Journal of Asthma and Allergy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy of Benralizumab in Reducing FeNO in Severe Eosinophilic Asthma: The Role of CRSwNP

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Background: Benralizumab, targeting the IL-5 receptor, reduces exacerbations and improves lung function in severe eosinophilic asthma. Data on its effect on fractional exhaled nitric oxide (FeNO), particularly in patients with and without chronic rhinosinusitis with nasal polyps (CRSwNP), are limited.

Objective: This study evaluates benralizumab's impact on FeNO levels in severe eosinophilic asthma, focusing on the presence of CRSwNP.

Methods: We retrospectively analyzed 43 patients with severe eosinophilic asthma treated with benralizumab. Patients were divided into CRSwNP (N=13) and non-CRSwNP (N=30) groups. Baseline characteristics, FeNO levels, FEV1, FVC, ACT scores, exacerbations, and oral corticosteroid (OCS) use were recorded at baseline, 3, 6, and 12 months.

Results: At baseline, FeNO levels were higher in CRSwNP patients than in non-CRSwNP (82.80 ppb vs 41.86 ppb, P = 0.019). Over 12 months, FeNO significantly decreased in CRSwNP patients (−29.69 ppb, P = 0.036) and remained stable in non-CRSwNP patients (+3.55 ppb, P = 0.036). Significant improvements were observed in FEV1 (0.59L vs 0.38L, P = 0.017) and ACT scores (6.46 vs 4.01, P < 0.001) in CRSwNP patients. Both groups showed a notable reduction in exacerbations, which was more pronounced in CRSwNP patients (−3.12 vs −3.60, P < 0.001). OCS withdrawal was achieved in 53.8% of CRSwNP patients and 43.3% of non-CRSwNP patients.

Conclusion: Benralizumab reduces FeNO levels and improves clinical outcomes in severe eosinophilic asthma, especially in patients with CRSwNP. Monitoring FeNO levels provides additional insights into treatment response, highlighting its potential role as a marker in specific patient subgroups.

Keywords: severe eosinophilic asthma, benralizumab, FeNO, CRSwNP, asthma management, biologic therapy, eosinophilic inflammation

Introduction

Severe asthma is a chronic disease that significantly affects patients' quality of life and represents a considerable challenge in terms of clinical management and disease burden globally.[1] Despite the availability of conventional treatments, a significant proportion of patients with severe asthma continue to experience persistent symptoms and frequent exacerbations.[2] This highlights the need for more effective and targeted therapies to control the underlying inflammation and improve clinical outcomes.[3]

Benralizumab is a monoclonal antibody directed against the alpha subunit of the interleukin-5 receptor (IL-5Rα) on eosinophils, leading to their apoptosis and elimination.[4] This treatment has proven effective in reducing exacerbations and improving lung function in patients with severe eosinophilic asthma. However, there are limited data on the effect of benralizumab on fractional exhaled nitric oxide (FeNO), a biomarker that reflects eosinophilic airway inflammation.[5,6]

FeNO is an important biomarker associated with a higher disease burden and has proven useful in guiding treatment with corticosteroids and biologic agents.[7] The reduction of FeNO with biologic treatments can provide additional insight into the

Received: 15 November 2024
Accepted: 5 May 2025
Published: 26 May 2025

treatment's efficacy in modulating eosinophilic inflammation. Although some studies have suggested that benralizumab can reduce FeNO levels, these data are limited, and further research is needed to better understand this relationship.[5]

The objective of our study was to evaluate the impact of benralizumab treatment on FeNO levels in patients with severe eosinophilic asthma, with a particular focus on the presence or absence of chronic rhinosinusitis with nasal polyps (CRSwNP). By exploring this relationship, we aim to provide a deeper understanding of how targeted therapy modulates eosinophilic inflammation in different clinical contexts and its potential to inform personalized treatment strategies.

Methods

Study Design and Population

From January 2020 to December 2023, 43 patients with severe eosinophilic asthma (SEA) treated with benralizumab at the Marqués de Valdecilla Hospital, Santander, Spain, were retrospectively included. Inclusion criteria: Adult patients (≥18 years) with a confirmed diagnosis of severe eosinophilic asthma according to GINA 2023 guidelines, with or without CRSwNP, treated with benralizumab for at least 12 months and available follow-up data. Exclusion criteria: Patients with missing follow-up data.

