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Benralizumab in severe eosinophilic asthma: A real-world, single-center, observational study from Mexico

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Abstract
Introduction: Urbanization has increased the prevalence of asthma in lower- and middle-income countries. Severe eosinophilic asthma (SEA), a subtype of asthma, can be refractory to standard therapy. Biologics such as benralizumab target interleukin-5 and have demonstrated effectiveness in managing SEA. There exists no real-world evidence on the effectiveness of benralizumab in Mexico. Therefore, this study presents data on the role of benralizumab in managing SEA in Mexican patients.
Objective: The effectiveness of benralizumab on the quality of life (QoL), asthma control, lung function, symptoms of asthma, and benralizumab's safety profile were assessed.
Methods: The study sample comprised 10 patients with SEA treated with a subcutaneous (SC) administration of benralizumab 30 mg once in 4 weeks for the first three doses followed by a dose every 8 weeks for 2 years. Laboratory tests, resting spirometry, and skin prick tests were conducted. Levels of fractional exhaled nitric oxide (FeNO) were evaluated, when possible, with the intent to phenotype asthma, as T2 high or non-T2, before starting benralizumab therapy. The Asthma Quality of Life Questionnaire (AQLQ), Asthma Control Questionnaire (ACQ), and Asthma Control Test (ACT) were administered to evaluate the effectiveness of benralizumab on asthma control and QoL.
Results: All patients showed significant symptom control, QoL, and lung function over 2 years. Mild adverse effects, such as headache and arthralgia, were observed.
Conclusion: Benralizumab appears to be a promising agent in controlling SEA. This study has focused on measuring tangible outcomes, such as a reduction in symptoms, a reduction in exacerbation, and an improvement in QoL. Thus, benralizumab may constitute an important addition to the arsenal of medications against SEA.

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Introduction

Globally, 4.4% of the population is affected by asthma.[1] Asthma was responsible for 21,600,000 disability-adjusted life years (DALYs), which is 20.8% of the DALYs (total) from chronic respiratory diseases.[2] Mexican epidemiologic data indicate that the prevalence of asthma in adults is 3.3% in males and 6.2% in females. In children and adolescents, the reported prevalence is 12.7%.[3] Affordability and accessibility of medications for managing asthma is a challenge in low- and middle-income countries (LMICs). Currently, the Asthma Drug Facility (an initiative to improve purchasing standards in LMICs) has been abandoned and no new initiative has been set.[4] In addition, the prevalence of asthma in LMICs has shown an upward trend in the last 4 decades due to a complex interplay of social, environmental, and biological factors related to urbanization.[5] Asthma has become a considerable burden on healthcare services in LMICs. The difficulties faced in this regard include no continuity of care, treatment not in line with the current guidelines, and an increasing number of individuals visiting emergency departments. A substantial loss in productivity has also been seen due to the poor management of asthma. A study evaluating how suboptimal treatment affected work-related absenteeism found that when assessed for 4 weeks, a minimum of a day's work each week was missed by 47% of patients receiving an inadequate dose of inhaled corticosteroids (ICSs) and by 18% of those receiving an adequate dose.[4] A systematic review on the affordability, cost, and availability of essential medications in asthma management in LMICs emphasized a need to increase the availability of effective treatments to improve the physical, social, and economic well-being of individuals affected by asthma.[6]

In severe eosinophilic asthma (SEA), a subtype of severe asthma, patients are often refractory to standard-of-care therapy. Interleukin (IL)-5 is an important target for biologic therapies because it participates in eosinophil differentiation, maturation, recruitment, and activation.[7] Many patients with severe asthma benefit from steroidsparing biologics that target IL-5 (reslizumab and mepolizumab) or the IL-5 receptor α (IL5RA) (benralizumab). Every patient responds uniquely to these ant-iIL5 biologics. Superresponders achieve complete asthma control, partialresponders demonstrate residual disease, and nonresponders either do not respond or worsen clinically.[8]

Benralizumab, a monoclonal antibody directed against IL5RA, rapidly and nearly completely depletes eosinophils via enhanced antibody-dependent, cell-mediated cytotoxicity. Multiple doses of subcutaneous (SC) benralizumab in mild-to-severe asthma significantly reduce eosinophil count in the airway wall and sputum.[9] The MELTEMI analysis reported a reduced exacerbation rate and blood eosinophil count in individuals with SEA on benralizumab during a 5-year follow-up.[10]

Real-world studies assessing the safety and efficacy of benralizumab are limited, and there are none from Mexico. To contribute to the pool of real-world evidence and enhance the literature on the effectiveness of this medication in the Mexican population, this study presents data from ten patients with SEA managed with benralizumab as an add-on maintenance therapy.

