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CASE REPORT & REVIEW

Tezepelumab for early-onset severe allergic asthma with persistent airflow limitation and small airway dysfunction: a treatable traits approach

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Abstract

We report the case of an 18-year-old woman with early-onset severe allergic asthma and no other type 2 biomarkers except the presence of IgE, complicated by persistent airflow limitation, air trapping and forced oscillation technique-defined small airway dysfunction, who achieved significant clinical improvement with first-line tezepelumab (TZP) therapy. Initial treatments, including high-dose extrafine-inhaler triple therapy with a beclomethasone–formoterol–glycopyrronium combination, failed to improve asthma control and lung function. Given the discordance between allergic phenotype and treatable traits, such as persistent airflow limitation and small airway dysfunction, TZP, a thymic stromal lymphopoietin inhibitor with broad anti-inflammatory effects, was initiated instead of omalizumab. After 6 months of treatment, the patient showed marked clinical and functional improvement: Asthma Control Test score increased from 12 to 22, forced expiratory volume in 1 second rose from 67% to 95%, residual volume normalized, and forced oscillation technique parameters improved substantially. This case illustrates how the identification of specific treatable traits can guide personalized biologic therapy, even when conventional phenotype-driven algorithms suggest otherwise. In patients with early-onset allergic asthma and atypical functional profiles, TZP may offer a superior therapeutic option by targeting upstream airway inflammation and reversing small airway dysfunction. Our findings support a precision medicine approach in severe asthma, emphasizing multidimensional assessment and biomarker-guided biologic selection.

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Keywords: FeNO, persistent airflow limitation, severe allergic asthma, small airway dysfunction, tezepelumab, type 2 inflammation.

Citation

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Introduction

In severe asthma, the allergic endotype is typically characterized by higher or lower levels of IgE and exaggerated responses to specific inhaled allergens compared with non-allergic endotypes. For patients with a clear allergic phenotype, characterized by sensitization to a perennial allergen and elevated serum IgE levels, omalizumab has long been a cornerstone of treatment. Omalizumab is a monoclonal antibody (mAb) that binds to circulating IgE, preventing initiation of the allergic cascade that results in airway inflammation. Omalizumab has shown consistent efficacy and safety over time, though it has not demonstrated particular benefits in enhancing respiratory function.[1] Subsequent research has identified other mAbs with potential for treating allergic asthma, as evidenced, for example, by the efficacy of anti-IL-4/IL-13 dupilumab.[2] Dupilumab necessitates the concurrent presence of type 2 biomarkers, fractional exhaled nitric oxide (FeNO) values of at

least 25 parts per billion (ppb) and/or blood eosinophils of at least 150 cells/mm³.[3] New mAbs, including tezepelumab (TZP), a biologic that blocks thymic stromal lymphopoietin (TSLP), present novel treatment options for patients with severe asthma. These mAbs target upstreaminflammatory pathways, and there is substantial evidence supporting their efficacy not only in improving asthma control but also in enhancing large airway respiratory function, as measured by spirometry, as well as small airway dysfunction (SAD).[4,5]

In the field of severe asthma, clinical remission is emerging as a key therapeutic goal, particularly with the advent of mAbs.[6] However, in the context of an increasingly complex scenario in patients with refractory asthma and persistent functional impairment, such as SAD and persistent airflow limitation (PAL), standard biomarkers of T2 inflammation may be insufficient to guide treatment decisions.

This article describes the clinical and functional evolution of a young patient with severe early-onset allergic asthma with impaired respiratory function treated with the anti-TSLP biologic agent TZP.

Case report

Patient consent and ethics

The patient's signed consent was not necessary because the data were de-identified so that the patient's identity could not be ascertained in any way. However, the patient provided consent for publication.

The patient was a white woman, who was a student, a non-smoker, and 18 years of age. She had a family history of asthma and a remote pathological history that includes recurrent bronchitis during childhood and a diagnosis of bronchial asthma at the age of 5 years. Her body mass index (BMI) was within normal limits (22.5 kg/m²). The patient's medical history revealed a history of allergic sensitization to pollen, cat dander, dust mites, peanuts and springtime allergic oculorhinitis. The patient underwent sublingual immunotherapy for grasses during childhood, which proved to be ineffective. Until 2022, the therapeutic approach involved the administration of salbutamol on an as-needed basis. However, due to the progressive deterioration in asthma control, the use of an extrafine pressurized metered dose inhaler (pMDI) containing a combination of beclomethasone and formoterol (200/6 µg) was initiated. Montelukast had been demonstrated to be ineffective. In June of 2022, spirometry revealed normal volumes, with forced expiratory volume in the first second (FEV_1) measuring 3.25 L (predicted value of 109%) and forced vital capacity (FVC) measuring 94.02 L. Additionally, the residual volume was 98% of the predicted value. The Asthma Control Test (ACT) score was 19/25.

