Positioning of Tezepelumab in severe asthma

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Abstract

Asthma is one of the most common chronic diseases, and the estimated prevalence of severe asthma is 3-10% of the total asthmatic population. There is a need for additional biologic treatments that have high efficacy across the spectrum of severe uncontrolled asthma**.** Currently available drugs inhibit one or two specific cytokines or IgE antibodies and thus only partially suppress the complex type 2 inflammation cascade. Biologics targeting more upstream molecules in the pathophysiological pathway of asthma could treat asthma more effectively.

Tezepelumab is a human monoclonal antibody immunoglobulin G2λ (IgG2λ) directed against the cytokine thymic stromal lymphopoietin (TSLP). It is the first marketed biologic against an epithelial-derivate cytokine, preventing the binding of TSLP to its receptor and reducing the immune stimuli that TSLP can perform in different endotypes of asthma. Tezepelumab reduces downstream biomarkers of inflammation, such as blood and airway eosinophils, FeNO, IgE, IL-5 and IL-13.

Tezepelumab provides a clinical benefit in severe asthma, reducing the annualised asthma *exacerbation* rate in patients with either high or low levels of T2 inflammation biomarkers, although the effect was greater among those with high levels, and it has been shown to improve asthma control, quality of life and lung function and reduce airway hyperresponsiveness. Therefore, tezepelumab can be used in the whole spectrum of patients with severe uncontrolled asthma, especially in T2-high patients.

This review includes a positioning statement by the authors, members of the SEAIC Asthma Committee.

Key words: Tezepelumab. Severe asthma. Efficacy. Positioning.

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Resumen

El asma es una de las enfermedades crónicas más frecuentes, y la prevalencia estimada del asma grave es del 3-10% de la población asmática total. Se necesitan tratamientos biológicos adicionales que tengan una alta eficacia en todo el espectro del asma grave no controlada. Los fármacos disponibles en la actualidad inhiben una o dos citocinas específicas o anticuerpos IgE y, por tanto, sólo suprimen parcialmente la compleja cascada de la inflamación de tipo 2. Los fármacos biológicos dirigidos a moléculas más proximales de la vía fisiopatológica del asma podrían tratar el asma con mayor eficacia.

El tezepelumab es un anticuerpo monoclonal humano, inmunoglobulina G2λ (IgG2λ), dirigido contra la citoquina linfopoyetina estromal tímica (TSLP). Es el primer biológico comercializado contra una citocina derivada del epitelio, que impide la unión de la TSLP a su receptor y reduce los estímulos inmunitarios que la TSLP puede realizar en diferentes endotipos de asma. Tezepelumab reduce los biomarcadores de inflamación, como los eosinófilos sanguíneos y de las vías respiratorias, el FeNO, la IgE, la IL-5 y la IL-13.

Tezepelumab proporciona un beneficio clínico en el asma grave, reduciendo la tasa anualizada de exacerbaciones de asma en pacientes con niveles altos o bajos de biomarcadores de inflamación T2, aunque el efecto fue mayor entre los que tenían niveles altos, y se ha demostrado que mejora el control del asma, la calidad de vida y la función pulmonar, y reduce la hiperreactividad de las vías respiratorias. Por lo tanto, tezepelumab puede utilizarse en todo el espectro de pacientes con asma grave no controlada, especialmente en pacientes con T2 alto.

Esta revisión incluye una declaración de posicionamiento de los autores, miembros del Comité de Asma de la SEAIC.

Palabras clave: Tezepelumab. Asma grave. Eficacia. Posicionamiento.

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Introduction

Asthma is one of the most frequent chronic diseases and is estimated to affect more than 300 million people worldwide. [1]. It is a heterogeneous disease with significant variability in severity, patterns of airway inflammation, and in achieving disease control with current medication. Lack of control is more commonly reported in patients with severe asthma.

The term severe asthma is used to describe asthma that requires treatment with high-dose inhaled glucocorticoids combined with a long-acting β2-agonist (LABA) and/or another controller drug for the previous year, or treatment with systemic glucocorticoids for at least half the previous year, to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy [2]. The estimated prevalence of severe asthma is 3-10% of the total asthmatic population [2,3], and a prevalence of 3.9% has been reported in Spain [4].

To reach a diagnosis of severe asthma, it is necessary to rule out common problems such as incorrect inhaler technique, comorbidities, ongoing environmental exposures, and poor adherence [5], and in this sense, the Severe Asthma Working Group of the Spanish Society of Allergology and Clinical Immunology (SEAIC) proposed a diagnostic algorithm of uncontrolled severe persistent asthma [6].

Patients suffering from severe asthma must be properly evaluated for the possibility of clinically relevant allergic sensitisation. This should include a consistent clinical record, evidence of specific IgE by skin testing and/or measurement of serum levels or specific challenge tests when necessary. When considered for biological therapy in severe asthma, it is critical to define the phenotype in order to select the correct drug and determine the

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most suitable candidate [5]**.** The following phenotypes can be distinguished based on the inflammatory mechanism involved: allergic T2 asthma, eosinophilic T2 asthma, and non-T2 asthma.

The first biologic agent used in severe asthma was omalizumab, followed by mepolizumab, reslizumab, benralizumab, and, more recently, dupilumab. These biological products have distinct ways of acting: omalizumab is directed at immunoglobulin E (IgE); mepolizumab and reslizumab target interleukin 5 (IL-5); benralizumab binds to the α-chain of the IL5 receptor (IL5RA) and induces natural killer cells to provoke apoptosis of the receptor-bearing cells; and dupilumab binds to IL-4RA, which IL-4 and IL-13 share, thus inhibiting the signals of both cytokines [7]**.**

These biological drugs have been shown to reduce the number of asthma exacerbations in patients with severe asthma. However, their treatment effects are mainly restrained to eosinophilic and allergic asthma, with limited efficacy in patients with blood eosinophil counts less than 150 cells/μL, and variable efficacy in patients with eosinophil counts of 150 to 300 cells/μL. Besides, their use in clinical practice and real-life studies show that there are a significant number of patients with severe asthma who, despite having these phenotypes eosinophilic and allergic, have only a partial or even inadequate response.

Consequently, there is a need for additional biological treatments that have high efficacy across the whole spectrum of severe uncontrolled asthma [8]**.** All these previously mentioned drugs inhibit one or two specific cytokines or IgE antibodies and thus only partially suppress the complex type 2 inflammation cascade; therefore, biologics targeting more upstream molecules in the pathophysiological pathway of asthma could treat asthma more effectively.

