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Expert Review of Respiratory Medicine

ISSN: 1747-6348 (Print) 1747-6356 (Online) Journal homepage: www.tandfonline.com/journals/ierx20

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To cite this article: Angelica Tiotiu (05 Dec 2025): The current evidence regarding the efficacy of tezepelumab administered for asthma on T2-related comorbidities, Expert Review of Respiratory Medicine, DOI: 10.1080/17476348.2025.2600110

To link to this article: https://doi.org/10.1080/17476348.2025.2600110

EXPERT REVIEW OF RESPIRATORY MEDICINE
https://doi.org/10.1080/17476348.2025.2600110

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SPECIAL REPORT

The current evidence regarding the efficacy of tezepelumab administered for asthma on T2-related comorbidities

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ABSTRACT

Introduction: T2-comorbidities are the most common in severe asthma (SA) patients and have a negative impact on disease outcomes but also an important socio-economic burden. Treating SA and its comorbidities by one medication is a very exciting possibility for the clinicians. Several biologics used for SA showed benefits on T2-comorbidities, but currently more limited data exists for tezepelumab, most recently developed in this domain.

Areas covered: This paper summarizes the available evidence regarding the efficacy of tezepelumab on T2-comorbidities of SA. Electronic search queries were applied to PubMed and Medline databases by using the following terms: 'tezepelumab,' 'severe asthma,' 'allergic rhinitis' (AR), 'chronic rhinosinusitis,' 'nasal polyps' (CRSwNP), 'aspirin exacerbated disease (AERD),' 'atopic dermatitis' (AD), 'eczema,' 'chronique spontaneous urticaria' (CSU),'food allergy' (FA), 'eosinophilic esophagitis' (EE).

Expert opinion: Tezepelumab treatment showed undeniable benefits on CRSwNP and AERD by improving sino-nasal and asthma outcomes. If the efficacy of tezepelumab on severe allergic asthma is well documented, current data are insufficient to conclude on its impact on AR. The effects of tezepelumab on AD and CSU were disappointing. No consistent data exists regarding FA and EE. Future studies are needed to confirm the efficacy of tezepelumab on AR, FA, and EE.

ARTICLE HISTORY
Received 11 October 2025
Accepted 2 December 2025

KEYWORDS
Efficacy; severe asthma; T2 comorbiditites; tezepelumab; safety

1. Introduction

Severe asthma (SA) represents only 5–10% of the global asthma population but is associated with a very high socio-economic burden [1]. Patients with SA have many symptoms, exacerbations, and hospitalizations, absence from work and medication side-effects (with those related to systemic corticosteroid use being the most dangerous) [2,3]. The development of biologics as add-on treatment for SA changed radically disease outcomes by decreasing the exacerbation rate and systemic corticosteroid use, improving symptoms control and lung function, but also the patients' quality of life (QoL) [1,3]. Comorbidities are more frequent in SA than in mild-moderate asthma, could contribute to worse asthma outcomes, impaired response to treatment, poor QoL and loss of patients' productivity [4–6]. Comorbidity-attributable healthcare costs are five-times higher than asthma-attributable costs in asthmatic patients [7]. Systematic assessment for the presence of comorbidities is recommended by current guidelines to improve SA patients' outcomes but also to reduce the overall socio-economic burden of the disease [1,3,4].

Asthma comorbidities are numerous and classified into three categories: type 2 (T2) inflammatory comorbidities; comorbidities related to oral corticosteroid (OCS) use and comorbidities that mimic or aggravate asthma symptoms [4]. T2-comorbidities are considered those sharing common underlying immune pathways with T2-high asthma, orchestrated by interleukin (IL)-4, IL-5 and IL-13 released by activated T helper 2 cells (Th2) and type 2 innate lymphoid cells (ILC2) inducing eosinophilic inflammation [5]. T2-comorbidities are common in SA population: allergic rhinitis – AR (49%), chronic rhinosinusitis – CRS (46%), nasal polyps – NP (21%), atopic dermatitis – AD (10%), urticaria (3.5%), food allergy (3.3%), aspirin sensitivity (1.6%) and eosinophilic esophagitis (0.5%). Almost 70% of patients with SA have at least one T2-comorbidity [4]. The negative impact of T2-comorbidites on asthma outcomes is now well documented, especially for AR, CRS with NP (CRSwNP) and without NP (CRSsNP) [1,4,8,9]. Several biologics (e.g. omalizumab, mepolizumab, benralizumab, and dupilumab) used in SA patients also showed benefits on T2-comorbidities outcomes [1,10–13]. More limited data are currently available for tezepelumab, recently developed as add-on treatment for SA.