With respect to biomarkers, the total IgE levels were determined to be 538 IU/mL. Specifically, the specific IgE levels indicated a robust sensitization to dust mites (*Dermatophagoides pteronyssinus* [d1] 72 IU/mL and *Dermatophagoides farinae* [d2] >100 IU/mL). Concurrently, eosinophil levels remained within normal limits as determined by complete blood count analysis. The FeNO level was found to be 9, 10 and 8 ppb in three consecutive measurements, thus within normal limits.

In 2023, the patient continued to experience suboptimal symptom control, moderate exertional dyspnoea and two moderate exacerbations. These exacerbations were treated with oral corticosteroid (OCS) prednisone 25 mg per day for 7 days and azithromycin 500 mg, one tablet per day for 3 days.

A spirometry test administered in March 2024 revealed a decrease in lung volume, accompanied by a sustained response to bronchodilator medication. However, the test results did not indicate a return to normal levels for the FEV_1/FVC ratio, which remained below the lower limit of normal: the patient's FEV_1 was 2.04 L, which is 63% of the predicted value; FEV_1/FVC ratio was 63 and the FEV_1 post bronchodilator was 2.81 L, which is 18% above normal. The FEV_1/FVC ratio post bronchodilator was 69. This finding suggests the presence of a PAL. Air trapping (residual volume 160% of predicted) was also present at baseline spirometry (Table 1). Furthermore, the results indicated that FeNO levels remained within the normal range throughout the observation period.

In April 2024, a treatment step-up with single extrafine-inhaler triple therapy with a beclomethasone–formoterol–glycopyrronium combination (BDP/FF/G), 172/5/9 µg, administered as two puffs twice daily. Notwithstanding the therapeutic interventions, the patient continued to experience respiratory symptoms on a nearly weekly basis, including chest tightness, dyspnoea on mild-to-moderate exertion (grade 2 Modified British Medical Research Council (mMRC) scale, ACT score 17/25), and the presence of phlegm, particularly in the morning, with exacerbation during the spring period and in response to allergen exposure. In the same month, a moderate exacerbation of asthma occurred, which was treated with a course of prednisone (37.5 mg per day, tapered over approximately 10 days) in addition to the usual inhalation therapy. As a subsequent diagnostic investigation, the patient underwent forced oscillation technique (FOT), which revealed the presence of SAD, as indicated by the patient's respiratory system resistance (Rrs) measurements of 5 Hz to 0.80, inspiratory 0.88, expiratory 0.73

Table 1. Clinical, spirometric and oscillometric evolution over 6 months.

Parameter	Baseline	1 month	3 months	6 months
ACT score (/25)	13	19	23	25
mMRC Dyspnoea Scale	Grade 2	Grade 2	Grade 1	Grade 0
Exacerbations (interval)	1 (moderate, OCS required)	0	1 (mild, no OCS)	0
FEV_1 (L, % predicted)	2.04 L (63%)	2.40 L (74%)	2.96 L (91%)	3.10 L (95%)
FeNO (ppb)	10	9	8	7
Blood eosinophils (/mm³)	60	50	60	40
FEV_1/FVC ratio (%)	63	68	77	80
RV (% predicted)	160	105	103	102
Rrs 5 Hz [$cmH_2O/(L/s)$]	0.80 (Z = +2.2)	0.60 (Z = +1.2)	0.30 (Z = +0.4)	0.10 (Z = 0.0)
Rrs 5–19 Hz [$cmH_2O/(L/s)$]	1.10 (Z = +2.5)	0.30 (Z = +1.0)	0.20 (Z = +0.5)	0.05 (Z = 0.0)
Xrs 5 Hz [$cmH_2O/(L/s)$]	-3.20 (Z = -3.2)	-0.88 (Z = -1.5)	-0.48 (Z = -0.8)	-0.20 (Z = -0.3)
AX [$cmH_2O/(L/s)$]	12.5 (Z = +3.0)	3.80 (Z = +1.2)	2.70 (Z = +0.6)	2.40 (Z = +0.3)
OCS (mg)	One course (25 mg/day for 7 days) in the previous month	None	None	None
BMI (kg/m²)	22.5	23	22	23