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On the other hand, response to monoclonal antibodies (mAbs) should be assessed comprehensively, considering all clinically significant therapeutic goals and not only exacerbations or reduction of oral corticosteroids, being symptoms, asthma control, and lung function also relevant [9,10].

Role of thymic stromal lymphopoietin (TSLP) in severe asthma and airway diseases

Asthma is a heterogeneous and chronic inflammatory disease with numerous processes involving innate and acquired immunity that promotes a feedback loop that increases bronchial mucosa thickness, hypersecretion and bronchial smooth muscle hyperreactivity. Depending on the immune mediators driving these processes, we have asthma with predominantly T2 inflammation (T2-High asthma), where IL-4, IL-5 and IL-13 are the key cytokines involved in the pathological processes, and asthma with few or no T2 inflammation (T2-low) driven by cytokines such as tumor necrosis factor (TNF) alpha, IL-17A and interferon (IFN) gamma [11-13]. However, in both inflammatory subtypes of asthma, the inflammatory response begins with the interaction of microbes, aeroallergens, diesel exhaust particles, tobacco smoke or endogenous triggers such as pro-inflammatory cytokines with the bronchial epithelium [14]. This interaction in some individuals can produce a deterioration of intercellular junctions, such as tight and adherens junctions or hemidesmosomes, which result in epithelial cells producing specific cytokines called alarmins [15]. These are thymic stromal lymphopoietin (TSLP), IL33, and IL25, cytokines that will interact with various immune system cells to produce inflammation in the airways.

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TSLP is a pleiotropic cytokine first described in 1994 as an IL-7-like cytokine, whose receptor is a heterodimer (TSLP receptor, a common gamma-receptor chain, plus IL7-receptor) [14]**.** It has two described isoforms, a short isoform involved in several immunoregulatory mechanisms and a long isoform involved in proinflammatory pathological processes [16]**.** It is secreted mainly by epithelial cells, being performed prior to pathogenic stimuli. Numerous other cells are TSLP producers, such as Th2 cells, eosinophils, mast cells, fibroblasts, macrophages, and group 2 innate lymphoid cells (ILC2), and numerous other cells have receptors for TSLP, including hematopoietic progenitor cells, eosinophils, basophils, mast cells, airway smooth muscle cells, ILC-2, lymphocytes, dendritic cells, and monocytes/macrophages. The broad spectrum of interactions between TSLP and the innate and acquired immune system indicates the power of TSLP to initiate and maintain the inflammatory response in airway diseases [17]**.**

In the case of allergic asthma, TSLP is released upon the interaction of the allergen with the epithelium. TSLP can subsequently induce OX40-ligand (OX40L) expression in the absence of IL-12 in dendritic cells. OX40L expressed in dendritic cells induced by TSLP results in the differentiation of T helper naïve cell (Th0) into T helper cell 2 (Th2) [18]**.** Th2 cells can produce IL4, IL5 and IL13, and these cytokines stimulate plasma cell differentiation into IgE-specific antibody-producing B cells that activate mast cells and basophils and activate, attract, and increase the survival of eosinophils. Besides, mast cells also have TSLP receptors, which imply a greater amplification of the allergic response and airway remodeling processes. On the other hand, in non-allergic eosinophilic asthma, TSLP binds to its receptor in ILC2, inducing the production of IL-

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5, IL-13, and according to some authors IL-4, resulting in eosinophilia in lung tissue in addition to significant mucus secretion and bronchial hyperreactivity. Furthermore, TSLP may also have a direct effect on eosinophils promoting eosinophils viability and decreasing eosinophils apoptosis. In T2-high asthma, due to the production of IL-13 in patients with epithelial disruption, the biomarkers that we will find elevated would be the exhaled fraction of nitric oxide (FeNO) and peripheral and sputum eosinophilia. Thus, the biomarkers that will decrease with TSLP blockade would be FeNO and eosinophils in sputum and blood [17,19]**.**

Although the mechanisms by which TSLP acts in low T2 asthma are poorly understood, TSLP could direct dendritic cell-mediated differentiation of Th0 cells to IL-17A-producing Th17 cells. IL-17 A can stimulate the bronchial epithelium, which through CXCL8 (C-X-C Motif Chemokine Ligand 8) and GM-CSF (Granulocyte-macrophage colony-stimulating factor), would cause neutrophilia in bronchial tissue. In addition, 1L-17A has a direct action on the bronchial smooth muscle, which translates into an increase in bronchial hyperreactivity. Furthermore, TSLP can induce the production of collagen by fibroblast cells and activate mast cells, promoting airway remodeling [17]**.**

Due to its significant role in the pathogenesis of asthma, TSLP has been identified as a potential therapeutic target for severe asthma. Several studies have investigated the use of TSLP-targeted therapies, such as monoclonal antibodies, to block the effects of TSLP. Tezepelumab is a human monoclonal antibody immunoglobulin G2λ (IgG2λ) directed against the cytokine thymic stromal lymphopoietin (TSLP). It is the first marketed biologic against an epithelial-derivate cytokine, preventing the binding of TSLP to its

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receptor and reducing the immune stimuli that TSLP can perform in different endotypes of asthma.

Clinical development of tezepelumab

The clinical development of tezepelumab comprises a growing number of clinical trials, delving into several clinical variables, as follows:

Proof of concept: ClinicalTrials.gov number, (NCT01405963.) [20]

This was a proof of concept double-blind, placebo-controlled study in which 31 patients with mild allergic asthma were randomly assigned to receive three monthly doses of AMG157 (anti-TSLP) (700 mg) or placebo intravenously on a 12-week treatment period (see supplementary Table**).** The researchers conducted allergen and methacholine challenges on days 42 and 84 to evaluate the effect of anti-TSLP in reducing the maximum percentage decrease in FEV_1. Other measured variables were the FeNO, blood and sputum eosinophils, and airway hyperresponsiveness. The primary endpoint was the late asthmatic response. (3-7 hours after the allergen challenge).

The maximum percentage reduction in FEV_1 during the late response with AMG 157 was 34.0% lower in the AMG-157 group than in the placebo group on day 42 (P=0.09) and 45.9% lower on day 84 (P=0.02). As a main conclusion, the authors stated that AMG 157 treatment decreased allergen-induced bronchoconstriction and airway inflammation indices before and after allergen provocation.