Tezepelumab is a fully human monoclonal antibody (Immunoglobulin G2λ) that specifically binds to thymic stromal lymphopoietin (TSLP), blocking the interaction with its heterodimeric receptor. TSLP is an alarmin released by airway epithelial cells in response to injuries induced by a variety of stimuli (e.g. allergens, microbes, and pollutants) and plays a crucial role in the initiation and persistence of multiple downstream processes involved in asthma pathophysiology, including T2 and non-T2 inflammation, bronchial hyperresponsiveness, and remodeling [14,15]. Tezepelumab is the first biologic approved as treatment of SA, with no phenotype or biomarker restrictions [1,3].

Currently, there is no review focused on tezepelumab's impact beyond asthma outcomes. The aim of this review is to summarize the current evidence on the efficacy of tezepelumab on T2-comorbidities of asthma including AR, CRSwNP,

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Article highlights

- T2 comorbidities of asthma are frequent and have a negative impact of disease outcomes.
- The efficacy of tezepelumab on chronic rhinosinusitis with nasal polyps and aspirin exacerbated respiratory disease is well documented.
- Tezepelumab treatment is effective to improve severe allergic asthma outcomes but its efficacy on allergic rhinitis should be confirmed.
- No significant benefit was found in patients with atopic dermatitis and chronic spontaneous urticaria receiving tezepelumab in addition to current standard care.
- The efficacy of tezepelumab on eosinophilic esophagitis and food allergy is under investigation.

CRSsNP, and aspirin exacerbated respiratory disease (AERD), AD, chronic spontaneous urticaria (CSU), food allergy, and eosinophilic esophagitis.

Electronic search queries were applied to PubMed and Medline databases up until 1 October 2025. The search terms used were as follows: 'tezepelumab,' 'severe asthma,' 'allergic rhinitis,' 'chronic rhinosinusitis,' 'nasal polyps,' 'AERD,' 'atopic dermatitis,' 'eczema,' 'chronic spontaneous urticaria,' 'food allergy,' 'eosinophilic esophagitis.' Randomized clinical trials (RCTs) and real-world studies were selected in priority. A case report was included considered as particularly informative. Results were limited to publications in English.

2. Impact of tezepelumab on SA with AR

AR and asthma often coexist sharing many common disease characteristics such as chronic airway inflammation mediated by immunoglobulin (Ig) E with symptoms related to allergen exposure, common genetic backgrounds, similar epithelial structure and pathologic features supporting the 'one airway, one disease' hypothesis [8,16] Patients with AR report frequent asthma exacerbations and emergency department (ED) visits but also have more difficulty to achieve symptoms control [4,8,17]. Treating coexisting AR by nasal steroids and/or antihistamines improves asthma control and decreases healthcare resource utilization [8,16]. Conversely, several specific treatments for asthma such as antileukotrienes and biologics (e.g. omalizumab, dupilumab) showed benefits on AR by improving nasal symptoms and disease-related QoL [11,18–20].

TSLP plays a central role in the airway allergic immune response. Following epithelial injury induced by airborne allergen, TSLP is released and facilitates antigen presentation by dendritic cells to naïve T cells promoting their differentiation to Th2 cells. IL-4, IL-5 and IL-13 produced by Th2 cells induce IgE switching in B cells, mast cells degranulation, mucus production from goblet cells and smooth muscle contraction. In addition, airway mast cells and basophils could be directly activated by TSLP and release T2 cytokines [14,21]. The efficacy of tezepelumab on allergic immune response in asthma is well documented by clinical and experimental data, together with the substantial reduction of T2 biomarkers [21,22]. Concerning AR, a RCT involving 112 patients with cat allergy showed that adding tezepelumab (700 mg intravenously every 4 weeks) to subcutaneous cat immunotherapy significantly reduced total nasal symptom scores compared to subcutaneous cat immunotherapy alone, but no significant differences were found in the tezepelumab monotherapy group vs placebo after 52 weeks of treatment [23].