ACT, Asthma Control Test; AX, reactance area; BD, bronchodilator; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FOT, forced oscillation technique; FVC, forced vital capacity; mMRC, Modified Medical Research Council; OCS, oral corticosteroids; Rrs 5, respiratory resistance at 5 Hz; Rrs 5–19 Hz, difference in respiratory resistance between 5 Hz and 19 Hz; RV, residual volume; Xrs 5, respiratory reactance at 5 Hz.

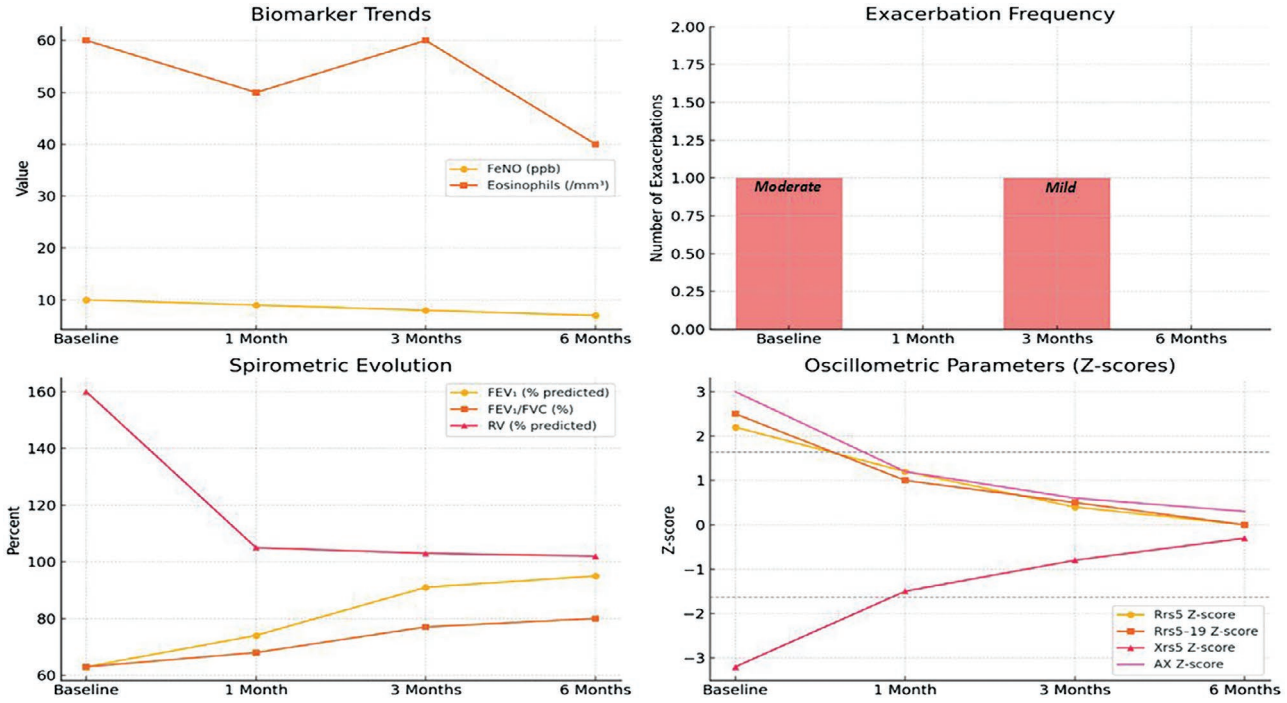
(Zeta [Z]-score), Rrs 5–19 Hz +2.2 (Z-score) and respiratory system reactance (Xrs) measurements of inspiratory –1.67, expiratory –0.70, total –1.08 (Z-score) and reactance area +3.0 (Z-score). On chest X-ray, the bronchial walls exhibited a modest thickening in the bilateral basal area, predominantly in the posterior sectors. The pleural cavities were found to be free of effusion, and the cardiomediastinal image was within normal limits. Given the patient's young age and the absence of suspicious conditions to be considered in the differential diagnosis, a chest computed tomography scan was deemed unnecessary. The ACT score had decreased to 13/25. A subsequent review of the inhaler technique and adherence to treatment did not reveal any problems attributable to thepatient.