Methods

This observational, prospective, single-center study included patients with SEA who visited the outpatient asthma clinic at the National Institute of Respiratory Diseases, Ismael Cosio Villegas (Mexico City), Mexico. A diagnosis of severe asthma was arrived at based on the European Respiratory Society/American Thoracic Society guidelines criteria.[11] A skin prick test (SPT) was conducted to complete the diagnostic workup and identify allergens indicating severe asthma. The SPT assesses atopic sensitization with cutoffs such as serum immunoglobulin E (IgE) >0.35 KU/L or a wheal of mean diameter ≥3 mm following exposure to extract from a whole allergen.[12] All patients provided informed consent to participate in the current study. Patients lost to follow-up were excluded. Patients were excluded if they discontinued treatment with anti-IL-5 for over 3 months or had received anti-IL-5 therapy before. Patients were administered benralizumab according to the local label (SC benralizumab 30 mg every 4 weeks for the first three doses, followed by a dose every 8 weeks). Demographic, phenotypic (allergic/nonallergic), clinical, functional history, comorbidity, and treatment data were recorded for all patients, and patients were followed up from the baseline visit up to 12 visits, ranging over 2 years.

For descriptive statistics, if the variables had a normal distribution, the mean and standard deviation were used, and if they did not have a normal distribution, the median and range values were used. For qualitative variables, percentages were used. For inferential statistics according to the behavior of the variables, the Student's or the Wilcoxon signed-rank test was used as suitable. A P value < 0.05 was considered statistically significant.

Evaluation of patients

Patients were evaluated at baseline and subsequently, every 6–8 weeks for 2 years, comprising 12 visits in total. At baseline, a detailed history was recorded for each patient, regarding asthma control, pharmacotherapy, smoking, sensitizations, exacerbations, and complications caused by systemic steroid therapy. At baseline and during subsequent visits, each patient underwent laboratory tests (including total American Thoracic Society/European Respiratory Society, 2005 criteria),[13] and SPTs; levels of fractional exhaled nitric oxide (FeNO) were determined when possible to allow for phenotyping of asthma before initiating benralizumab therapy. Due to the emergence of the coronavirus disease 19 pandemic and subsequent disruptions to supply chains, there has been a shortage of the Niox Vero® sensor starting from visit 8 onwards, therefore FeNO values could not be determined at later visits. At baseline and during every follow-up visit, all patients completed the Asthma Quality of Life Questionnaire (AQLQ), the Asthma Control Questionnaire (ACQ), and the Asthma Control Test (ACT). The AQLQ used was the validated version for Mexico (www.qoltech.co.uk), and the data were filled out in printed questionnaires. At baseline, details of steroid use (both short- and long-term use of inhalational and systemic steroids) were recorded. The occurrence of adverse events was recorded during the overall study period.[14–16]

Results

The study included 10 women with SEA. The average age of these women was 50.5 years (standard deviation = 14.4, ranging from 20 to 65 years), with an average body mass index of 29.1. Of the 10 participants, 6 had prior smoking history, and 4 had no history of smoking. One patient had a positive SPT, eight had atopy, and five had comorbidities. Nasal polyposis was present in five patients, whereas seven had a history of rhinitis, and two had atopic eczema (Table 1).

All patients with SEA had a significant improvement in all parameters with long-term (2-year) benralizumab treatment. Absolute eosinophil counts decreased by 0.4 ± 0.2×10^9/L from baseline to visit 12 (Table 2). The comparison between values at baseline and the 12th visit for forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) is shown in Figure 1. The improvements in FEV1, FEV1/FVC, and FeNO from baseline to the 1st, 4th, 8th, and 12th weeks are shown in Table 2.

A statistically significant (P = 0.002) improvement in the patient's perception of quality of life (QoL) was observed, as evidenced by the increase in the AQLQ score from baseline to visit 12. A statistically significant improvement was seen in the ACT (P = 0.03) and ACQ (P = 0.002) scores from baseline to the 12th week (Table 3).

A few adverse events consistent with the known safety profile of benralizumab, such as headache or arthralgia, were reported, and all events were mild. The number of patients who encountered each adverse event is given in Table 4.

The comparison of scores for ACT and ACQ between the baseline and the 12th visit is represented in Figure 2.

Table 1 Baseline characteristics.