Currently, there are no studies designed specifically to analyze the efficacy of tezepelumab on AR outcomes when administered in SA patients. However, several data are available in patients with SA and AR from subgroups analyses in the NAVIGATOR study. In this phase 3 multicentre study, patients with uncontrolled SA (12–80 years-old) were randomized 1:1 to receive tezepelumab 210 mg or placebo subcutaneously every 4 weeks for 52 weeks to analyze the efficacy of this treatment in reducing asthma exacerbations. There were 528 patients included in the treatment group and 531 patients in the placebo group [24]. The subgroup of patients with AR involved 356 patients treated with tezepelumab and 368 patients receiving placebo. Tezepelumab reduced the annualized asthma exacerbation rate (AAER) by 58% (95%CI: 47, 67) over 52 weeks compared with placebo in patients with AR and by 50% (95%CI: 30, 64) in those without AR. Patients with exacerbations triggered by allergen exposure experienced the greatest reduction in AAER (71% [95%CI: 47, 84] compared to those with other exposure (46% [95%CI: 20, 65]). The effect of tezepelumab on AAER was most important in patients with monosensitization to perennial aeroallergen (84% [95%CI: 69, 91]) than in those with 2–3 sensitizations (44% [95%CI: 21, 60]) [25].

The pooled analyses from the PATHWAY and NAVIGATOR studies ($n = 665$ patients receiving tezepelumab and $n = 669$ placebo) proved a similar efficacy in patients with and without perennial aeroallergen sensitization on AAERs reduction and exacerbation-related hospitalization or ED visits, improvement of lung function, asthma symptoms control and QoL [26].

Another subgroup analysis in the NAVIGATOR study involving patients with AR (448 sensitized to seasonal aeroallergens, 452 sensitized to perennial aeroallergens and 450 sensitized to perennial aeroallergens and seasonal aeroallergens) showed seasonal variations in AAERs with higher rates reported in fall and winter than in spring and summer due to changes over time in allergen exposure but also to coexisting respiratory viral infections. More pronounced seasonal peaks in the AAERs across the year were noted in patients with seasonal aeroallergen sensitization than in those with perennial aeroallergen sensitization. Tezepelumab reduced the AAERs vs placebo by 63% (95% CI: 52, 72) in winter, 46% (95%CI: 26, 61) in spring, 62% (95%CI: 48, 73) in summer, and 54% (95%CI: 41, 64) in fall. The benefit of the treatment was comparable in patients with exacerbations induced by seasonal allergens (including ragweed) and in those with perennial allergens (including house dust mite aeroallergens) [15].

The PASSAGE study assessed the efficacy of tezepelumab in real-world US population, including 208 patients with SA treated for 52 weeks and confirmed the results from previous RCTs. Tezepelumab decreased the AAER by 76% (95%CI: 69, 81) in the overall population and by 75% (95%CI: 66, 81) in patients with AR [27]. Another real-world study performed in Germany compared the response to tezepelumab after 6 months of treatment in 71 patients with allergic background and 36 patients nonallergic. The response rates were 88.1% in the first group and 78.2% in the second group without significant difference between groups [28].

3. Impact of tezepelumab on SA with CRS

CRS is another frequent T2 comorbidity of SA. Clinical characteristics of patients with this association are older age at diagnosis, longer duration of nasal symptoms, higher incidence of AR, airway obstruction, increased computed tomography and endoscopy scores, greatest number of sinonasal surgeries and poorer QoL [8]. Patients with SA and NP have more frequently late-onset asthma, poor symptoms control, increased risk for exacerbations with OCS use, airway obstruction and higher levels of T2 biomarkers [2,4,8,29]. Treatment of CRS with nasal steroids or surgery could improve asthma outcomes, while several asthma medications (e.g. montelukast, macrolides, and biologics) showed some benefits on CRS scores [3,8,12].

As for asthma, TSLP is involved in CRSwNP pathogenesis. TSLP released locally in response to a variety of stimuli (e.g. microbes, allergens, irritants, and physical trauma) stimulates differentiation of Th2 cells, potentiates T2 inflammation by promoting eosinophil recruitment, survival, and degranulation but also the activation of ILC2. Charcot-Leyden crystals identified in eosinophilic NP may promote T2 inflammatory processes but also neutrophilic inflammation *via* IL-8, independently of IL-17 [29]. In these conditions, the efficacy of tezepelumab in CRSwNP has been further assessed.