A diagnosis of severe refractory asthma was confirmed due to the persistent poor control of the patient's asthma. Consequently, the patient initiated a course of subcutaneous anti-TSLP mAb TZP 210 mg administered via a single, one-vial injection administered every 4 weeks, commencing in December 2024. A subsequent reassessment was scheduled, encompassing a follow-up visit, spirometry, FeNO and oscillometry at 1, 3 and 6 months, respectively, from the initiation of therapy. The standard treatment regimen at present entails the administration of BDP/FF/G 172/5/9 µg via a pMDI, with two puffs twice daily, in conjunction with BDP/FF 100/6 µg administered as needed through a pMDI.

Following the initiation of TZP, the patient exhibited substantial clinical improvement, with the spirometric parameters and FOT returning to normal levels as early as 1 month after the initial TZP administration. The patient no longer reports cough, phlegm or nocturnal awakenings due to dyspnoea. The occurrence of wheezing is limited to periods of sports activity. Notwithstanding a mild exacerbation occasioned by a viral respiratory infection in January 2025, the patient was treated solely with an augmented dosage of inhalation therapy as required, with BDP/FF administered for several days. A physical examination of the patient's thorax revealed the presence of soft, rustling sounds during auscultation of the patient's chest. No abnormal sounds, such as wheezing or crackling, were detected. The ACT score demonstrated a notable improvement, reaching 23/25. Furthermore, the patient reported a reduction in sensitivity upon exposure to dust, accompanied by a significant decrease in rhinitis and bronchial symptoms compared with the pretreatment state.

One month after the initiation of TZP, the patient underwent spirometry, FOT and FeNO testing, all of which yielded normal results (Table 1 and Figure 1). After a period of 6 months, specifically in June 2025, the parameters measured by these tests demonstrated stability. Furthermore, the patient exhibited no additional exacerbations and had discontinued the use of OCS.

Figure 1. Longitudinal variation of lung function, FOT measures and biomarkers.



AX, reactance area; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FOT, forced oscillation technique; FVC, forced vital capacity; Rrs 5, respiratory resistance at 5 Hz; Rrs 5–19 Hz, difference in respiratory resistance between 5 Hz and 19 Hz; RV, residual volume; Xrs 5, respiratory reactance at 5 Hz.

With regards to patient-reported outcomes, the ACT score was 25/25 and the mMRC score was 0, indicating a substantial improvement over the baseline (Figure 2).