Characteristic	Baseline values n = 10
Age in years (mean ± SD)	50.5 ± 14.4
Female	10
Male	0
Height in cm (mean ± SD)	154.7 ± 7.0
Weight in kg (mean ± SD)	69.7 ± 13.4
BMI (mean ± SD)	29.1 ± 4.9
Duration of asthma in months (mean ± SD)	178 ± 119.5
Exacerbations in the last 12 months (mean ± SD)	0.7 ± 1.2
IgE (IU/mL) (median)	109
Comorbidities (n [%])	
Rhinitis	7 (70)
Nasal polyposis	5 (50)
Atopic eczema	2 (20)
Long-term use of oral corticosteroids	4 (40)
ICS/LABA	10 (100)

BMI: Body mass index; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; LABA: Long acting β agonist; SD: Standard deviation.

The comparison of AQLQ from baseline to visit 12 is represented in Figure 3.

Discussion

In this real-world, single-center study from Mexico, all patients with SEA demonstrated a favorable response to long-term treatment (2 years) with benralizumab. Mexico is a middle-income country with a large segment of its population living in urban regions. The prevalence of asthma in Mexico is increasing while patients continue to be underdiagnosed and poorly controlled.[17] The Global Initiative for Asthma 2022 report recommends that severe asthma refractory to treatment with ICS (high dose) and long-acting ß-agonists should be treated with a biologic as an add-on maintenance therapy.[17,18] Benralizumab has demonstrated improved asthma control and steroid-sparing effect.[19] Oral corticosteroid (OCS) use has significant adverse effects, such as increased susceptibility to infections, osteoporosis, hypertension, diabetes, weight gain, cataracts, and psychiatric disorders, which in turn increases the need for healthcare resources and expenses.[19,20] In comparison, treatment with benralizumab has shown fewer adverse effects.[19,20]

In this study, all 10 patients experienced a marked decrease in daily symptoms and activity limitation following treatment with benralizumab, as demonstrated by an improvement in the ACQ and ACT scores. A retrospective, observational, real-world study observed a significant improvement in the ACQ score (P < 0.0001) and respiratory function (P = 0.0006), which has been demonstrated by an increase of 21.3% in the average prebronchodilator FEV1 from baseline.[20] A multicenter, cross-sectional study on patients with refractory SEA reported improved lung function and asthma control following a year of treatment with benralizumab.[21]

The patients in this study reported a statistically significant improvement in the AQLQ scores, indicating an improvement in the patient's QoL. Regarding AQLQ, improvements were noted in all four health domains studied: activity limitation, symptom perception, environmental stimulation, and emotional function, with a statistically significant improvement in the overall AQLQ score from baseline. A previous study has emphasized that respiratory symptoms affecting QoL were associated with greater severity of depression in patients with asthma.[22] Additionally, increased feelings of depression and anxiety linked to severe asthma, in turn, impaired the QoL.[23]

Levels of FeNO accurately predict eosinophilic airway inflammation.[24] In this study, FeNO was used for the phenotyping of asthma before the initiation of benralizumab therapy. Due to the unavailability of the sensor, FeNO could not be measured after visit 8; however, this did not affect the evaluation of the results of the study as FeNO was used only to categorize asthma as T2 high or non-T2. Treatment response was ascertained using FEV1 and FEV1/FVC values and the AQLQ, ACT, and ACQ scores. Benralizumab is known for its ability to rapidly deplete eosinophils in the blood due to the mechanism of action and design of the monoclonal antibody.[25] In this study, it was found that benralizumab significantly reduced blood eosinophils in patients with SEA and decreased airflow obstruction in parallel. In the