A post-hoc analysis on the NAVIGATOR study evaluated the efficacy of tezepelumab vs placebo on SA outcomes in the subgroup of patients with NP in the 2 years before randomization ($n = 118$) compared to those without NP ($n = 941$). After 52 weeks of treatment, the AAER was decreased by 85% (95% CI: 72, 92) in the group with NP and by 51% (95%CI: 40, 60) in that without NP with improvement of asthma control, lung function and QoL in both groups. Tezepelumab reduced also the Sino-Nasal Outcome Test (SNOT)-22 scores compared to placebo by least-squares (LS) mean difference of −12.6 points (95%CI: −19.4, −5.7) at 28 weeks and −10.6 points (95%CI: −17.8, −3.4] at 52 weeks of treatment [29]. The greatest improvement was registered in the sleep domain (LS mean change of −0.7 [95%CI: −1.1, −0.3]), followed by the function (LS mean change of −0.6 [95%CI: −1.0, −0.2]) and nasal domains (LS mean change of −0.5 [95%CI: −0.9, −0.2]) [29].

Another analysis issue from the same study compared the efficacy of tezepelumab in patients with SA and history of CRSwNP ($n = 165$) vs those without history of CRSwNP ($n = 894$). The history of CRSwNP was defined as the mention of this diagnosis at any time before randomization. Compared to placebo, tezepelumab treatment improved the SNOT-22 total score from baseline at week 28 by LS mean difference of −12.0 [95%CI: −18.8, −5.2]) and at week 52 by −11.1 (95%CI: −17.8, −4.4). Similarly, the percentage change in SNOT-22 total score was also greater in the group tezepelumab vs placebo from baseline at week 28 (LS mean difference −26% [95%CI: −49, −3]) and at week 52 (−28% [95%CI: −47, −9]). The greatest improvement was found for sense of smell (LS mean change of −1.0 [95%CI: −1.51, −0.39]), followed by nasal blockage (−0.9 [95%CI: −1.4, −0.4]), reduced productivity (−0.7 [95%CI: −1.2, −0.3]), waking up tired (−0.6 [95%CI: −1.0, −0.1]) and cough (−0.6 [95%CI: −1.0, −0.2]) [30].

In the real-world study PASSAGE, 83 patients with CRSsNP and 18 patients with CRSwNP were included. A greater reduction in AAERs was found in patients with CRSwNP than in those with CRSsNP (by 85% [95%CI: 65, 93] vs 65% [95%CI: 52, 75]). The LS mean change of SNOT-22 total score from baseline at 24 weeks was higher in the group with CRSwNP (−26.1 [95%CI: −34.6, −17.6] than in those with CRSsNP (−12.6 [95%CI: −16.1, −9]). The response to treatment on SNOT-22 total score was assessed using the usual cutoff of ≥8.9. The rates of responders at 24 weeks of treatment were 79% in the group CRSwNP and 55% in the group CRSsNP [27].

The efficacy of tezepelumab on CRSwNP was assessed specifically in the WAYPOINT study including 203 patients treated by tezepelumab (210 mg every 4 weeks) and 205 patients receiving placebo. Significant improvements were found in the group tezepelumab vs placebo at 52 weeks of treatment in the NP endoscopic score (mean difference −2.1 [95%CI: −2.4, −1.7], nasal-congestion score (−1.0 [95%CI: −1.2, −0.9]), loss of smell (−1.0 [95%CI: −1.2, −0.8]), SNOT-22 score (−27.3 [95%CI: −32.3, −22.2]), total symptom score (−6.9 [95%CI: −8.0, −5.8]), and Lund-Mackay score (−5.7 [95%CI: −6.4, −5.1] (all $p < 0.001$). Treatment with tezepelumab significantly decreased the need for surgery (0.5% in the group tezepelumab vs 22.0% in the group placebo, $p < 0.001$) and systemic corticosteroid use (5.2% in the group tezepelumab vs 18.3% in the group placebo, $p < 0.001$). Among patients with coexisting asthma ($n = 122$ receiving tezepelumab and $n = 126$ placebo), tezepelumab treatment improved symptoms control score vs placebo but no apparent difference between the groups was found for the lung function change from baseline at week 52 [31]. Due to the undeniable benefits of tezepelumab on CRSwNP, it has been recently approved as add-on medication in this indication in the U.S.A. and Europe.

