalmol Soc. 1994;92:477. **13.** Lazarus JH. Best Pract Res Clin Endocrinol Metabol. 2012;26(3):273-9. **14.** Patel VK, et al. Endocr Pract. 2022;28(2):159-64. **15.** Sharma A, et al. J Clin Endocrinol Metab. 2022;107(Suppl_1):S27-s35. **16.** Vargason CW, et al. Semin Ophthalmol. 2016;31(4):409-14. **17.** Wang Y, et al. Endocr Pract. 2022;28(9):842-6. **18.** Schwensen CF, et al. Eur J Endocrinol. 2017;176(6):669-76. **19.** Bartalena L, et al. Eur Thyroid J. 2020;9(Suppl 1):3-16. **20.** Bruscolini A, et al. Autoimmun Rev. 2018;17(7):639-43. **21.** Smith TJ, et al. JAMA Ophthalmol. 2023;141(2):159-66. **22.** Woo T, et al. Thyroid. 2022;32(2):177-87. **23.** Singh G, et al. J Endocrine Soc. 2021;5(Supplement_1):A843-A. **24.** Ponto KA, et al. J Clin Endocrinol Metabol. 2013;98(1):145-52.

25. Cockerham KP, et al. Ophthalmol Ther. 2021;10(4):975-87. **26.** Horizon Therapeutics plc. Named Patient Use Program for TEPEZZA® (teprotumumab-trbw). 2021. https://www.horizontherapeutics.com/media-center/horizon-resources/named-patient-use-program-for-tepezza. Accessed 19 March 2024. **27.** BioSpace. TEPEZZA® (teprotumumab) Approved in Brazil for the Treatment of Active Thyroid Eye Disease (TED). 26 June 2023. https://www.biospace.com/article/releases/tepezza-teprotumumab-approved-in-brazil-for-the-treatment-of-active-thyroid-eye-disease-ted-/#:~:text=Career%20Advice%20(3%2C874)-,TEPEZZA%C2%AE%20(teprotumumab)%20Approved%20in%20Brazil%20for%20the%20Treatment%20of,Active%20Thyroid%20Eye%20Disease%20(TED)&text=DUBLIN%2D%2D(BUSINESS%20WIRE)%2D%2D,the%20treatment%20of%20active%20TED. Accessed 19 March 2024. **28.** Lim SL, et al. Thyroid. 2008;18(12):1297-301. **29.** Yu CY, et al. Indian J Ophthalmol. 2022;70(7):2335-45. **30.** Dosiou C, et al. J Endocrine Soc. 2021;5(5). **31.** Hoang TD, et al. Endocrinol Metab Clin North Am. 2022;51(2):287-304. **32.** Kossler AL, et al. J Clin Endocrinol Metab. 2022;107(Suppl_1):S36-s46. **33.** Li X, et al. Int Ophthalmol. 2023;43(4):1437-49. **34.** Wolf J, et al. Expert Opin Drug Saf. 2022;21(7):881-912. **35.** Pérez-Moreiras JV, et al. J Clin Med. 2021;10(4):1-18. **36.** PI. T. Horizon Therapeutics. Tepezza (teprotumumab-trbw) for injection, for intravenous use. July 2023. https://www.hzndocs.com/TEPEZZA-Prescribing-Information.pdf. Accessed 27 October 2023. **37.** Stan MN, et al. J Clin Endocrinol Metab. 2023;108(9):e654-e62.

CONTACT INFORMATION

Liesl Gildea, MSc
Market Access and Outcomes Strategy

RTI Health Solutions

Phone: +44.161.447.6036
Email: lgildea@rti.org

Presented at: ISPOR 2024; 5-8 May 2024; Atlanta, GA, United States