Discussion and review

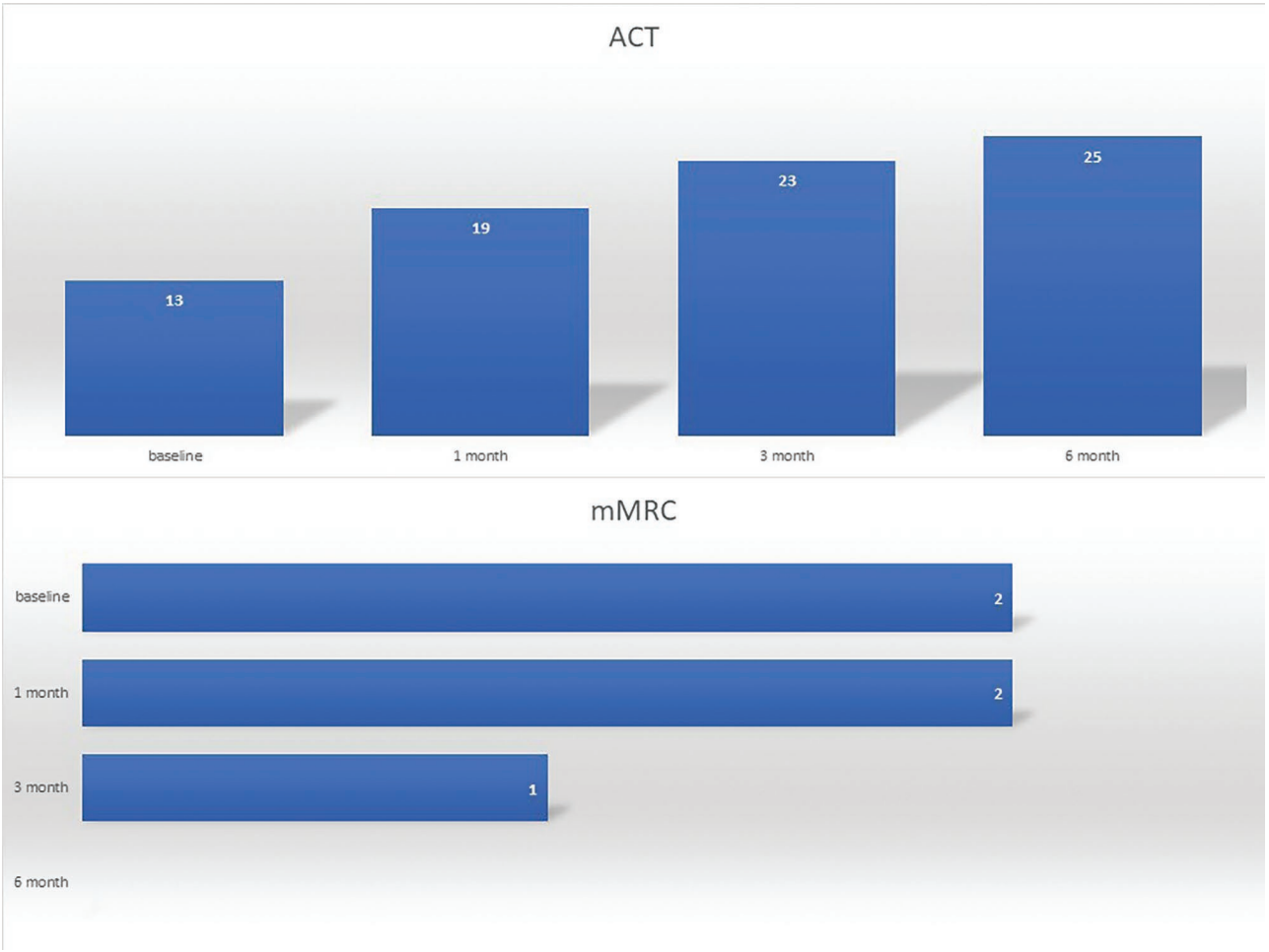
The present clinical case illustrates the efficacy of TZP in the treatment of severe allergic refractory asthma in a patient who, despite her young age, already had PAL, SAD and progressive worsening of lung function. The amelioration of symptoms, as evidenced by the absence of cough, sputum and nocturnal awakenings, along with the augmentation of the ACT score, signifies a noteworthy and expeditious enhancement in disease management. The rapid and complete improvement of the patient after the initiation of TZP suggests a complete clinical remission, enhanced by the resolution of PAL and SAD.

This decision was primarily influenced by the observation that TZP exhibited a higher degree of efficacy in comparison to the anti-IgE omalizumab as a first-line biologic treatment in young patients diagnosed with early-onset allergic asthma,[7] in the absence of elevated levels of additional T2 inflammatory biomarkers, including blood and sputum eosinophils, and FeNO.

For nearly 20 years, omalizumab has served as the gold standard and preferred treatment option for severe allergic asthma, exhibiting both efficacy and safety. Extensive research has demonstrated that omalizumab enhances asthma control and reduces the occurrence and severity of exacerbations in patients with moderate-to-severe allergic asthma. Additionally, omalizumab has been shown to decrease OCS use and healthcare utilization in these patients. This mAb has demonstrated a favourable safety profile, making it suitable for use even during pregnancy, and has exhibited sustained efficacy and safety over an extended period of treatment.[8–10] However, evidence regarding lung function is more controversial. A paucity of studies has identified a significant improvement in FEV_1 after omalizumab treatment, whilst others have demonstrated consistent improvements in respiratory function.[11–16]

Dupilumab, a fully human mAb that blocks the shared receptor component for IL-4 and IL-13, has demonstrated substantial efficacy in patients with moderate-to-severe allergic asthma characterized by type 2 inflammation.[17] By inhibiting IL-4 and IL-13 signalling, dupilumab reduces IgE synthesis, eosinophilic inflammation and airway hyper-responsiveness — key features of allergic asthma pathophysiology. A multitude of clinical trials, including the LIBERTY ASTHMA QUEST study,

Figure 2. Patient-reported outcomes over 6 months.