4. Impact of tezepelumab on AERD

AERD consists of the association of asthma, NP and sensitivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Its prevalence in SA is estimated at 14.9%. Patients with AERD usually have more severe asthma, frequent exacerbations requiring intubation, higher systemic corticosteroid use and healthcare resource utilization than those with aspirin-tolerant asthma. Ingestion of aspirin or NSAIDs in patients with AERD results in increased production of cysteinyl leukotrienes and prostaglandin D2 by inhibition of cyclooxygenase-1. Prostaglandin D2 induces bronchoconstriction, vasodilatation, and acts as chemoattractant to eosinophils, basophils, Th2 cells, and ILC2 leading to increased inflammation in the upper and lower airways. TSLP amplifies the effects of mast cell-derived prostaglandin D2 on T2 inflammatory responses in patients with AERD and cysteinyl leukotrienes enhance the inflammatory effect of TSLP [32]. In this context, the evaluation of the efficacy of tezepelumab in patients with AERD seems very important.

A post-hoc analysis in the NAVIGATOR study was performed in the subgroup of patients with AERD ($n = 43$) to compare the efficacy of tezepelumab vs placebo. Compared to the control group, at baseline, patients with AERD had more frequent maintenance OCS use (14.0 vs 9.3%), higher median blood eosinophil count (330 vs 250 cells/μL) and median fractional exhaled nitric oxide (FeNO) levels (34 vs 30 ppb). In patients with AERD, compared to placebo, tezepelumab treatment reduced the AAER by 79% (95%CI: 35, 93), improved Asthma Control Questionnaire (ACQ)-6 score (LS mean difference: −1.1 [95%CI: −1.8, −0.5]), Asthma QoL questionnaire score (1.2 [95%CI: 0.5, 1.8]), SNOT-22

score (−25.2 [95%CI: −37.1, −13.2) and prebronchodilator Forced Expiratory Volume in 1 s (FEV1) by 0.38 L (95%CI: 0.12, 0.63) from baseline to week 52.

The response to treatment was assessed at 52 weeks regarding the ACQ-6 score (defined as a decrease from baseline of ≥0.5), lung function (improvement in prebronchodilator FEV1 >100 mL or >5% from baseline), exacerbations (≥50% decrease in the AAER), Clinical Global Impression of Change (CGI-C) score (minimally, much or very much improved), and SNOT-22 total score (a decrease from baseline of ≥8.9). Greater rates of clinical responses were found in the group tezepelumab vs placebo for decrease of exacerbation number (odds ratio OR = 8.3 [95%CI: 0.8, 84.6], improvement of lung function (OR = 12.7 [95%CI: 2.3, 71.2]), ACQ-6 score (OR = 7.7 [95%CI: 1.2, 50.5]), SNOT-22 score (OR = 6.9 [95%CI: 1.2, 40.8]) and CGI-C score (OR = 13.3 [95%CI: 2.0, 89.3]). The complete response at week 52 (defined as a clinical response for all four asthma-related criteria) was achieved in the group treated by tezepelumab with an OR = 32.0 (95%CI: 3.3, 311.1) vs placebo [32].

5. Impact of tezepelumab on other T2-related comorbidities

Although preclinical data suggest that TSLP may play a role in the pathogenesis of AD and CSU, two phase 2 studies ALLEVIAD and INCEPTION failed to demonstrate significant efficacy of tezepelumab compared to placebo on the outcome of these diseases [33,34].

In ALLEVIAD study, 113 adult patients with moderate-to-severe AD were randomized 1:1 to receive tezepelumab 280 mg or placebo every 2 weeks in addition to class 3 topical corticosteroids (TCS). The primary efficacy endpoint was the percentage of patients achieving a ≥ 50% reduction in the Eczema Area and Severity Index (EASI50) from baseline to week 12. A numerically greater percentage of patients treated by tezepelumb plus TCS achieved an EASI50 response (64.7%) compared to placebo plus TCS (48.2%) but the treatment difference was not significant (OR 2.0 [95%CI: 0.9, 4.3], $p = 0.091$) [33].