PATHWAY (ClinicalTrials.gov number NCT02054130)

doi: 10.18176/jiaci.0949

This was a phase 2, randomised, double-blind, placebo-controlled trial, which assessed subcutaneous (sc) tezepelumab at three dose levels (70mg/4 weeks, 210mg/4weeks and 280mg/2weeks) over a 52-week treatment period [21] **(**see Supplementary Table**).** It was the first clinical trial proving tezepelumab efficacy in adults with severe uncontrolled asthma. The primary endpoint was the annualised rate of asthma exacerbations (AAER) at week 52.

The study showed that tezepelumab caused a statistically significant reduction in AAER at week 52 of 0.27 (low dose), 0.20 (medium dose) and 0.23 (high dose), resulting in a relative decrease in exacerbations rates versus placebo of 62%, 71% and 66%, respectively. Comparable results were noticed regardless of blood eosinophil counts at inclusion. Interestingly, the time to the first asthma exacerbation was longer in the tezepelumab groups than in the placebo group. The risk of having any exacerbation was lower in the low-dose (Hazard ratio (HR): 0.62), medium-dose (HR:0.45), and high-dose (HR:0.54) tezepelumab groups than in the placebo group.

Regarding asthma control, ACQ-6 scores were significantly reduced in the medium dose (-0.29) and high dose regimens (-0.31). In terms of quality of life, AQLQ(S)+12 score significantly improved in the high dose scheme (0.34) compared with placebo. In this clinical trial, the use of systemic glucocorticoids was not specifically evaluated.

FEV_1 improved significantly over placebo with all 3 doses used, the increase being 0.12 with the low dose, 0.11 L with the medium dose, and 0.15 with the high dose. When stratified by eosinophil level, significant differences in FEV_1 were only achieved in patients with >250 eosinophils/μL (0.16, 0.17, and 0.21 L, respectively).

doi: 10.18176/jiaci.0949

The PATHWAY study concluded that tezepelumab reduced clinically significant asthma exacerbations by 62-71% compared with placebo, independent of baseline eosinophil counts.

Moreover, a post hoc analysis of the Phase 2b PATHWAY study shows that tezepelumab reduced to a higher extent the AAER in patients with nasal polyps compared with those without nasal polyps (75% vs 73%, respectively) [22]**.**

In another post-hoc analysis of the phase 2b PATHWAY study, treatment with tezepelumab reduced exacerbations, improved lung function, and reduced type 2 biomarkers versus placebo in patients with severe, uncontrolled asthma with or without sensitisation to perennial aeroallergens [23]**.**

UPSTREAM (ClinicalTrials.gov number NCT02698501)

The UPSTREAM trial was a phase II, double-blind, placebo-controlled randomised trial, which assessed adult patients with asthma and airway hyperresponsiveness (AHR) to mannitol who received intravenous (iv) 700 mg tezepelumab or placebo (iv) every four weeks for 12 weeks [24] **(**see Supplementary Table**).**

The primary endpoint was the change in AHR from baseline to week 12 [change in PD15 to inhaled mannitol from baseline to week 12, supported by the number of subjects who reached a negative mannitol test at week 12]. Secondary outcomes were changes in airway inflammation. AHR to mannitol and bronchoscopy were carried out at baseline and after 12 weeks.

AHR to mannitol improved, although not significantly, from baseline to week 12 in subjects treated with tezepelumab in comparison to the placebo group, being the mean

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change in PD15 of 1.9 (95% CI 1.2–2.5) versus 1.0 (95% CI 0.3– 1.6) DD. Interestingly, patients with eosinophilic asthma benefited even more, but both patients with ≥250 eosinophils/μL and/or sputum eosinophils ≥3% and those ≤250 and/or sputum eosinophils ≤3% showed an improvement in AHR to mannitol. A negative mannitol test was significantly observed to a greater extent in patients treated with tezepelumab compared with placebo, although the small number of patients shall be considered.

ACQ-6 decreased non-significantly by 1.0 (95% CI −0.6–−1.4) points in the tezepelumab group compared with 0.5 (95% CI −0.1–−0.9) points in placebo patients. Moreover, AQLQ improved in the tezepelumab group and with the placebo (1.0 and 0.7, respectively).

The UPSTREAM study concluded that a 12-week treatment period with tezepelumab by blocking TSLP signaling reduced the proportion of patients with AHR compared with placebo, although not statistically significant.

CASCADE (ClinicalTrials.gov number NCT03688074)

The CASCADE trial was a phase II, exploratory, double-blind, placebo-controlled, parallel-group randomised trial, which evaluated adult patients with moderate-to-severe asthma who received subcutaneous (sc) 210 mg tezepelumab or placebo every four weeks for 28 weeks (extended to 52 weeks in the case of COVID-19-related disruption) and who underwent bronchoscopy with transbronchial biopsy [25,26] **(**see Supplementary Table**)**.

The primary endpoint was the change in the number of airway submucosal inflammatory cells in bronchoscopic biopsy samples from baseline to week 28. The study was conducted in 5 countries (27 sites), including 116 adult patients (18-75 years of age).

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There was a significant reduction in airway submucosal eosinophils from baseline to the end of treatment versus placebo in the active group. Moreover, as an exploratory outcome, the reduction in AHR to mannitol was significantly greater in the tezepelumab group than with placebo.

ACQ-6 decreased non-significantly by 1.10 points in the tezepelumab group compared with 0.66 points in placebo patients. AQLQ was not assessed in this study.

The CASCADE study concluded that the improvements exerted by tezepelumab in clinical asthma outcomes in previous studies are probably motivated partially by reductions in eosinophilic airway inflammation, regardless of baseline blood eosinophil counts. The study showed that tezepelumab significantly reduced eosinophils in the submucosa versus placebo across blood eosinophil count subclasses despite low mean submucosal eosinophil counts at baseline. The reduction in AHR to mannitol indicates that blocking TSLP could have further benefits beyond decreasing airway type 2 inflammation.

Phase III studies. Designs

NAVIGATOR (ClinicalTrials.gov number, NCT03347279)

The NAVIGATOR study was a phase 3, multicenter, randomised, double-blind, placebo-controlled trial which assessed sc tezepelumab at 210 mg/4 weeks or placebo/4 weeks over a 52-week treatment period [27]**.** The primary endpoint was the AAER at week 52 **(**see Supplementary Table**).**

A recent exploratory analysis evaluated the efficacy of tezepelumab in patients from NAVIGATOR study with severe allergic asthma defined in several ways [28]**.** The

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definitions included sensitisation to common perennial aeroallergens, concomitant sensitisation to both perennial and seasonal aeroallergens, and confirmed allergy with reported symptoms, as well as by eligibility for omalizumab treatment in the European Union (EU) and the United States (US).