Patient characteristics, clinical parameters, number of exacerbations, and maintenance OCS doses were evaluated. Patients were classified into two groups: those with CRSwNP and those without CRSwNP.

Diagnosis of CRSwNP: All patients were evaluated by the Otorhinolaryngology Department, where the presence of nasal polyps was diagnosed using nasal endoscopy and confirmed by computed tomography (CT) when necessary.

Patients received benralizumab at a dose of 30 mg administered subcutaneously. The dosing regimen followed the approved schedule of an initial dose at baseline, followed by additional doses at week 4, week 8, and every 8 weeks thereafter, as per the product label.

FeNO Measurement

Fractional exhaled nitric oxide (FeNO) levels were measured at our center following the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[8] The NIOX VERO® device (Circassia, UK) was used for all measurements. Patients exhaled at a constant flow rate of 50 mL/s for 10 seconds. Measurements were performed prior to spirometry, with the patient seated and having refrained from eating, exercising, or smoking for at least one hour before the test.

Parameters and Assessments

The following data were collected at baseline, 3, 6, and 12 months: FeNO (Fractional Exhaled Nitric Oxide): Measured in ppb, ACT (Asthma Control Test): Scores to assess asthma control, FEV1 (Forced Expiratory Volume in 1 second): Measured in milliliters (mL), FVC (Forced Vital Capacity): Measured in milliliters (mL), Eosinophils: Peripheral blood eosinophil count, Exacerbations: Number of annual exacerbations, Hospital Admissions: Number of hospital admissions due to asthma exacerbations.

Exacerbations were defined as worsening of asthma symptoms requiring systemic corticosteroids for at least three days, an unscheduled medical visit, an emergency department visit, or hospitalization.

The Asthma Control Test (ACT) is a validated questionnaire used to assess asthma control, with scores ranging from 5 (poor control) to 25 (complete control). A score ≤19 indicates uncontrolled asthma, 20–24 indicates partially controlled asthma, and a score of 25 reflects fully controlled asthma.[9]

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the baseline characteristics of the study population, including means and standard deviations for continuous variables and frequencies and percentages for categorical variables.

Paired t-tests were employed to compare the differences in FeNO, ACT, FEV1, FVC, exacerbations, and OCS doses between baseline and follow-up visits at 3, 6, and 12 months within each group (with and without CRSwNP). Independent t-tests were used to assess differences between the two groups at each time point. The normality of the data was assessed using the Shapiro–Wilk test.

The chi-square test was utilized to compare categorical variables, such as the proportion of patients achieving the minimal clinically important difference (MCID) in ACT scores and the proportion of patients discontinuing OCS. For non-normally distributed variables, the Mann–Whitney *U*-test was applied.

Given the relatively small sample size, more complex statistical models, such as propensity score matching or additional multivariable adjustments, were considered but not applied due to limited statistical power. However, a mixed-effects linear model was conducted to evaluate the longitudinal changes in FeNO, FEV1, FVC, and ACT over time, accounting for repeated measures within subjects. The model included fixed effects for time, group (CRSwNP vs non-CRSwNP), and the interaction between time and group.

A p-value < 0.05 was considered statistically significant for all analyses. No corrections for multiple comparisons were performed, as the study was exploratory in nature and aimed at generating hypotheses rather than drawing definitive conclusions.

Ethical Procedures

This study complies with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of Cantabria, Spain, and informed consent was obtained from all participants prior to inclusion in the study.

Results

Of the 43 patients, 13 (30.2%) had CRSwNP and 30 (69.8%) did not have CRSwNP. A total of 41.9% of the patients were OCS therapy at the time of inclusion. The average OCS dose was 10.09 mg (range: 1–30 mg, SD: 7.94). (Table 1).

At 12 months, more patients in the SEA with CRSwNP group achieved the minimal clinically important difference (MCID) in the Asthma Control Test (ACT) (increase of ≥3 points from baseline) (84.6% vs 66.7%, P = 0.042) (Figure 1). Statistically significant differences were recorded in favor of the SEA with CRSwNP group in pre-bronchodilator FEV1 (L) (increase of 0.59L [0.35–0.83] vs 0.38L [0.12–0.64], P = 0.017) (Figure 2) and in pre-bronchodilator FVC (L) (increase of 0.40L [0.18–0.62] vs 0.43L [0.15–0.71], P = 0.034) (Table 2).