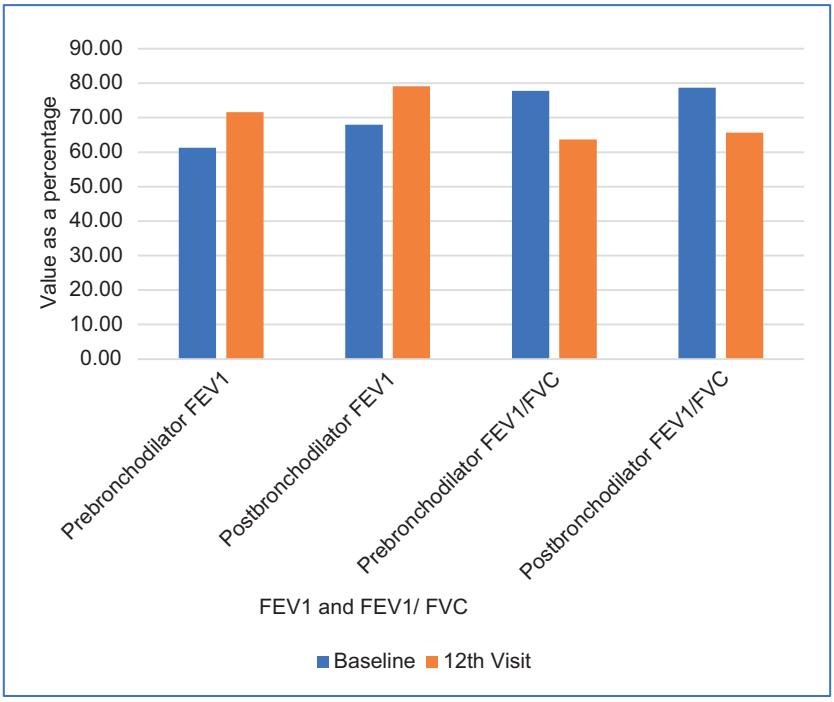

Figure 1 Comparison of FEV1(%) and FEV1/FVC (%) between baseline and Visit 12.

Table 2 Parameters assessed at baseline,1st, 4th, 8th, and 12th visits.

Parameter measured	Baseline	1st visit	4th visit	8th visit	12th visit
White blood cell count (×10^9/L) (mean ± SD)	8.8 ± 4.2	8.1 ± 2.1	9.3 ± 4.8	-	7.8 ± 0.8
Eosinophil (%) (mean ± SD)	5.9 ± 3.5	-	-	-	0.7 ± 1.5
Absolute eosinophil count (×10^9/L) (mean ± SD)	0.5 ± 0.3	-	-	-	0.1 ± 0.1
Daytime symptoms greater than twice a week.n (%)	3 (30)	3 (30)	1 (10)	0 (0)	2 (20)
Any nocturnal awakening due to asthma. n (%)	1 (10)	0 (0)	1 (10)	1 (10)	1 (10)
Reliever needed for symptoms greater than twice a week. n (%)	3 (30)	2 (20)	0 (0)	0 (0)	1 (10)
Activity limitation due to asthma. n(%)	4 (40)	2 (20)	1 (10)	1 (10)	2 (20)
GINA asthma control					
Well controlled n(%)	4 (40)	7 (70)	5 (50)	6 (60)	5 (50)
Partly controlled n(%)	4 (40)	2 (20)	2 (20)	1 (10)	1 (10)
Uncontrolled n(%)	1 (10)	1 (10)	0 (0)	0 (0)	1 (10)
Spirometry parameters					
Prebronchodilator FEV1/FVC(mean ± SD)	77.8 ± 16.4	79.4 ± 10.1	83.9 ± 12.1	63.3 ± 10.4	63.7 ± 7.1
Prebronchodilator FEV1 (%) (mean ± SD)	61.3 ± 12.7	71.6 ± 11.5	77.9 ± 12.5	69.9 ± 9.6	71.6 ± 10.2
Prebronchodilator FEV1 (L) (mean ± SD)	1.6 ± 0.8	1.7 ± 0.7	1.7 ± 0.8	1.7 ± 0.5	1.9 ± 0.6
Postbronchodilator FEV1/FVC (mean ± SD)	78.7 ± 16.8	81.7 ± 14.0	88.6 ± 14.1	73.9 ± 14.9	65.7 ± 7.7
Postbronchodilator FEV1 (%) (mean ± SD)	68.0 ± 15.1	77.6 ± 15.3	86.6 ± 15.1	76.7 ± 14.1	79.1 ± 9.6
Postbronchodilator FEV1 (L) (mean ± SD)	1.7 ± 0.9	1.8 ± 0.8	2.0 ± 1.1	1.8 ± 0.4	1.9 ± 0.5
FeNO (mean ± SD)	29.9 ± 20.2	61.7 ± 47.2	32.4 ± 19.4	NR	NR

FeNO: Fractional exhaled nitric oxide; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GINA: Global Initiative for Asthma; NR: Not recorded.

Table 3 Comparison of various rating scales at the 1st, 4th, 8th, and 12th visits.