The primary patient population of interest in this study was subjects sensitised to perennial aeroallergens, including house dust mites, cockroaches, cat dander, dog dander, and molds. Patients without sensitisation to perennial aeroallergens were considered the reference group. In addition, patients with sensitisation to seasonal aeroallergens were also investigated, which included grass pollen, mixed ragweed pollens, and tree pollens.

To assess the efficacy of tezepelumab in patients with severe allergic asthma, the primary endpoint (AAER over 52 weeks) was first evaluated in patients with and without sensitisation to perennial aeroallergens [28]**.** Other endpoints assessed included changes in pre-bronchodilator FEV_1 and patient-reported outcomes (ACQ-6, AQLQ, ASD and SGRQ) from baseline to week 52. Further analyses were performed in other subgroups according to allergic status: patients sensitised to both perennial and seasonal aeroallergens; patients with confirmed symptomatic sensitisation to perennial aeroallergens; and patients who were candidates for omalizumab therapy according to the EU or US prescribing information [28]**.** Confirmed symptomatic sensitisation to perennial aeroallergens was defined by a researcher-reported history of allergy to house dust mites or animal allergens (cats and/or dogs) and a positive ImmunoCAP result to the corresponding allergen at baseline.

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SOURCE (ClinicalTrials.gov number NCT03406078)

The SOURCE trial was a phase 3, multicentre, randomised, double-blind, placebo-controlled study which evaluated sc Tezepelumab 210 mg or placebo every four weeks during a 48-week treatment period [29]**.** The primary endpoint was the categorised percentage reduction from baseline in daily oral corticosteroid dose at week 48 without losing asthma control **(**see Supplementary Table**)**.

DESTINATION (ClinicalTrials.gov number NCT03706079)

The DESTINATION study was the first long-term extension study of a biological treatment for severe asthma, including a placebo arm [30,31]**.** Patients who completed either the NAVIGATOR or SOURCE studies were eligible, and the aim was to assess the long-term (1 year) tolerability and safety of tezepelumab compared with placebo. Therefore, out of 1061 previously randomised patients of the NAVIGATOR study, 570 entered extended follow-up (DESTINATION study), and out of 150 randomised from the SOURCE study, 109 completed the extended follow-up (DESTINATION study). If required, physicians were allowed to up or down-titrate participants' medication during this study. Those patients who were randomised to receive tezepelumab 210 mg every four weeks (Q4W) in either predecessor study continued to receive this regimen for one year; those who were previously randomised to receive placebo were re-randomized (1:1) to receive either tezepelumab 210 mg Q4W or placebo for one year. The primary endpoints were exposure-adjusted incidence of adverse events and serious adverse events. The secondary endpoint was the AAER over 104 weeks. Both primary and secondary endpoints were evaluated from week 0 (predecessor studies) to week 104 (DESTINATION study) **(**see Supplementary Table**)**.

doi: 10.18176/jiaci.0949

Phase III studies. Results

Exacerbations

The NAVIGATOR study showed a lower AAER in the group of sc tezepelumab 210 mg/4 weeks (0.93) compared with placebo (2.10) (rate ratio, 0.44; 95% CI, 0.37 to 0.53; P<0.001, noticed regardless of blood eosinophil counts at inclusion but showing a higher effect in patients with ≥300 eosinophils, FENO≥25 ppb and those with positive sensitisation to perennial allergens. Also, the time to first exacerbation was longer in the tezepelumab group [32]**.** The NAVIGATOR study concluded that tezepelumab reduced asthma exacerbations compared with placebo, independent of baseline eosinophil counts, with greater effects in patients ≥300 eosinophils/μL but also in the <150 eosinophils/μL [32]**.**

In the exploratory study of NAVIGATOR in patients with evidence of severe allergic asthma [28], tezepelumab therapy decreased the AAER compared with placebo by 58% (95% CI: 47-67) in patients sensitised to perennial aeroallergens, by 58% (95% CI 42-70) in patients with both perennial and seasonal allergy, by 59% (95% CI 41-71) in patients with perennial allergy only, and by 60% (CI 95% 43-71) in patients with confirmed symptomatic perennial allergy. In patients who were candidates for omalizumab in accordance with EU and US labels, tezepelumab reduced the AAER compared with placebo by 68% (95% CI 55-77) and by 60% (CI 95% 44-71), respectively. Similar results were observed in non-allergic subjects and patients ineligible for omalizumab.

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AAER was the key secondary endpoint in the SOURCE study, and the tezepelumab group had an AAER of 1.38 (95% CI 0.98–1.95) over 48 weeks compared with 2.00 (1.46–2.74) in the placebo group. The rate ratio (RR) was 0.69 (95% CI 0.44–1.09), corresponding to a reduction of 31%. According to baseline blood eosinophil count, the RR was 0.43 (0.24–0.76) in those patients with a blood eosinophil count of at least 150 cells per μL and 0.29 (0.14–0.63) in those with a count of at least 300 cells per μL (corresponding to a reduction of 57% and 71%, respectively), and was 1.35 (0.64–2.87) in participants with counts below 150 cells per μL [33].

In DESTINATION [31]**,** tezepelumab reduced AAER over 104 weeks compared with placebo, both in patients initially participating in the NAVIGATOR study (0.42; 95% CI 0.35 to 0.51) and the SOURCE study (0.61; 95% CI 0.38 to 0.96). In participants from NAVIGATOR, the AAER was systematically inferior in the tezepelumab group than in the placebo group, regardless of baseline inflammatory biomarkers and clinical features over 104 weeks; time-to-first exacerbation of asthma in these subjects was longer in the tezepelumab group than in the placebo group (hazard ratio 0.64, 95% CI 0.54–0.75. Exacerbation reductions were generally seen independently of baseline clinical characteristics and biomarkers. However, there were greater reductions in patients with elevated levels of type 2 inflammatory biomarkers or nasal polyposis.

The DESTINATION study concludes that tezepelumab achieves clinically meaningful reductions in asthma exacerbations in adolescents and adults with severe uncontrolled asthma.