ACT, Asthma Control Test; mMRC, Modified British Medical Research Council scale.

as well as real-life studies, have demonstrated that dupilumab significantly reduces annual asthma exacerbation rates, improves lung function (as measured by FEV_1), and enhances asthma control in patients with elevated IgE levels and sensitization to perennial allergens.[18–21] Its therapeutic benefits are further amplified in patients with high blood eosinophil counts or elevated FeNO — biomarkers associated with type 2 inflammation.[22] Dupilumab is well tolerated and is now endorsed by international asthma guidelines as an add-on treatment for patients with severe asthma, including those with an allergic phenotype who are not adequately managed with standard therapy.[23]

The phase IV VESTIGE study demonstrated that dupilumab significantly improved outcomes in patients with uncontrolled, moderate-to-severe type 2 asthma with airway remodelling and SAD.[24] After 24 weeks, a higher proportion of patients receiving dupilumab achieved clinical remission — defined by no exacerbations, no systemic steroid use, improved lung function and better symptom control — compared with placebo (38.9% *versus* 18.9%). Dupilumab has also been shown to reduce airway inflammation (FeNO <25 ppb in 57% *versus* 11%) and improve small airway function and mucus plugging on imaging, thereby confirming its broad therapeutic effect in allergic and eosinophilic asthma phenotypes. Dupilumab is a biological agent with solid evidence of efficacy in controlling asthma, an OCS-sparing effect and improvement in respiratory function. However, in the case of our patient, it was not possible to prescribe it because the biomarkers necessary to define her eligibility were within normal limits (haematic eosinophils and FeNO below the threshold of 150 cells/mm³ and 25 ppb, respectively).

The patient exhibited not only severe allergic asthma but also a decline in respiratory function, as indicated by a decrease in FEV_1, as well as PAL and SAD. These findings led to the decision to withhold treatment with omalizumab, given the absence of evidence supporting its efficacy in addressing these critical clinical and pathophysiological respiratory aspects.

Therefore, TZP was selected, a first-in-class humanized IgG2λ mAb that targets TSLP, a pivotal epithelial 'alarmin' that plays a crucial role in the early phases of inflammatory cascades involving both type 2 and non-type 2 pathways.[25] By targeting TSLP, TZP modulates multiple downstream pathways, including those involving IL-4, IL-5, IL-13 and IgE, making it effective across a broad range of asthma phenotypes, including allergic asthma. In the phase III NAVIGATOR trial, TZP demonstrated a significant reduction in annualized asthma exacerbation rates amongst patients diagnosed with severe, uncontrolled asthma. This reduction was observed in patients with sensitization to perennial allergens and elevated serum IgE levels.[26] Subgroup analyses revealed significant benefits for patients diagnosed with allergic asthma, as evidenced by improvements in lung function, symptom control and reductions in biomarkers such as blood eosinophils, FeNO and total IgE.[27] In contrast to therapies that target a single cytokine, the upstream mechanism of TZP demonstrates broader efficacy, making it a valuable treatment option for patients with allergic asthma, particularly those who are unresponsive to anti-IgE or anti-IL-5 therapies.

In a pooled analysis of the phase IIb PATHWAY and phase III NAVIGATOR trials, TZP demonstrated a 62% reduction in the annualized asthma exacerbation rate over 52 weeks in patients with allergic asthma, a 71% reduction in those with eosinophilic asthma (≥300 cells/μL), and a 71% reduction in patients with both allergic and eosinophilic features.[28] These findings underscore the extensive anti-inflammatory action of TZP through upstream inhibition of TSLP, positioning it as a promising therapeutic option for patients with severe asthma driven by type 2 inflammation. The effectiveness of this biological agent is also attributable to its direct action on epithelial dysfunction, which is increasingly recognized as a central driver of airway remodelling and SAD in asthma.