The INCEPTION study evaluated the efficacy of tezepelumab in patients with CSU despite treatment with second-generation H1 antihistamines. One hundred eighty-three adult patients were included 52 treated with tezepelumab 210 mg every 4 weeks, 52 treated with tezepelumab 420 mg every 4 weeks, 31 with omalizumab 300 mg every 4 weeks and 48 with placebo. The primary endpoint was a change in Urticaria Activity Score (UAS7) from baseline at 16 weeks. The change from baseline in UAS7 at week 16 in both tezepelumab groups was not significantly different than the change observed in the placebo arm (LS mean [SE]: tezepelumab 420 mg, −14.7[1.5]; tezepelumab 210 mg, −13.5[1.6]; placebo, −13.6[1.6]; $p = 0.60$ and $p = 0.99$, respectively) [34].

Data on tezepelumab efficacy in food allergy and eosinophilic esophagitis is lacking. A case of remission in an adolescent with eosinophilic esophagitis was reported on treatment with tezepelumab [35]. Two incoming RCTs will assess the efficacy of tezepelumab in eosinophilic esophagitis (NCT05583227) and peanut oral immunotherapy (NCT07015996).

Table 1 represents a summary compiling the main findings of the studies discussed in this paper and Figure 1 summarizes the current evidence on the efficacy of tezepelumab on T2 comorbidities of asthma.

Table 1. Efficacy of tezepelumab on T2-comorbidities of asthma.

Comorbidity	Type of study	Population	Endpoints	Main findings	Reference
Allergic rhinitis	RCT CATNIP	121	Change of TNSS during the first hour after nasal allergen challenge in patients with cat allergy treated by tezepelumab/SCIT and SCIT for 52 weeks	Significant reduction of TNSS in patients receiving tezepelumab/SCIT vs SCIT alone ($p = 0.028$) without difference between tezepelumab and placebo groups ($p = 0.139$)	[23]
CRS	Post-hoc analysis RCT NAVIGATOR	1059	Changes of AAER, FEV1, ACQ-6, AQLQ, SNOT-22 scores from baseline to week 52 in patients with and without NP	Reduction of AAER and SNOT-22 scores in patients treated by tezepelumab compared to placebo with improvement of FEV1, ACQ-6 and AQLQ scores	[29]
	Post-hoc analysis RCT NAVIGATOR	1059	Change of SNOT-22 score in patients with asthma and history of CRSwNP vs those without CRS at week 52	Sustained improvement in the tezepelumab group vs placebo in SNOT-22 score (LS mean difference: − 11.08 [95%CI: − 17.80, − 4.35])	[30]
	Real-world study PASSAGE	208	Changes of AAER, FEV1, ACQ-6 and SNOT-22 scores, health-related quality of life after 24 weeks of treatment	Decrease in AAER with concomitant improvement of FEV1, ACQ-6, SNOT-22 and health-related quality of life scores	[28]
	RCT WAYPOINT	408	Changes in endoscopic total NP, patient-reported mean nasal-congestion, SNOT-22, nasal symptoms, Lund-Mackay scores, needs for surgery and systemic glucocorticoid use over 52 weeks	Significant reductions in size of NP, severity of nasal congestion and sinonasal symptoms, use of NP surgery and systemic glucocorticoids in the group tezepelumab vs placebo (all $p <$ 0.001)	[31]
AERD	Post-hoc analysis RCT NAVIGATOR	1059	Changes of AAER, FEV1, ACQ-6, AQLQ, SGRQ and SNOT-22 scores at week 52	Significant improvement in all studied parameters in the tezepelumab group vs placebo	[30]
Atopic dermatitis	RCT ALLEVIAD	113	Rate of response for ≥50% reduction in EASI50 at 12 weeks of treatment	Greater rate of response in the group tezepelumab (64.7%) vs placebo (48.2%) ($p =$ 0.091)	[33]
CSU	RCT INCEPTION	183	Change in UAS7 from baseline at 16 weeks	No difference between the tezepelumab group vs placebo	[34]

Abbreviations: RCT: randomized clinical trial; TNSS: total nasal symptom score; SCIT: subcutaneous allergen immunotherapy; CRS: chronic rhinosinusitis; AAER: annualized asthma exacerbation rate; FEV1: forced expiratory volume in 1 second; ACQ-6: Asthma Control Questionnaire-6; AQLQ: Asthma Quality of Life Questionnaire; SNOT-22: Sino-Nasal Outcome Test; NP: nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps; LS: least-squares; CI: confidence interval; AERD: aspirin-exacerbated respiratory disease; SGRQ: St George's Respiratory Questionnaire; EASI50: Eczema Area and Severity Index; CSU: chronic spontaneous urticaria; UAS7: Urticaria Activity Score.

