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Four-month real-life response to Tezepelumab in patients with multi-failure to other biologics

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Abstract
To evaluate the response to Tezepelumab in real clinical practice, we performed an analysis of the clinical, functional, and inflammatory characteristics of 13 patients with severe asthma after completing four doses of Tezepelumab was performed. When comparing clinical parameters such as asthma control test (ACT), FENO value, exacerbations in the last 4 months, blood eosinophils and FEV1%, before receiving Tezepelumab and after four doses of Tezepelumab, statistically significant differences were found in ACT levels (p=0.0072), exacerbations (p=0.018) and FEV1% (p=0.012) before and after four doses of Tezepelumab. No statistically significant differences were found in blood eosinophils or FeNO levels, however, a mean reduction of 102.5±231 cells/mm^3 and 14.67±30 ppb, respectively, was observed. Patients with a high T2 profile had significantly higher baseline FeNO (p<0.05), but no significant improvement in lung function or asthma control was observed in this group. Patients with Aspirin-exacerbated respiratory disease (AERD) were evaluated separately. There was no difference in ACT, FeNO, or lung function changes after tezepelumab use compared to patients without AERD (all p>0.05). We demonstrated, in a multicenter study, the clinical improvement associated with tezepelumab treatment in severe uncontrolled asthma, independent of inflammatory biomarkers, eosinophilic profile, or previous biological failure.

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Introduction

Severe asthma accounts for about 3–10% of asthmatic patients[1], leading to a higher disease burden, increased social and health costs, and diminished patient quality of life.[2] Improved management of asthma through effective treatment could potentially reduce the costs associated with this disease.

Tezepelumab was developed to inhibit or reduce immune responses from the innate immune system; it targets thymic stromal lymphopoietin (TSLP), a molecule released by the epithelium in response to aggressive agents such as allergens, viruses, and pollutants, which exerts pleiotropic effects on various blood populations.[3] Clinical trials have demonstrated that Tezepelumab can reduce exacerbations and improve lung function, asthma control, and quality of life in both severe uncontrolled T2 and non-T2 asthma.[4] However, there is limited evidence regarding its effectiveness in real-life settings.

To evaluate the response to tezepelumab in real clinical practice, we conducted an analysis of the clinical, functional, and inflammatory characteristics of 13 patients with severe asthma from the Allergy Department of Fundación Jimenez Diaz Hospital in Madrid and Complexo Hospitalario Universitario A Coruña in A Coruña, after they completed four doses of Tezepelumab. The study included 7 men and 6 women, with a mean age of 51.9 years (SD 14.97), all of whom provided signed informed consent. A T2 high inflammatory profile was diagnosed if peripheral blood eosinophils (PBE) were ≥150 cells/µl, FeNO was ≥20 ppb, or if the patient was undergoing anti-IL5 biological treatment.[5] The ethics committees of both participating hospitals approved this study. Quantitative variables were described as means and standard deviations (SD), while qualitative variables were represented by absolute and relative frequencies (N, %). Inter-group comparisons were performed using the chi-square test or Fisher's exact test for qualitative variables, and ANOVA or Kruskal-Wallis test for quantitative variables. A p-value of less than 0.05 was considered significant. Statistical calculations and graphs were performed using GraphPad Instat 9 (GraphPad Software Inc, San Diego, CA).

All patients included in the study exhibited poor asthma control, with a mean Asthma Control Test (ACT) score of 10.8 ± 3.8. They also demonstrated compromised lung function, with a mean FEV1 of 68% ± 18 and an FEV1/FVC ratio of 61 ± 15.7. Additionally, each patient had experienced at least one severe asthma exacerbation in the previous year, with a mean of 1.9 ± 2.07 exacerbations. Regarding comorbidities, 46% of the patients had clinically relevant allergies (mean total IgE 296 ± 218), 31% had Aspirin-Exacerbated Respiratory Disease (AERD), and 15% had chronic rhinosinusitis with nasal polyps (CRSwNP). In terms of inflammatory data, the mean peripheral blood eosinophils (PBE) count was 187 cells/µL ± 190, and mean FENO levels were 37 ± 42 ppb. A T2 high profile was present in 84.6% (11) of patients, with 63.6% (7) having PBE ≥ 150 cells/µL and 36.4% (4) undergoing anti-IL5 treatment. Notably, 69% (9) of the patients had previously undergone at least one biologic treatment without achieving a satisfactory clinical response; among these, 78% (7) had tried at least two biologics, and 44% (4) had attempted three or more biologics without success.

When comparing clinical parameters such as ACT, FENO values, exacerbations over the last four months, PBE, and FEV1% before and after four doses of Tezepelumab, statistically significant differences were observed in ACT levels ($p = 0.0072$), exacerbations ($p = 0.018$), and FEV1% ($p = 0.012$). No statistically significant differences were found in PBE or FeNO levels; however, a mean reduction of 102.5 ± 231 cells/µL and 14.67 ± 30 ppb was noted, respectively (Figure 1). No relevant side effects were reported. Focusing on patients who had not responded to at least two previous biologic treatments, statistically significant differences were observed in FEV1% ($p = 0.039$), with a mean improvement of 9.6 ± 7.1%. Although there was a trend towards significance in ACT ($p = 0.06$), no statistically significant differences were found in exacerbations or FENO values. Patients with a T2 high profile exhibited significantly higher baseline FeNO levels ($p < 0.05$), but no significant improvement in lung function or asthma control was observed in this group. AERD patients were evaluated separately, revealing no differences in ACT, FeNO, or lung function changes after Tezepelumab compared to non-AERD patients (all $p > 0.05$).