Table 1 Baseline Characteristics of Patients with and Without CRSwNP

Characteristic	with CRSwNP (N=10)	without CRSwNP (N=21)	p-value
Age (years)	62.54 ± 13.12	64.87 ± 9.98	0.490
Sex (% female)	53.85	66.67	
BMI	28.50 ± 4.87	26.54 ± 4.97	0.297
Years with Asthma	21.31 ± 13.28	19.47 ± 12.93	0.733
Smoking (% non-smokers)	61.54	63.33	
Previous Biologic (% no)	69.23	66.67	
OCS (% yes)	46.15	40.00	
OCS Dose (mg)	8.46 ± 8.52	10.85 ± 7.65	0.411
Eosinophils (cells/μL) Baseline	629.54 ± 353.17	531.17 ± 288.97	0.324
Baseline FeNO (ppb)	82.80 ± 61.20	41.86 ± 31.67	0.019
Baseline ACT	15.08 ± 4.49	16.07 ± 4.52	0.650
Baseline FEV1 (mL)	2022.50 ± 593.12	1806.82 ± 703.46	0.465
Baseline FVC (mL)	3272.50 ± 1156.86	2861.36 ± 822.49	0.255

Abbreviations: CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; FeNO, Fractional Exhaled Nitric Oxide; OCS, Oral Corticosteroids; ACT, Asthma Control Test; FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity.

https://doi.org/10.2147/JAA.S506835

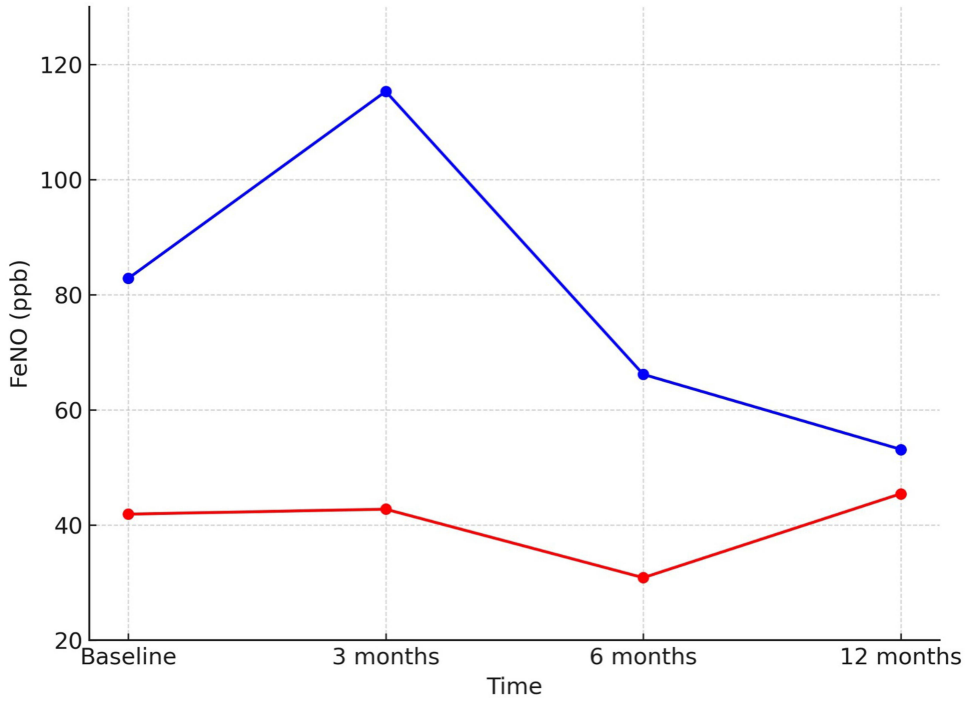

Figure 1 FeNO evolution between patients with and without CRSwNP over 12 months of benralizumab treatment. Blue line: Patients with CRSwNP. Red line: Patients without CRSwNP.