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Reduction of oral corticosteroids

The SOURCE study yielded no significant differences between groups in the percentage reduction in daily oral corticosteroid dose (OCS). After grouping by baseline eosinophil count, those patients with >150eosinophils/μL showed greater reductions in oral corticosteroid use [33]**.** The reduction of daily oral corticosteroid dosage noted in the placebo group in SOURCE was higher than in previous studies of biological drugs in asthma regarding oral corticosteroid saving effect, and SOURCE had a considerably longer tapering phase than other studies of saving oral corticosteroids with asthma biologics, giving all participants a prolonged period to lower their oral corticosteroid dosage. In post-hoc analyses of the SOURCE study, when the treatment time was reduced from 48 to 20 weeks, and researchers were not allowed to further decrease the oral corticosteroid dose in subjects who had 1 or 2 exacerbations or did not fulfill the criteria of asthma control, the percentage of subjects assigned to placebo who had a daily oral corticosteroid dose of 0 mg was lower. The SUNRISE study [34] is currently underway to try to demonstrate the effect of tezepelumab in reducing the use of oral corticosteroids.

Lung function

In NAVIGATOR [32]**,** FEV1 significantly improved over placebo: 0.23 vs. 0.09 liters; difference, 0.13 liters; (95% CI, 0.08 to 0.18; P<0.001). However, when stratified by eosinophil level, significant differences in FEV1 were only achieved in patients with >150 eosinophils, 0.17 L (0.11, 0.23).

In the study in patients with severe allergic asthma [28]**,** FEV1 improved by 0.15 L in patients receiving tezepelumab versus placebo, regardless of allergic status.

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In SOURCE [33], the change in FEV1 was 0.21 L in the tezepelumab group and −0.04 L in the placebo group (least squares mean difference 0.26 L (95% CI 0.13–0.39). These differences were also significant in patients with more than 150 eosinophils: 0.32 L (95% CI 0.17, 0.48), but they did not achieve statistical significance in patients with less than 150 eosinophils: 0.16 (95% CI −0.06, 0.38).

FEV1 also improved with Tezepelumab vs placebo in DESTINATION **(31)** 0.08 L (95% CI 0.02, 0.15) in patients from NAVIGATOR and 0.19 L (95% CI 0.03, 0.35) in those coming from SOURCE.

Patient Reported Outcomes

In NAVIGATOR [32]**,** regarding asthma control, ACQ-6 scores were significantly reduced in the tezepelumab group: -0.33 (95% CI -0.46, -0.20). In terms of quality of life, AQLQ(S)+12 score significantly improved by 0.34 (95% CI 0.20, 0.47) compared with placebo. The Asthma Symptom Diary (ASD) score improved significantly -0.12 (95% CI -0.19, -0.04) in the active group. These improvements in patient-reported outcomes were observed regardless of the allergic status of the patients [28]**.**

The tezepelumab group also had improvement vs placebo in ACQ-6: −0·37 (95% CI −0.71, −0.02) and AQLQ(S)+12: 0.36 (95% CI 0.01, –0.70) scores in the SOURCE study **(33) (**with no improvement in ACQ-6 in patients with less than 150 eosinophils per μL), and ACQ-6 and SGRQ (St George's Respiratory Questionnaire) throughout the whole treatment period in DESTINATION [31].

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Effect on biomarkers

In summary, tezepelumab reduces but does not entirely abolish, downstream biomarkers of inflammation, such as blood and airway eosinophils, FeNO, and IgE [21,32,35,36]**,** and lowers serum interleukin (IL)-5 and IL-13 in patients with severe, uncontrolled asthma to levels approaching those observed in healthy individuals [37]. In addition, tezepelumab reduced airway inflammation, as measured by decreases in bronchial submucosal eosinophils compared with placebo [26]**.**

Across studies, tezepelumab reduced blood eosinophil counts from baseline compared with placebo, with effect seen for 2 to 4 weeks and maintained for up to 52 weeks. Results were generally comparable across studies and, in global data, the average reduction in blood eosinophils was 40-45% in the first four weeks and 50-55% at the end of the studies (48 or 52 weeks) [36]**.**

Tezepelumab reduced FeNO levels from baseline compared with placebo, with effect seen for 2 to 4 weeks and maintained for up to 52 weeks. Results were comparable across studies, and the average reduction was similar at four weeks as at the end of the studies (30-35 %) [36]**.**

Study results show that tezepelumab reduced total serum IgE levels gradually from baseline to end of treatment compared with placebo. The average reduction in Ig E levels was around 10% in the first four weeks and 25-30 % at the end of the studies [36]**.**

Across studies, tezepelumab reduced serum IL-5 levels from baseline compared with placebo, with effect seen for 2 to 4 weeks and maintained for up to 52 weeks. In global

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data, the average reduction in IL-5 levels was 45-50 % in the first four weeks and 55-60 % at 52 weeks [36]**.**

Tezepelumab reduced serum IL-13 levels from baseline compared with placebo, with effect seen for 2 to 4 weeks and maintained for up to 52 weeks. Results were generally comparable across studies, and the average reduction was similar at four weeks as at the end of the studies (50-55 %) [36]**.**

PATH-HOME (ClinicalTrials.gov number NCT03968978)

The PATH-HOME study was a phase III, open-label, parallel-group, randomised trial, which assessed 216 adult currently non-smoking patients from 12 to 80 years of age with severe uncontrolled asthma who received six subcutaneous doses of tezepelumab 210 mg via an accessorised pre-filled syringe (APFS) or an autoinjector (AI), being the first dose administered by a healthcare professional (HCP). First, second, third (weeks 0, 4 and 8) and final doses were administered in the clinic (week 20) [38]**.** The fourth and 5th doses, weeks 12 and 16, were administered at home **(**see supplementary Table**).**

The primary endpoint was to evaluate the success of administering tezepelumab 210 mg (sc) with an APFS or AI in the clinic and at home by HCP and patients or caregivers.

Clinically meaningful improvements in ACQ-6 score were observed after 24 weeks in 81.1% and 76.2% of the patients in the APFS and AI groups, respectively.

A 91.7% of HCPs, patients or caregivers successfully administered tezepelumab via APFS. Similarly, tezepelumab was successfully administered by 92.4% via autoinjector. At weeks 12 and 16, at-home administration of tezepelumab was successful in 95.4% of

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the patients/caregivers in the APFS group. Regarding the AI device, 97.1% of the patients or caregivers administered it successfully at home.

The former data indicate that treatment with tezepelumab after at-home self-administration using an APFS or AI is sufficient to achieve the clinical effect found in the PATHWAY study.