Damage to the airway epithelium, resulting from allergens, pollutants or viral infections, disrupts barrier integrity and triggers the release of alarmins; for example, TSLP, IL-33 and IL-25 have been identified as key drivers of type 2 inflammation, leading to the activation of fibroblasts and myofibroblasts within the epithelial–mesenchymal trophic unit.[29,30] Prolonged epithelial–mesenchymal trophic unit activation has been associated with the development of subepithelial fibrosis, smooth muscle hypertrophy and goblet cell hyperplasia. These changes result in the thickening of the airway wall and the narrowing of the lumen calibre, particularly in smaller airways with a diameter of less than 2 mm.[31] These structural changes manifest clinically as SAD, which is characterized by air trapping, reduced mid expiratory flow rates and ventilation heterogeneity.[32] These characteristics correlate with symptom severity and treatment resistance in severe asthma.

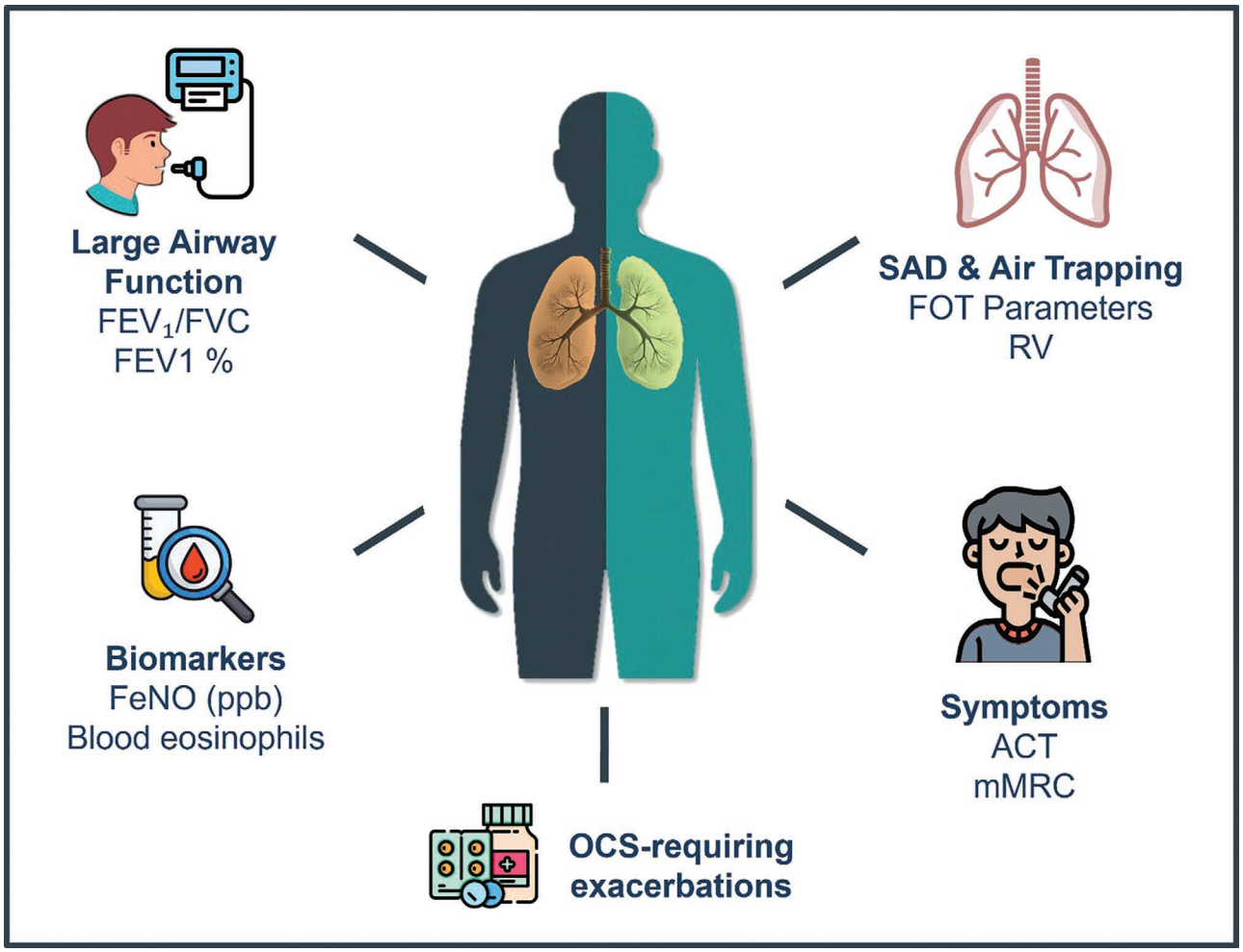
It has been demonstrated that TZP exerts an inhibitory effect on bronchial hyper-responsiveness by impeding the action of TSLP. In the phase II CASCADE trial, TZP demonstrated a significant increase in the mannitol provocation dose, resulting in a ≥15% decrease in FEV_1 relative to placebo (least-squares mean change: 197.4 mg *versus* 58.6 mg; p=0.03).[33] In an allergen challenge study, TZP inhibited both early and late asthmatic responses and preserved methacholine PC20 values relative to placebo.[34] Furthermore, the UPSTREAM trial revealed that a greater proportion of patients exhibited non-responsiveness to mannitol after 12 weeks of TZP treatment in comparison to the placebo group.[35] This finding emphasizes the impact of TZP on airway smooth muscle reactivity.