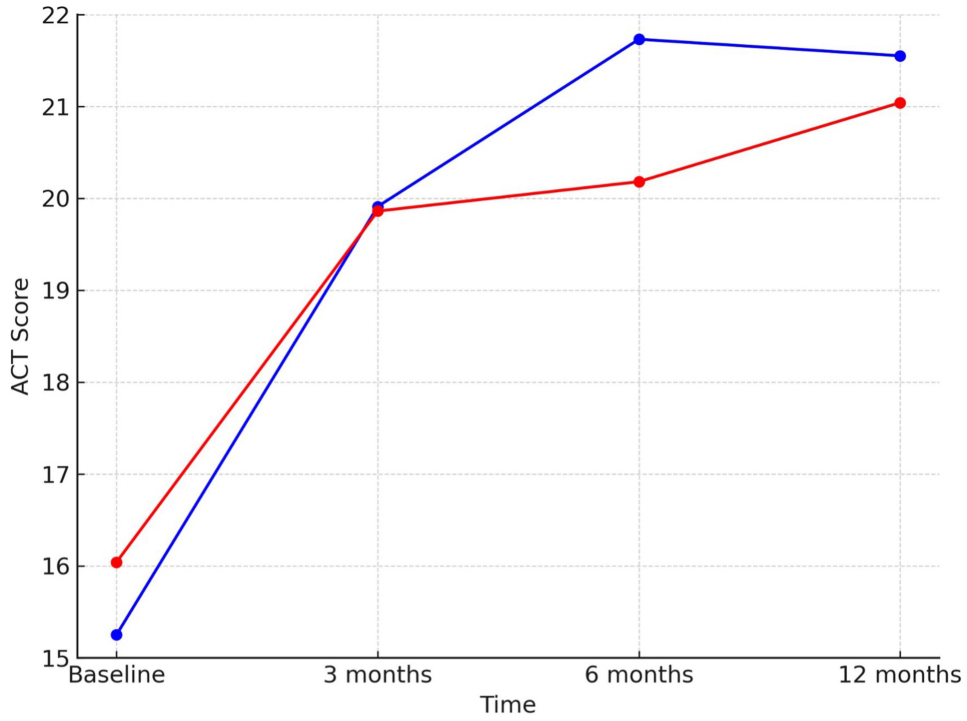

Figure 2 ACT score evolution between patients with and without CRSwNP over 12 months of benralizumab treatment. Blue line: Patients with CRSwNP. Red line: Patients without CRSwNP.

Table 2 Comparison of Clinical Outcomes, Including FeNO Levels, Asthma Control (ACT Score), Lung Function (FEV1), and Exacerbations, Across Patients with and Without CRSwNP Over 12 months of Benralizumab Treatment

Variable	CRSwNP (Baseline)	CRSwNP (3 Months)	CRSwNP (6 Months)	CRSwNP (12 Months)	No CRSwNP (Baseline)	No CRSwNP (3 Months)	No CRSwNP (6 Months)	No CRSwNP (12 Months)	p-value for Change
FeNO (ppb)	82.80 ± 61.20	115.29 ± 103.21	66.14 ± 85.90	53.11 ± 57.31	41.86 ± 31.67	42.72 ± 41.80	30.82 ± 19.67	45.41 ± 48.62	
FeNO Change Baseline-12 months (ppb)				−29.69 ± 57.31				+3.55 ± 48.62	0.036
ACT Score	15.08 ± 4.49	19.91 ± 3.08	21.73 ± 2.45	21.55 ± 2.62	16.07 ± 4.52	19.86 ± 3.35	20.18 ± 4.26	20.04 ± 4.37	
ACT Change Baseline-12 months				+6.46 ± 2.62				+4.01 ± 4.37	< 0.001
FEV1 (mL)	2022.50 ± 593.12	2391.25 ± 481.92	2310.00 ± 510.43	2616.00 ± 450.12	1806.82 ± 703.46	1928.64 ± 532.11	2161.43 ± 492.65	2182.17 ± 501.22	
FEV1 Change Baseline-12 months (mL)				+593.50 ± 222.17				+375.35 ± 189.65	0.018
FVC (mL)	3272.50 ± 1156.86	3150.00 ± 1025.67	3341.43 ± 1112.23	3392.86 ± 987.10	2861.36 ± 822.49	3391.43 ± 801.11	3435.91 ± 890.76	3419.57 ± 910.22	
FVC Change Baseline-12 months (mL)				+464.01				+446.24	0.034
Exacerbations	3.67 ± 2.27			0.55 ± 0.69	3.83 ± 2.81			0.23 ± 0.53	
Exacerbations Change Baseline-12 months				−3.12±0.69				−3.60±0.53	0.002
Withdrawal of OCS (n, %)				7 (53.8%)				13 (43.3%)	

Notes: Values are presented as mean ± standard deviation (SD), unless otherwise stated. Values in parentheses represent the number of patients and the corresponding percentage. Exacerbations are expressed as the mean number of events per patient (± standard deviation) during the study period.