Type of rating scale	Baseline	1st visit	4th visit	8th visit	12th visit	Comparison between baseline and the 12th visit (P)
ACT (score) (mean ± SD)	19.9 ± 7.6	20.4 ± 4.8	21.7 ± 4.0	23.0 ± 2.8	22.0 ± 3.7	0.0313*
ACQ (score) (mean ± SD)	1.6 ± 1.1	1.6 ± 1.0	1.0 ± 0.4	0.8 ± 0.5	0.9 ± 0.5	0.002*
AQLQ (symptoms) (mean ± SD)	63.4 ± 26.3	68.6 ± 17.4	77.1 ± 5.9	78.4 ± 7.4	7 ± 8.4	0.0078*
AQLQ (activity limitation) (mean ± SD)	56.0 ± 24.8	56.4 ± 19.6	60.1 ± 22.6	66.1 ± 11.6	65.1 ± 13.0	0.0078*
AQLQ (emotional function) (mean ± SD)	16.3 ± 11.0	19.2±11.7	18.3 ± 11.2	24.4 ± 9.2	26.7 ± 9.6	0.0078*
AQLQ (environmental stimuli) (mean ± SD)	18.6 ± 9.9	18.5 ± 10.5	20.3 ± 8.6	21.1 ± 8.1	21.7 ± 6.9	0.0469*
AQLQ (total) (mean ± SD)	154.3 ± 69.1	163.0 ± 57.6	175.9 ± 43.3	190.1 ± 31.4	191.4 ± 36.8	0.002*

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire.
**P < 0.05 is considered statistically significant based on Wilcoxon signed-rank test.*

Table 4 Adverse events observed in patients on benralizumab.

SL No.	Adverse event	Number of patients (N)
1.	Headache	2
2.	Fatigue	3
3.	Diarrhea	1
4.	Arthralgia	1
5.	Odynophagia	1
6.	Fever	3
7.	Cough	2
8.	Hyaline rhinorrhea	1
9.	Nasal congestion	1
10.	Malaise	1
11.	Upper airway symptoms	1
12.	Asthma exacerbation	1

present study, the prebronchodilator FEV1 values showed an improvement by 300 ± 200 mL at Visit 12 when compared with that at the baseline. Similar results were found in another study where benralizumab, when administered for 4 weeks, reduced blood eosinophil numbers significantly by 763.4 ± 194.8 cells/μL (P < 0.0001) and improved prebronchodilator FEV1 by 446 ± 79.4 mL (P < 0.001). The study emphasized that benralizumab improves lung function by rapidly resolving bronchial eosinophilic inflammation.[26] The results of the present study with benralizumab being effective in improving lung function in SEA are in line with the results of several randomized controlled trials, such as SIROCCO and CALIMA.[15,16] The prebronchodilator FEV1 was significantly greater than that for the placebo at both 4 and 8 weeks in the SIROCCO (increase by 0.106 L at 4 weeks and 0.159 L at 8 weeks) and CALIMA trials (increase by 0.125 L at 4 weeks and 0.116 L at 8 weeks).[15,16]

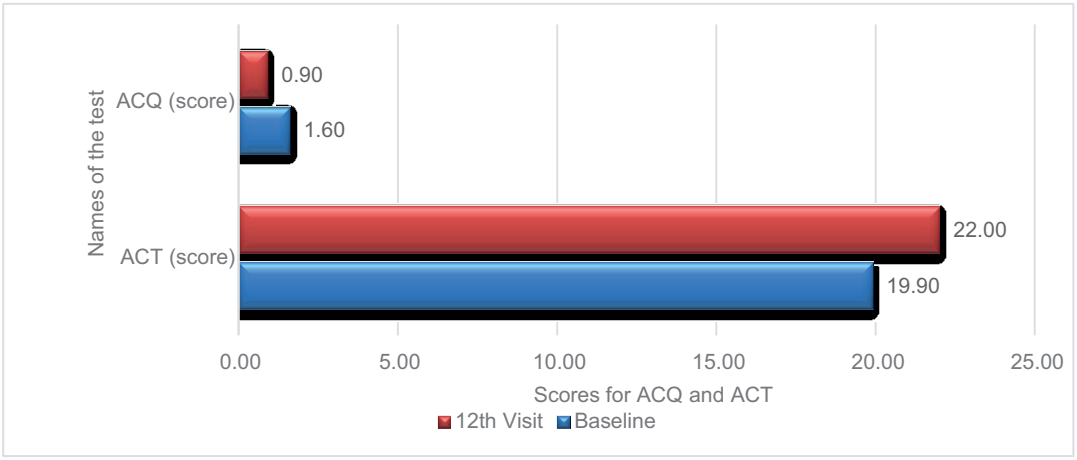

Figure 2 Comparison of the ACQ and ACT scores from baseline to Visit 12.
ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test.