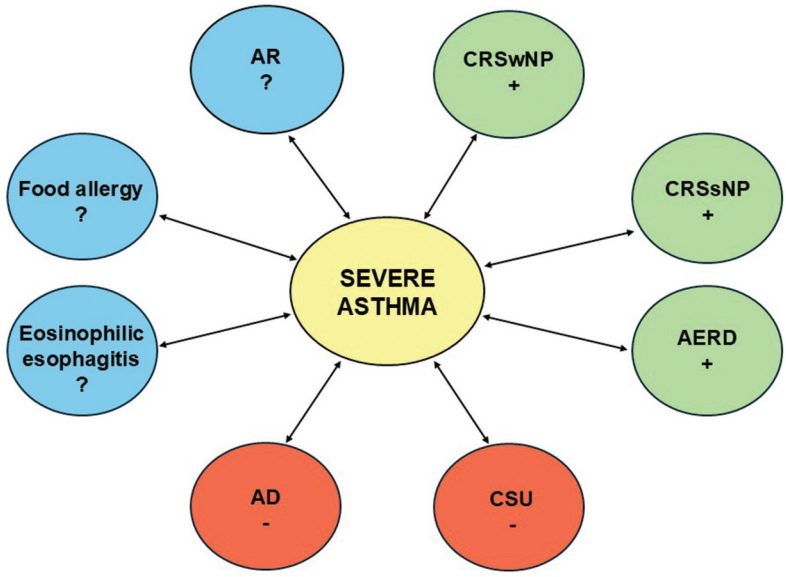

Figure 1. Summary on current data on the efficacy of tezepelumab on T2 comorbidities of SA.

Abbreviations: AR: allergic rhinitis; CRSwNP: chronic rhinosinusitis with nasal polyps; CRSsNP: chronic rhinosinusitis without nasal polyps; AERD: aspirin exacerbated respiratory disease; CSU: chronic spontaneous urticaria; AD: atopic dermatitis.

Green color (+): positive effect; Red color (-): negative effect; Blue color (?): uncertain effect.

6. Safety and tolerability

Tezepelumab treatment showed a good safety profile across studies [23,24,26,27,29,33,34]. The number of adverse events (including those considered as serious) was comparable in the group treated by tezepelumab vs placebo in most RCTs. No anaphylactic reaction or death was reported due to the treatment. The most common adverse events occurred during the treatment were nasopharyngitis, upper respiratory tract infections, and headaches [23,24,29,33,34]. These findings were confirmed by real-world data [27]. A low proportion of patients (<4%) discontinued the treatment due to adverse events [24,27,31,33]. Less than 5% of patients treated with tezepelumab developed neutralizing anti-drug antibodies [24,31]. Injection-site effects were reported by a low proportion of patients (<5.5% of patients) across studies [24,33].

7. Conclusion

Current evidence supports the efficacy of tezepelumab in patients with the association SA – CRSwNP and AERD by improving both sino-nasal and asthma outcomes. Considering the limited number of patients with AERD included in the RCTs, validation is needed in larger cohorts and real-world studies. If tezepelumab treatment showed undeniable benefits in patients with severe allergic asthma with and without rhinitis, its effects on AR are not yet well documented. Future studies are needed to specifically assess its efficacy on AR as the most frequent T2 comorbidity of SA. The tezepelumab treatment showed only limited efficacy on AD and CSU as the results of both RCTs were disappointing without significant improvement of assessed skin scores. No consistent data exists on the impact of tezepelumab on eosinophilic esophagitis and food allergy, but the incoming RCTs will probably respond to this question. As most of current findings come from RCTs, large real-world studies are needed to confirm the efficacy of tezepelumab on T2 comorbidities of SA.