Abbreviations: CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; FeNO, Fractional Exhaled Nitric Oxide; OCS, Oral Corticosteroids; ACT, Asthma Control Test; FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity.

At the end of the study period, a numerical difference was observed in favor of patients with SEA and CRSwNP who were able to discontinue OCS (7 of 13 [53.8%] vs 13 of 30 [43.3%], P = 0.217) and remained free of exacerbations despite OCS discontinuation (6 of 13 [46.2%] vs 11 of 30 [36.7%], P = 0.161). However, these findings were not statistically significant.

Evolution of FeNO in Patients with and without CRSwNP (Figure 3)

FeNO levels were significantly higher in patients with chronic rhinosinusitis with CRSwNP at baseline (82.80 ppb vs 41.86 ppb, p = 0.019). A notable decrease in FeNO was observed in the CRSwNP group at 6 and 12 months, while in the non-CRSwNP group, FeNO levels showed a slight increase over time (decrease of 29.69 ppb [16.66–42.72] in CRSwNP vs increase of 3.55 ppb [1.23–5.87] in non-CRSwNP, P = 0.036). The difference in FeNO levels at 12 months between patients with and without CRSwNP was not statistically significant (p = 0.322).

Withdrawal of OCS and CRSwNP

OCS withdrawal was achieved in 53.8% of patients with CRSwNP and in 43.3% of patients without CRSwNP. The OCS dose in patients with CRSwNP decreased from an average of 9.5 mg (range: 0–30 mg) to 3.8 mg (range: 0–10 mg) at 12 months, while in patients without CRSwNP the dose decreased from an average of 10.6 mg (range: 0–30 mg) to 3.1 mg (range: 0–10 mg) (Figure 4).

Discussion

In this study, we observed significant differences in the evolution of key clinical parameters, including FeNO, FEV1, and ACT, between patients with asthma and concomitant CRSwNP and those without CRSwNP. Specifically, FeNO levels showed a greater decrease in the CRSwNP group compared to the non-CRSwNP group over the 12-month follow-up period (p = 0.036). Additionally, improvements in FEV1 and ACT were also more pronounced in patients with CRSwNP (p = 0.018 and p < 0.001, respectively). These findings suggest that the presence of CRSwNP may influence the response to benralizumab, particularly in terms of airway inflammation and lung function improvement.