Currently recruiting/open clinical studies:

SUNRISE (ClinicalTrials.gov Identifier: NCT05398263) [34], PASSAGE (ClinicalTrials.gov Identifier: NCT05329194) [39], DIRECTION (ClinicalTrials.gov Identifier: NCT03927157) and WAYFINDER (ClinicalTrials.gov Identifier: NCT05274815) are currently open clinical studies (see supplementary Table).

Safety

The Primary Safety Pool included 615 subjects receiving tezepelumab 210 mg Q4W for up to one year. Adverse Events (AEs) incidence was generally similar between the tezepelumab group and placebo. The most often reported adverse reactions during treatment were pharyngitis (4.1%), injection site reactions (4 %) and arthralgia (3.8%). The most common Serious Adverse Events (SAE) appeared in the respiratory, thoracic, and mediastinal disorders (15 patients [2.3%]) and infections and infestations (13 patients [2.0%]). The most frequent SAE in both groups was asthma symptoms, reported by 15 subjects (2.3%) in the group of tezepelumab and 46 subjects (6.9%) in the group of placebo. Besides the SAE of asthma, no SAE was reported in > 2 subjects in the tezepelumab group [36].

doi: 10.18176/jiaci.0949

Tezepelumab may produce inhibitory effects on immune responses mediated by Th2 cells. However, for the AE of severe infections, the number of SAEs was low and similar in both treatment groups, 2% for tezepelumab vs 2.2% for placebo in the Primary Safety Pool. No opportunistic or helminth infections occurred in the main safety group or the SOURCE study. However, a warning is included in the datasheet for parasitic (helminth) infection, sustained in that TSLP may be involved in the immune response to some helminth infections [35]**.** Neither anaphylactic nor severe allergic reactions to tezepelumab appeared in the Primary Safety Pool or the SOURCE study. For malignancies, in the Primary Safety Pool, a similar, though slightly higher, number of patients reported a malignancy in the on-study period in the tezepelumab group compared to the placebo group [36]**.**

In the extension study DESTINATION [31]**,** the incidence per exposure of any AE, SAE, and AE leading to treatment stopping in the treatment period was lower in the tezepelumab group than in the placebo group in both main studies. In the primary safety analysis set, the most frequent adverse events (occurring in ≥10% of patients) were nasopharyngitis, upper respiratory tract infection, headache, asthma, and bronchitis in the treatment arms of both main studies.

A numerical imbalance in serious cardiac events was demonstrated, with more events in the Tezepelumab group compared to placebo [31]**.** However, a causal relationship between tezepelumab and these events has not been established, nor has a patient population at risk of these events been identified. It must be assessed that the DESTINATION safety study has a placebo arm, unlike other long-term studies of other biologics for severe asthma, which are open-label. The rate of cardiac SAEs in the placebo

doi: 10.18176/jiaci.0949

group was lower than the rate observed in the real-world population with severe asthma and the pooled various papers with a placebo dataset of severe asthma subjects. The incidence rates of cardiac disorder SAEs with tezepelumab were consistent with what has been estimated based on published data with other biologics evaluated in severe asthma populations **(36).** If the patients present a severe cardiac event while receiving treatment with tezepelumab, treatment should be discontinued until the acute event is stabilised [35]**.**

Tezepelumab in concomitant T2 diseases

Chronic Rhinosinusitis with nasal polyps

The prevalence of chronic rhinosinusitis with nasal polyps (CRwNP) in severe asthma patients rises to 40% in some populations. Moreover, these patients usually experience a more severe burden disease, and many of the histological and inflammatory features presented in T2-asthma are also present in CRwNP [40]**.** With the disruption of the epithelial barrier, TSLP expression is increased in response to allergens and other environmental factors damaging the airway epithelium, leading to promote T2 and, quite possibly, also initiating non-T2 inflammation and tissue remodelling in the nose [41]**.** The number of eosinophils in the nasal polyps' tissue has been related to the levels of TSLP [42]**.**

Since tezepelumab prevents the interaction between TSLP and its receptor, it might induce a synergic effect in patients with asthma and CRwNP, although there is still lacking evidence. In 2021, it was published a *post-hoc* analysis from the Phase 2b pivotal Pathway study [22]**,** which evaluated the effect of three different regimens of tezepelumab

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(70 mg Q4W, 210 mg Q4W or 280 mg Q2W) in 550 patients with severe uncontrolled asthma despite medium or high dose of inhaled corticosteroids, with (n=82) or without self-reported CRwNP. At baseline, patients with CRSwNP had higher blood eosinophil counts and FeNO levels than those without NP. Tezepelumab 210 mg reduced the AAER versus placebo in both groups to a similar extent (CRSwNP, 75% [95% CI: 15, 93], n=23; vs CRwoNP, 73% [95% CI: 47, 86], n=112) but, interestingly, greater reductions in blood eosinophil count and levels of FeNO, than placebo-treated patients, were observed irrespective of NP status. Nevertheless, one important limitation of this *post-hoc* study was the small sample of patients with CRSwNP, a lower proportion compared to other similar studies, probably related to NP status was self-reported, whereas diagnosis was confirmed endoscopically in other studies [43]**.** Furthermore, similar findings have been observed in the post-hoc analysis of the phase III NAVIGATOR study, supporting the benefits of tezepelumab in a broad population irrespective of NP status. Currently, there is an ongoing multicentre, randomised, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of tezepelumab in adults with severe CRwNP. It is intended to recruit approximately 400 subjects, and the primary outcome is to measure the change from baseline in total Nasal Polyp Score over a 52-week treatment period [44]**.**

Allergic rhinitis

A recent study reported that the addition of tezepelumab to subcutaneous immunotherapy with cat extract for one year improved the efficacy and reduced the early allergic nasal response to specific nasal allergen challenge compared to allergen immunotherapy alone in patients with allergic rhinitis [45].

doi: 10.18176/jiaci.0949

Allergic bronchopulmonary aspergillosis

Theoretically, tezepelumab could be a suitable treatment in patients with allergic bronchopulmonary aspergillosis (ABPA) since TSLP is implicated in multiple downstream processes, including IL-13, that plays an important role in mucus hypersecretion and IL-5 which drives airway eosinophilia [46,47]**.** Fungal presence activates the production of TSLP by epithelial cells and, probably, by other cells under certain inflammatory conditions, including fibroblasts, smooth muscle cells, dendritic cells, and mast cells, ultimately leading to the production of T2 pro-inflammatory cytokines and also contributing to initiating a Th17 response [48]**.** To the best of our knowledge, only one isolated clinical case has been published, showing a corticosteroid-sparing effect of tezepelumab in an 82-year-old man despite being treated with mepolizumab through diminishing mucus plugs in parallel with the improvement of asthma control [46]**.**