Early response to Tezepelumab has been shown in short patient series[6–8] within six months of treatment, demonstrating improvements in asthma control (ACT increases ranging from 2 to 8 points[6,7]), exacerbation rates (0 exacerbations in 66-100% of patients[7,8]), and lung function with FEV1 increases of 290-[7,8]570 ml. These findings align with our results, which indicate the clinical efficacy of Tezepelumab, independent of inflammatory biomarkers, eosinophilic profiles, or prior biological failures. In our study, we observed an improvement in asthma control (an ACT increase of 5 points), a reduction in exacerbation rates (-4%), and a slight increase in FEV1 (+5%). Additionally, our study and others noted a non-significant decrease in FeNO and PBE levels.[6]

Up to 14% of severe asthma patients on biological treatment experience clinical failure with at least one therapy.[9] Tezepelumab has shown effectiveness even in these patients, likely due to its broad-spectrum molecular mechanisms of action,[8] which aligns with our findings. A significant proportion of our patients, around 69%, had previously switched to a second biological treatment due to clinical inefficacy before starting Tezepelumab. In both our study and others[6,8], patients with prior failures to any biological treatments demonstrated improvements in exacerbation rates and lung function following Tezepelumab treatment, despite potential airway remodeling and the duration of exacerbations and disease.

The Tezepelumab RCT[5] demonstrated greater improvements in T2 high severe uncontrolled asthma, particularly among patients with nasal polyps, which contrasts with findings from other real-life studies[6] and our own. This is evidenced by the lack of clinical differences observed in patients with AERD and those with the T2 high asthma phenotype.

No adverse events or clinical failures were reported in our population following Tezepelumab administration, which contrasts with the 17% switch rate observed in the German study.[6]

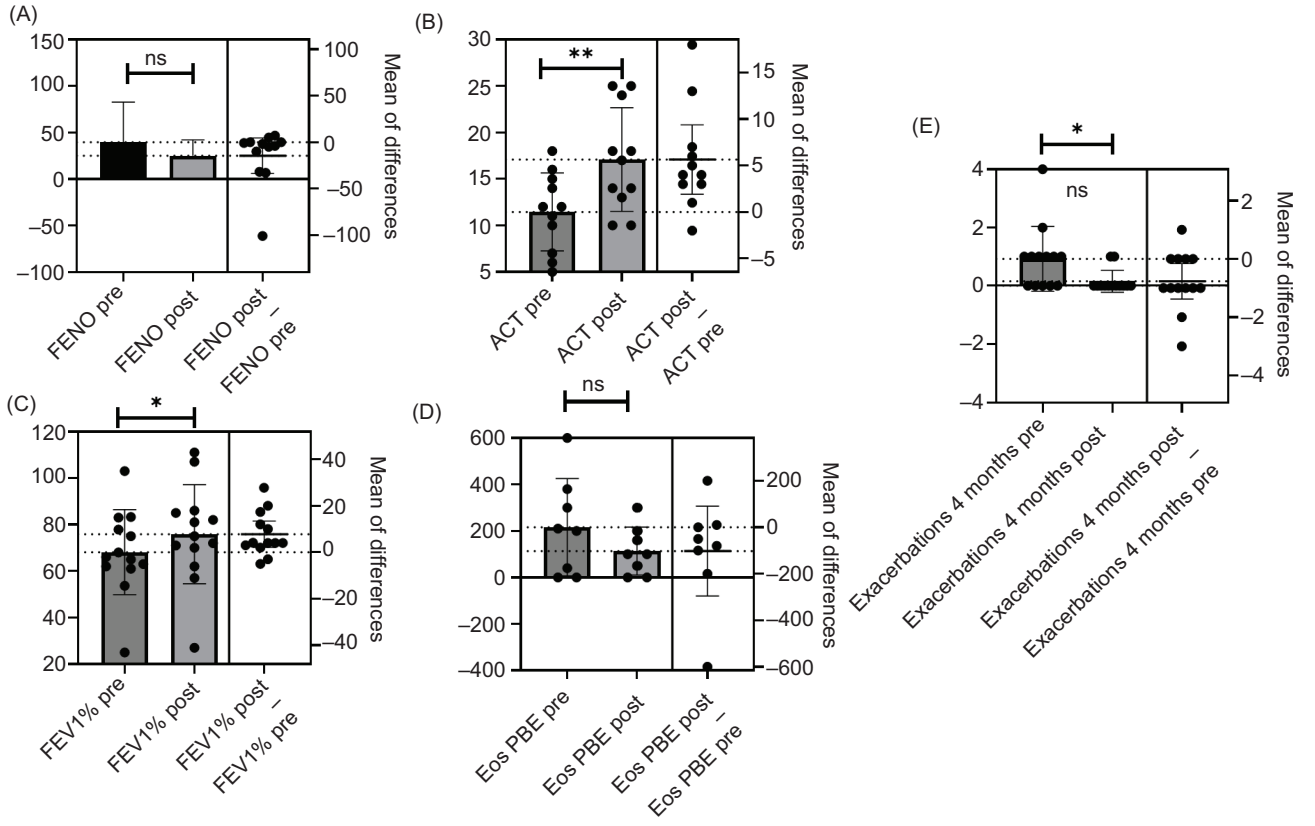

Figure 1 Changes in baseline levels after 4 doses of Tezepelumab: (A) FENO, (B) ACT scores, (C) FEV1%, (D) Peripheral blood eosinophils count, and (E) Severe exacerbations in the last 4 months. *p > 0.05, **p < 0.01, ns: not significant.

In conclusion, our multicentric study demonstrates the clinical improvement associated with Tezepelumab treatment in severe uncontrolled asthma, independent of inflammatory biomarkers, eosinophilic profiles, or prior biological failures. Further research is needed to assess the clinical effects of Tezepelumab in larger real-life cohorts.

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