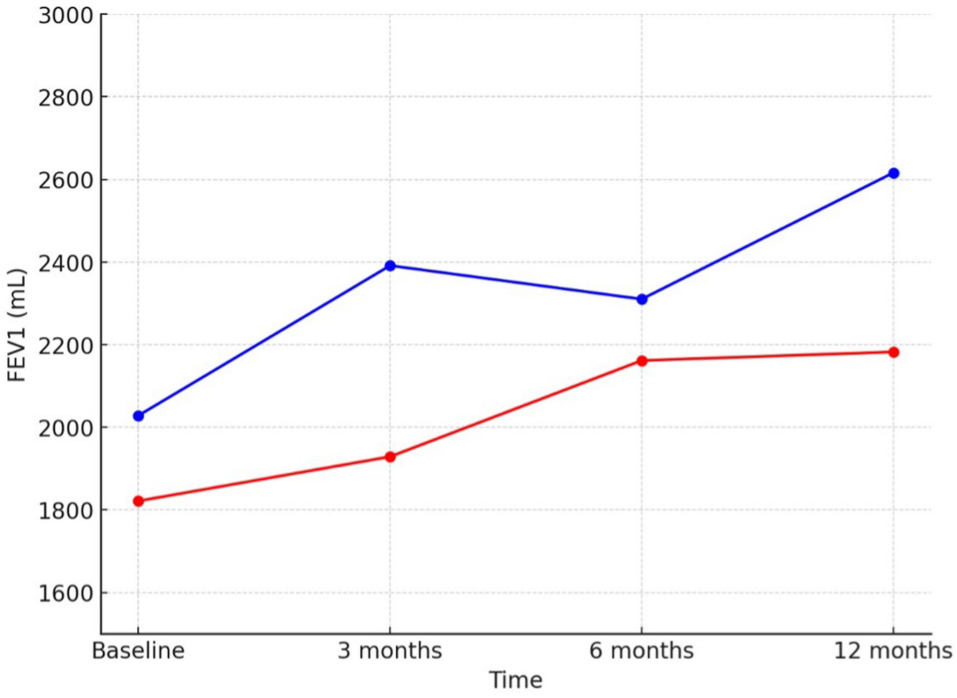

Figure 3 FEV1 evolution between patients with and without CRSwNP over 12 months of benralizumab treatment. Blue line: Patients with CRSwNP. Red line: Patients without CRSwNP.

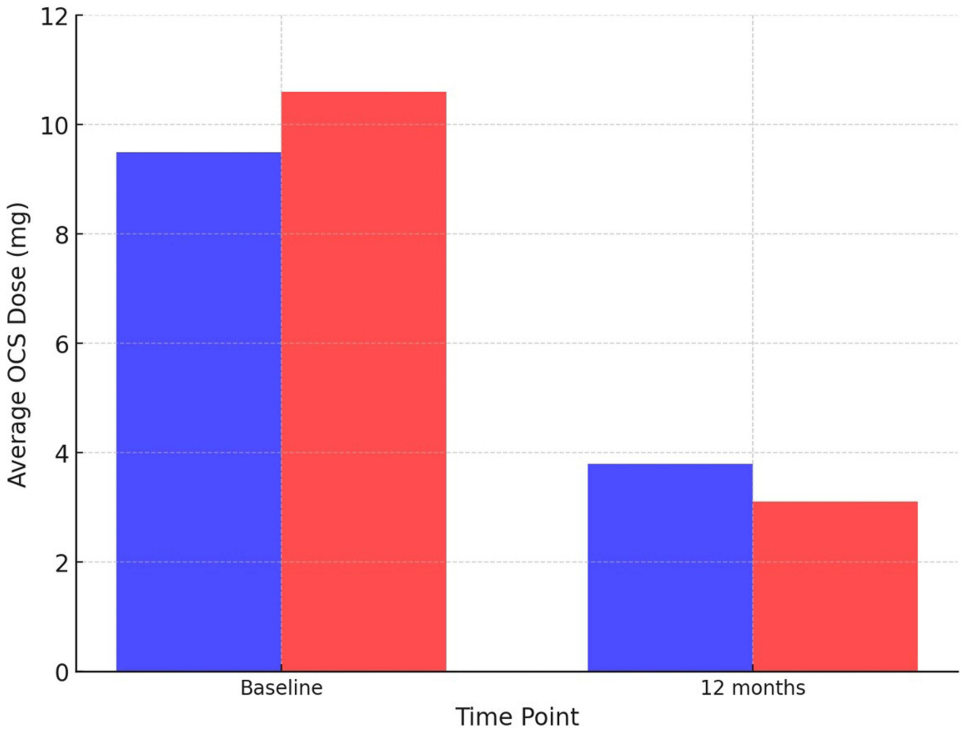

Figure 4 Changes in exacerbation rates between patients with and without CRSwNP before and after 12 months of benralizumab treatment. Bars represent the mean exacerbation rate per patient before and after treatment.

The review by Pianigiani et al[5] highlights that while FeNO levels may not significantly decrease in the initial months of treatment with biologics such as benralizumab, most studies report a significant reduction after at least four months of treatment. This confirms that nitric oxide production is not primarily dependent on the IL-5 pathway, which is consistent with our findings of an initial increase in FeNO at three months and a significant decrease at six months in patients with CRSwNP treated with benralizumab.

However, a recent study by Pianigiani et al[10] offers a new perspective by demonstrating that FeNO values can decrease as early as one month after treatment with benralizumab (and dupilumab), and that this early reduction is associated with a higher likelihood of achieving clinical remission at 12 months. This finding suggests that the response to biologics may vary significantly among individuals and highlights the need for continuous and personalized monitoring. Additionally, the study by Pelaia et al[11] clarifies that these modifications are not dependent on atopic status, reinforcing the relevance of considering CRSwNP comorbidity rather than atopy in FeNO monitoring.