Consequently, the targeted modulation of epithelial alarmins and their associated downstream pathways holds considerable potential in the prevention of remodelling and worsening of SAD in the context of asthma. In this regard, there is already substantial and recent real-life evidence of the efficacy of TZP not only in improving asthma control but also respiratory function and SAD.[5,36] Furthermore, the presence of worse airflow obstruction and SAD but not of other type 2 biomarkers, more accurately identifies possible super-responders to TZP.[5,37] These parameters should therefore be taken into greater consideration, as was the case with the patient in question, for whom these previous findings were confirmed.

In support of these statements, the ATLANTIS study identified SAD in 91% of patients with asthma, irrespective of disease severity, and associated this finding with poorer overall asthma control in this subgroup.[38] A *post hoc* analysis further revealed that 33% of participants exhibited PAL, which was strongly associated with increased exacerbation rates and progression to severe asthma.[39] Moreover, PAL severity correlated with the degree of SAD, suggesting a close interplay between these two pathophysiological features. Notably, both SAD and PAL were observed not only in patients with severe asthma but also in those with milder cases, where PAL was found to be associated with eosinophilic inflammation and an elevated risk of exacerbations. Collectively, these findings suggest that SAD and PAL function as autonomous predictors of subsequent exacerbations and suboptimal asthma control, thereby emphasizing the necessity to incorporate both parameters into routine clinical assessments.

In the domain of personalized medicine, the inflammatory phenotype and the presence of specific respiratory function alterations, such as SAD and PAL, are significant treatable traits in severe asthma.[40] These traits require an

Figure 3. Multidimensional response to tezepelumab.



This figure illustrates the broad benefits of tezepelumab across clinical outcomes, lung function, and laboratory parameters.
ACT, Asthma Control Test; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FOT, forced oscillation technique; FVC, forced vital capacity; mMRC, Modified British Medical Research Council scale; OCS, oral corticosteroid; RV, residual volume; SAD, small airway dysfunction.

integrated diagnostic approach to ensure precise definition and selection of the most suitable therapeutic options. This approach deviates from the conventional paradigm, such as the early-onset severe allergic asthma/omalizumab combination, which requires re-evaluation in light of the latest evidence and the current scenario.

Conclusion

This clinical case demonstrates that TZP represents a valid therapeutic option for early-onset severe allergic refractory asthma, leading to a significant improvement not only in clinical terms but also in the respiratory function of the large and small airways, measured with a holistic multidimensional assessment using inflammatory biomarkers, spirometry and FOT (Figure 3). The present study hypothesizes that the selection of TZP over omalizumab resulted in the observed outcomes, which likely would not have been as apparent with the anti-IgE biologic. It is also important to note that the commencement of high-dose single, extrafine-inhaler triple therapy occurred during the therapeutic step-up phase. However, this approach did not yield any clinical or functional respiratory benefits, contrasting with the observations that emerged subsequent to the implementation of TZP, despite the existence of positive data in the literature on this latter.[41] The diagnostic and therapeutic management of patients with severe asthma cannot be disentangled from a comprehensive assessment that encompasses not only an accurate evaluation of inflammatory biomarkers but also the study of respiratory function that transcends spirometry, which remains very important but is no longer sufficient, particularly in more complex cases.

Contributions: FM design designed, wrote, and approved the manuscript. The others authors contributed equally to the preparation of this manuscript. All authors contributed equally to the preparation of this manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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