Other possible indications

With no published results, a phase 2 study has been completed to evaluate tezepelumab in adults with Chronic Spontaneous Urticaria (INCEPTION). (NCT04833855) [49]**.**

Finally, regarding food allergy, it has been published that the expression of alarmins, including TSLP, was elevated in EoE compared to normal esophageal tissues [50]**,** and currently, there is an ongoing randomised, double-blind, placebo-controlled multicenter, phase 3 study to evaluate the efficacy and safety of tezepelumab in adult and adolescent patients with EoE (NCT05583227) [51]**.**

Positioning of tezepelumab

doi: 10.18176/jiaci.0949

Tezepelumab acts by blocking TSLP, an epithelial cytokine, and exerts its effect early in the asthma inflammatory cascade, so an effect on different phenotypes of asthma patients, in which different biomarker profiles are expressed, is to be expected (Figure 1). Consistently, clinical trials have demonstrated efficacy in both T2 and non-T2 asthma patients [52]**.** This broad range of action of tezepelumab is already reflected in GEMA guideline 5.3 [53]**.**

Tezepelumab has been shown to improve asthma control, quality of life, and lung function and reduce AHR. However, the best results have been obtained in patients with elevated eosinophilia [28]**,** and although in patients with <150 eosinophils/µL in peripheral blood tezepelumab has been shown to reduce exacerbations, no significant improvement in lung function has been observed [32]**.**

In the SOURCE study [33]**,** no significant differences in oral steroid dose reduction could be demonstrated, probably due to study design problems (in the placebo group, 46% were able to discontinue oral steroids), although patients with more than 150 eosinophils per µL showed a significantly higher OR over the placebo group. To clarify this aspect, the SUNRISE study is currently underway [34]**.**

Another possible indication for tezepelumab would be in patients with uncontrolled severe asthma who have several elevated biomarkers, such as IgE, eosinophils, and FeNO, and in those who are not adequately controlled with anti-IgE, anti-IL-5, or anti-IL-4/13 drugs and show elevation of some of these parameters, in which case tezepelumab could avoid the use of a second biologic.

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Given that TSLP expression has been shown to be increased in nasal polyps [54], tezepelumab is being evaluated for nasal polyposis in the WAYPOINT study [44].

Figure 2 shows an algorithm for the use of tezepelumab in patients with uncontrolled severe asthma.

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Conflicts of Interest

Juan Carlos Miralles López has received consultancy fees from Chiesi and Astra Zeneca and speaker fees from Novartis, GSK, Astra Zeneca, Sanofi, Chiesi, Bial and Organon.

Darío Antolín-Amérigo has received consulting fees from ALK-Abelló, Astra Zeneca, Chiesi and Gebro, as speaker from Astra Zeneca, Chiesi, Gebro, GSK, Leti Pharma, Mundipharma, Novartis, Roxall, Sanofi.

Ismael Garcia-Moguel has been on Advisory boards from Novartis, AstraZeneca, GSK, Sanofi Genzyme, and Stallergenes, and has received speaker's honoraria from Novartis, AstraZeneca, Teva, Novartis, GSK, Sanofi Genzyme, Chiesi, Allergy therapeutics, Leti, Stallergenes, ALK-Abelló, Mundipharma, Pfizer, and Orion Pharma.

Javier Dominguez-Ortega has been on Advisory boards and received speaker's honoraria from AstraZeneca, Teva, Novartis, GSK, Sanofi Genzyme, Chiesi, Allergy therapeutics, Leti Pharma and ALK-Abelló.

Julio Delgado-Romero made advisory boards for Bial and Sanofi. Received speaker's honoraria from AstraZeneca, Bial, Chiesi, GlaxoSmithKline, Novartis, Sanofi and TEVA. Received Grant/Research Support from AstraZeneca and Orion.

Santiago Quirce has been on advisory boards for and has received speaker's honoraria from ALK, Allergy Therapeutics, AstraZeneca, Chiesi, GlaxoSmithKline, Leti, Mundipharma, Novartis, Sanofi-Regeneron and Teva.

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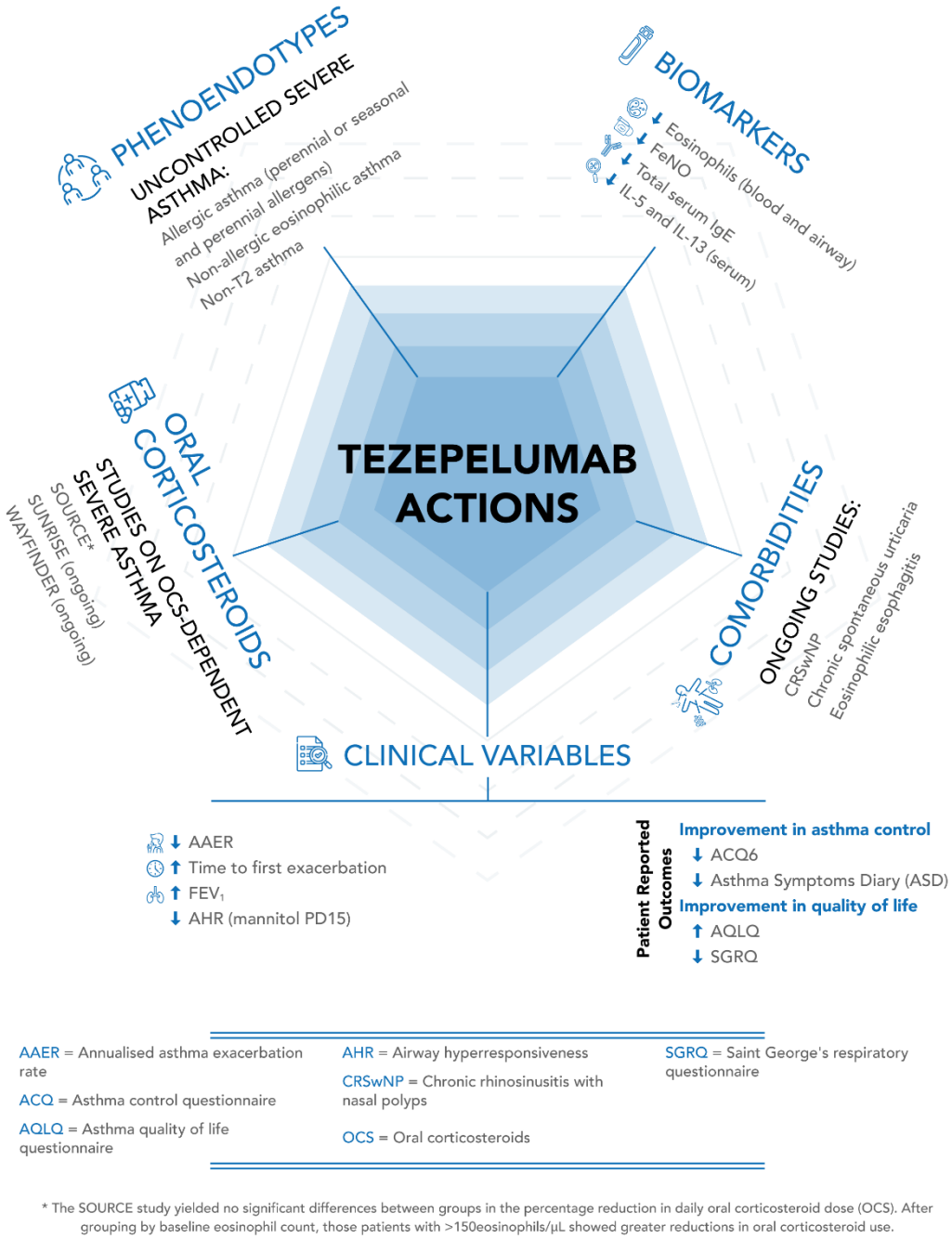
FIGURES