Previous studies have shown that patients with CRSwNP present elevated levels of various cytokines, including IL-13, IL-5, and CCL26, in nasal mucus.[12] These cytokines play a crucial role in eosinophilic inflammation and asthma pathogenesis. IL-13, in particular, is an immunoregulatory and effector cytokine known to increase FeNO (fractional exhaled nitric oxide) levels by inducing nitric oxide production in airway epithelial cells.

Eosinophils, when activated, can produce IL-13.[13] This process is induced by cytokines such as GM-CSF and IL-5, which are essential for eosinophil differentiation and activation. In inflammatory conditions, such as in patients with CRSwNP, eosinophils infiltrated in nasal tissues produce IL-13, contributing to elevated FeNO levels.[14] This mechanism could explain why patients with CRSwNP have significantly higher FeNO levels compared to those without this condition.

Benralizumab is a monoclonal antibody targeting the IL-5 receptor (IL-5Rα) on eosinophils, leading to their apoptosis and elimination. By depleting eosinophils, benralizumab could reduce the source of IL-13 in patients with severe eosinophilic asthma.[15] This is consistent with our findings that FeNO levels significantly decrease in these patients after benralizumab treatment. The reduction in FeNO in patients with CRSwNP treated with benralizumab can be explained by decreased IL-13 production. The depletion of eosinophils in nasal mucosa, mediated by benralizumab,

https://doi.org/10.2147/JAA.S506835

could result in lower IL-13 production, which in turn would reduce nitric oxide synthase induction in airway epithelial cells. This mechanism is not observed in patients without CRSwNP, where IL-13 production and, therefore, FeNO levels remain more stable.

The study by Mukherjee et al[15] provides additional evidence that benralizumab reduces IL-13 levels in the sputum of patients with severe asthma who were not adequately responding to other anti-IL-5 treatments (mepolizumab and reslizumab). In this study, IL-13 levels were higher when patients were treated with mepolizumab and reslizumab compared to after completing benralizumab treatment, suggesting greater efficacy of benralizumab in reducing IL-13 and thus eosinophilic airway inflammation.

This transient increase at three months could be attributed to the initial persistence of airway eosinophilic inflammation despite benralizumab therapy. Given that FeNO production is driven by IL-13 rather than IL-5, a delayed suppression of nitric oxide synthesis may occur as eosinophilic depletion progresses over time. Additionally, a temporary adjustment period in airway remodeling and inflammatory signaling may explain this biphasic response, which is not observed in patients without CRSwNP.

In real-world clinical practice, measuring FeNO during the follow-up of patients with severe eosinophilic asthma treated with benralizumab is uncommon.[16] A prominent example is the XALOC-1 study, the largest real-world program to date with over 1000 patients with severe eosinophilic asthma (SEA).[17] This study provides valuable data on the efficacy and safety of benralizumab in a broad patient population but has a significant limitation in FeNO monitoring. The XALOC-1 study does not include FeNO measurement in all patients at baseline, let alone during the 48-week follow-up. This lack of FeNO data limits the ability to fully assess eosinophilic inflammation and treatment response in patients with severe eosinophilic asthma and CRSwNP. The absence of FeNO monitoring in the XALOC-1 study underscores the need for studies that include this measurement as a key biomarker.

This study has several strengths, including the comprehensive evaluation of all patients by the Otolaryngology department for accurate characterization of CRSwNP. This detailed assessment allows for a more holistic approach in managing severe eosinophilic asthma. Additionally, meticulous monitoring of FeNO levels and other clinical parameters provides a complete view of eosinophilic inflammation and response to benralizumab treatment.

However, the study has several limitations that should be considered. The small sample size, particularly in the CRSwNP subgroup, limits the generalizability of the findings, and the retrospective nature of the study introduces potential selection and information biases, which prevent the establishment of definitive causal relationships. Additionally, the lack of a control group and the absence of a prospective design limit our ability to make stronger inferences about the observed effects of benralizumab on FeNO levels and other clinical outcomes.