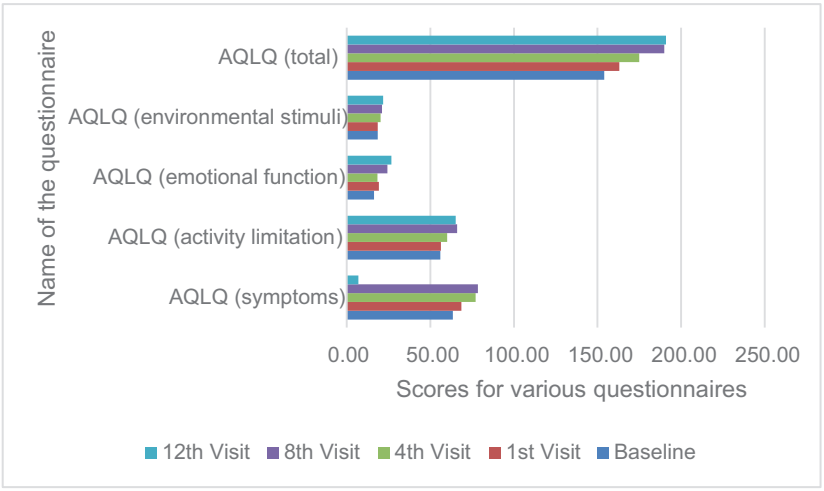

Figure 3 Comparison of the AQLQ scores from baseline to Visit 12.
AQLQ: Asthma Quality of Life Questionnaire.

The substudy data from the ANDHI NP analysis demonstrated that individuals with SEA and nasal polyps showed improvement in the symptoms of rhinosinusitis and nasal polyps with benralizumab.[27] Chronic rhinosinusitis with nasal polyps shows similarities to eosinophilic asthma, such as an association with sensitivity to aspirin and atopy and an eosinophilic inflammatory pattern. Therefore, an improvement in the control of asthma in patients with nasal polyps and SEA may, in part, be attributable to simultaneous improvements in both conditions. The present study has also observed the benefit of benralizumab in SEA associated with nasal polyps. As a result, the clinician may be able to select the most appropriate biologic for patients with nasal polyps for precise and "personalized" treatment of severe asthma. Although one patient in the present study had coronavirus disease-19 pneumonia, there was no exacerbation of asthma symptoms and mechanical ventilation was not necessary. Benralizumab demonstrated adequate safety and mild adverse events among patients in this study. Reports support the use of benralizumab in the long-term treatment of patients with uncontrolled SEA and have allayed concerns regarding the immunosuppressive actions of benralizumab, thus establishing its safety profile.[28,29]

Strengths, Limitations, and Conclusion

The strength of this study is that it emphasized the advantages of biologic treatment for SEA in terms of improved QoL and symptom control. This study was limited by the number of patients enrolled, the inclusion of only women, and the failure to include different comorbidities in the study population. Furthermore, there was no placebo control group; however, the use of a placebo in a real-world setting would be unethical when a proven effective treatment is available. Even when living in a developing country, it is possible to phenotype patients properly, which is critical to ensure adequate response to new biologics. The real-world studies conducted on benralizumab have, nevertheless, reported comparable or even greater improvements in clinical parameters in SEA, over and above the pivotal study results. Biologics demonstrate variations in efficacy based on race and ethnicity; hence, real-world data on specific ethnicities are required to study the outcomes with these agents. The findings revealed that benralizumab reduced asthma attacks in patients with SEA and demonstrated significant improvement in SEA management with a reduction in OCS use and episodes of exacerbation. These findings reiterate that benralizumab can be added to the standard treatment for SEA.

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Conflict of Interest

Miguel Reyes José Luis has received speaking fees in the past 12 months from AstraZeneca, GlaxoSmithKline, and Sanofi and consulting fees from GlaxoSmithKline, and Cano Salas Maria del Carmen has received speaking and consulting fees in the past 12 months from AstraZeneca and Boehringer Ingelheim and speaking fees from GlaxoSmithKline and Sanofi.

Authors' Contributions

Miguel Reyes José Luis and Cano Salas Maria del Carmen contributed to the study concept, design, review, and approval. López Estrada Erika del Carmen, Arroyo Rojas Monserrat Arroyo, Salas Hernández Jorge, Castañeda Valdivia Mauricio, and Escobar Preciado Monserrat contributed to review and approval.

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