Figure 1. Actions of Tezepelumab



AAER = Annualised asthma exacerbation rate

ACQ = Asthma control questionnaire

AQLQ = Asthma quality of life questionnaire

AHR = Airway hyperresponsiveness

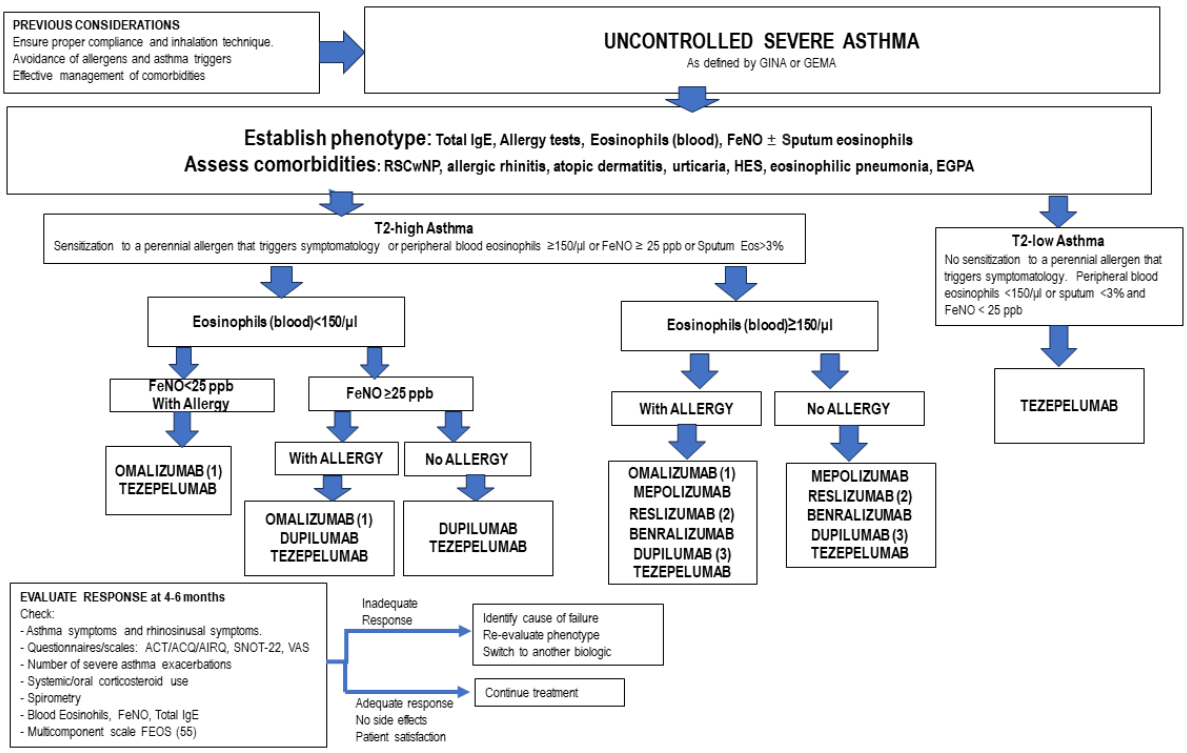
CRSwNP = Chronic rhinosinusitis with nasal polyps

OCS = Oral corticosteroids

SGRQ = Saint George's respiratory questionnaire

* The SOURCE study yielded no significant differences between groups in the percentage reduction in daily oral corticosteroid dose (OCS). After grouping by baseline eosinophil count, those patients with >150eosinophils/µL showed greater reductions in oral corticosteroid use.

Figure 2. Positioning of Tezepelumab in Uncontrolled Severe Asthma. Modified from GEMA 5.3. (53).



EGPA: Eosinophilic Granulomatosis with Polyangiitis; Eos: Eosinophils; FeNO: Fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; GEMA: Spanish Asthma Management Guidelines (*Guía Española de Manejo del Asma*); HES: Hypereosinophilic syndrome; IgE: Immunoglobulin E, RSCwNP: Chronic rhinosinusitis with nasal polyposis.

1. Omalizumab: with IgE from 30 to 1500 UI/ml.
2. Reslizumab: with blood eosinophils ≥400/µl
3. Dupilumab: do not use if eosinophils ≥1500/µl .

Comorbidities: Omalizumab is indicated in Chronic urticaria and RSCwNP. Mepolizumab is indicated in RSCwNP, EGPA, and HES. Dupilumab is indicated in Atopic dermatitis, RSCwNP, and Eosinophilic esophagitis.

Mepolizumab, Reslizumab, Benralizumab, and Dupilumab have been shown to reduce the use of oral corticosteroids.

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