Variability in FeNO measurement due to individual factors and technical differences may also affect the accuracy of the results. Baseline FeNO levels were notably higher in patients with CRSwNP compared to those without this comorbidity. This difference may partially explain the greater reduction in FeNO observed in the CRSwNP group, as there was more "room for improvement" in patients with initially elevated levels. We acknowledge this as a potential confounding factor, which underscores the need for careful interpretation of our results. Including a non-CRSwNP control group with similar baseline FeNO levels would have allowed for a more direct assessment of benralizumab's impact on FeNO independent of baseline differences. Future studies should consider this approach to better isolate the specific effects of benralizumab in different patient subgroups.

Although we reported lung function (FEV1 and FVC) in absolute values, using z-scores could have provided a more standardized comparison before and after benralizumab therapy, accounting for age, sex, height, and ethnicity. Z-scores are recommended by the Global Lung Initiative (GLI) and allow for comparisons relative to predicted normal values across different populations. Future studies should consider incorporating z-scores to enhance the interpretability of lung function changes in this patient population.

Although paired and independent t-tests were used to evaluate changes within and between groups, we acknowledge that baseline differences in FeNO, particularly in the CRSwNP group, may have confounded the observed effects of benralizumab. Mixed-effects modeling could provide further insight by accounting for within-subject variance over time. Additionally, more robust statistical techniques, such as propensity score matching or multivariable adjustments, could

mitigate baseline imbalances and better isolate the effects of benralizumab on FeNO changes. Future studies should consider these methods to enhance the accuracy of longitudinal analyses in similar clinical contexts.

The use of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) was not specifically evaluated in this study, and potential differences in dosing between groups were not accounted for. However, in routine clinical practice, the presence of CRSwNP does not typically influence ICS/LABA dosing adjustments. Therefore, both groups are expected to have received similar ICS/LABA treatment regimens.

An additional limitation is that adherence to inhaled corticosteroids (ICS) was not assessed during the follow-up period. This limits our ability to determine whether either group reduced or discontinued ICS use after achieving better asthma control with benralizumab. Recent studies have shown that reducing ICS in patients receiving benralizumab can lead to increased FeNO levels, which could have influenced the current results. This aspect should be considered in future studies to evaluate the combined effect of benralizumab and ICS adherence on FeNO evolution and asthma control.

While the 12-month follow-up provides valuable information, a longer follow-up would offer a more comprehensive view of the sustained effects of benralizumab. Future studies should consider a prospective design with a control group and a larger sample size to address these limitations, as this would provide a more robust assessment of the effects of benralizumab on FeNO and asthma-related outcomes.

This study did not include an evaluation of nasal polyp burden or sinonasal symptoms. Neither the Sino-Nasal Outcome Test-22 (SNOT-22) nor an endoscopic nasal assessment was performed to measure changes in nasal polyps. Therefore, the potential impact of benralizumab on CRSwNP severity and symptomatology could not be determined.

Despite these limitations, our study makes important contributions to the understanding of severe eosinophilic asthma management and highlights the potential role of FeNO monitoring, especially in patients with CRSwNP. The inclusion of otolaryngological evaluation and detailed clinical data collection reinforces the relevance of these findings for clinical practice.

Conclusion

This study provides evidence of the relevance of measuring FeNO during the follow-up of patients with severe eosinophilic asthma treated with benralizumab, particularly in those with CRSwNP. Our findings suggest that FeNO monitoring can serve as a useful marker for assessing airway inflammation and treatment response in this subgroup.

The inclusion of FeNO data offers a deeper understanding of the underlying mechanisms and therapeutic response, specifically reflecting nasal inflammation in patients with CRSwNP. These results highlight the potential value of FeNO measurement in future studies focusing on patients with severe eosinophilic asthma and comorbidities such as CRSwNP, contributing to a more tailored approach for these specific cases.

Abbreviations

ACT, Asthma Control Test; BMI, Body Mass Index; CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; FeNO, Fractional Exhaled Nitric Oxide; FEV1, Forced Expiratory Volume in One Second; FVC, Forced Vital Capacity; IL-5Rα, Interleukin-5 Receptor Alpha; MCID, Minimal Clinically Important Difference; OCS, (maintenance) Oral Corticosteroids; SEA, Severe Eosinophilic Asthma.

Disclosure

The authors report no conflicts of interest in this work.

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