8. Expert opinion

More than 80% of patients with SA have T2-high phenotype driven by cytokines produced by activated Th2 and ILC2 with eosinophilic inflammation and increased FeNO levels. The most common comorbidities in SA are those sharing the same inflammatory pathways as T2-high asthma and include AR, CRS with or without NP, AD, CSU, food allergy and eosinophilic esophagitis. These comorbidities are associated with frequent exacerbations, long-term use of OCS, poor asthma control, impaired QoL and high overall socioeconomic burden. Several biologics targeting T2-inflammatory pathways in asthma showed benefits on these comorbidities with pathogenesis orchestrated by the same cytokines (e.g. omalizumab on AR, NP, CSU and food allergy; dupilumab on NP, AD, AR, eosinophilic esophagitis).

By blocking TSLP, an epithelial-cell – derived cytokine implicated in multiple downstream processes, T2 and non-T2 mediated, involved in asthma pathogenesis, tezepelumab is the first biologic approved as add-on treatment for SA with no phenotype or biomarker restrictions. Previous studies proved the efficacy of tezepelumab on SA outcomes by reducing AAER and by improving symptoms control, lung function and health-related QoL, irrespective of the atopic status, blood eosinophil count and FeNO levels. However, the benefit seems greatest in patients with SA and T2 inflammation.

Regarding the presence of T2-comorbidities of SA, current data suggests a higher efficacy of tezepelumab on disease

outcomes in patients with CRSwNP and AERD. Greater decrease in AAERs was observed in SA patients with CRSwNP than in those without this comorbidity in RCT with concomitant improvement of SNOT-22 scores. Real-world data confirmed these findings and showed a higher benefit of tezepelumab treatment in patients with CRSwNP than in those with CRSsNP. Conversely, when administrated in patients with CRSwNP and asthma, tezepelumab treatment significantly decreased nasal symptoms scores, NP endoscopic scores, sinus imaging scores, needs for surgery, and OCS use with concomitant improvement of asthma symptoms control. Similarly, in the analysis performed in the subgroup of patients with AERD from the RCT NAVIGATOR, tezepelumab showed undeniable benefits compared to placebo by improving SNOT-22 scores, AAER, asthma control, lung function, and health-related QoL. However, this analysis included a very limited number of patients and currently no real-world data is available to confirm these findings.

If the efficacy of tezepelumab in decreasing the AAER is well demonstrated in patients with severe allergic asthma with and without rhinitis, its effects on nasal outcomes in patients with AR were not assessed specifically, nor its impact on rhinitis-related QoL. When administered in patients with AR due to cat allergy, tezepelumab improved nasal symptoms when added to subcutaneous specific immunotherapy but the results at 52 weeks of treatment were not significant compared to placebo when administered in monotherapy. Concerning skin T2 comorbidities, tezepelumab treatment showed efficacy comparable to standard-of-care treatment for AD and CSU. Currently, no consistent data exists for the efficacy of tezepelumab treatment on food allergy and eosinophilic esophagitis.

To the best of our knowledge, this is the first review focused on tezepelumab's impact beyond asthma outcomes. Now more evidence supports the efficacy of tezepelumab treatment in the association SA & CRSwNP and AERD. However, most of current data come from RCTs and the number of real-world studies in these associations is still limited. The efficacy of tezepelumab in the domain of food allergy and eosinophilic esophagitis should be analyzed and confirmed. Treating SA and T2 comorbidities concomitantly with biologic therapy represents an interesting way to apply personalized medicine in respiratory care. However, unmet needs remain. We have more biologics available as add-on treatment for SA with benefits on various T2 comorbidities, but head-to-head comparisons on their efficacy in different associations and cost-effectiveness studies are lacking. Future directions should include conducting head-to-head biologic trials to comparatively assess their efficacy on disease outcomes in patients with SA and T2 comorbidities to help clinicians to choose the right biologic for each patient. We also need more real-world evidence to confirm the efficacy of biologics on multimorbidities in SA, new studies on biomarkers to guide patient selection for a biologic treatment, as well as pharmacoeconomic analyses to support cost-effective personalized care. Ongoing research and innovation are essential to realize a future medicine in which treatment decisions are guided by precision, accessibility, and sustained disease control.

Declarations of interest

A Tiotiu reports honoraria for lectures, presentations, speakers' bureaus, educational events from AstraZeneca, BMS, Roche; support for attending meetings and/or travel from AstraZeneca, Chiesi, Sanofi; consulting fees from AstraZeneca, Chiesi, Sanofi. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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