

Real word effectiveness of benralizumab in mexican patients with severe eosinophilic asthma: Responders and super-responders.

Efectividad real de benralizumab en pacientes mexicanos con asma eosinofílica grave: respondedores y superrespondedores.

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Abstract

OBJECTIVE: To evaluate the type and intensity of response to benralizumab and identify responders and super-responders amongst patients with severe uncontrolled eosinophilic asthma managed in Mexico.

METHODS: A multicenter study in 3 hospitals in Mexico evaluating the Asthma Control Test and Asthma Control Questionnaire (ACT) scores; mini Asthma Quality of Life Questionnaire; peripheral blood eosinophils; exhaled fraction of nitric oxide; forced expiratory volume in 1 second before and after benralizumab treatment and the number of exacerbations at 12 months.

RESULTS: The record of 28 patients with severe uncontrolled eosinophilic asthma were included. At 12-months, 82.1% were considered in asthma control, where 82% were responders and 64% classified as super-responders. 75% of patients had no exacerbations, with ACT scores improvement in 89% and 79% of patients discontinued maintenance corticosteroids. A total of 82% presented forced expiratory volume in 1 second values over 500 ml. ACT scores showed an average decrease of 1.35 points and a statistically significant decrease in serum eosinophils was observed.

CONCLUSION: This is the first study in Mexico to evaluate the subgroup of super-responders to benralizumab who had clinical, laboratory and quality of life improvements. Besides the vast majority were responders and 64% super-responders at 12-months of treatment.

KEYWORDS: Benralizumab; Asthma; Asthma Control Test and Asthma Control Questionnaire (ACT); Eosinophils; Exhaled fraction of nitric oxide; Corticosteroids; Quality life.

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Resumen

OBJETIVO: Evaluar el tipo e intensidad de respuesta a benralizumab, e identificar a los pacientes respondedores y superrespondedores con asma eosinofílica grave.

MÉTODOS: Estudio multicéntrico llevado a cabo en tres hospitales de México. Se evaluaron pacientes a través del Cuestionario de Control del Asma, mini cuestionario sobre calidad de vida en asma; además de la determinación de eosinófilos en sangre periférica, fracción exhalada de óxido nítrico, volumen de espiración forzada en 1 segundo (VEF1), antes y después de recibir tratamiento con benralizumab, y cantidad de exacerbaciones en 12 meses.

RESULTADOS: Se analizaron los expedientes de 28 pacientes con asma eosinofílica grave, mal controlada. A los 12 meses, un 82.1% de los casos se clasificó en control, donde 82% fueron respondedores y 64% superrespondedores. El 75% de los pacientes no tuvo exacerbaciones, 89% mejoraron el puntaje ACT y 79% discontinuaron el tratamiento con corticosteroides. Un 82% mostró un VEF1 mayor de 500 mL. Los puntajes de ACT demostraron una reducción promedio de 1.35 puntos y se reportó una reducción estadísticamente significativa de eosinófilos en sangre.

CONCLUSIÓN: Este es el primer estudio en México que evalúa al subgrupo de pacientes superrespondedores a benralizumab con mejoría clínica, de laboratorio y calidad de vida. La mayoría fueron respondedores y 64% superrespondedores a los 12 meses de tratamiento.

PALABRAS CLAVE: Benralizumab; Asma; Prueba de control del asma y Cuestionario de control del asma (ACT); Eosinófilos; Fracción exhalada de óxido nítrico; Corticosteroides; Calidad de vida.

BACKGROUND

Asthma is a chronic disease that affects approximately 315 million people around the world, with 3-10% of these patients suffering from a severe form of asthma.¹ In Mexico, INEGI (National Institute of Statistics and Geography) estimates that 7.8% of the population lives with asthma, where 5 to 10% of patients diagnosed with asthma classify as severe and 3.6% remains uncontrolled.^{2,3}

Severe asthma is defined as asthma that remains uncontrolled despite good adherence to treatment as at the highest steps (4-5) of treatment proposed by the Global Initiative for Asthma (GINA), which include high doses of inhaled glucocorticoids and long-acting beta-adrenergics or leukotriene modifiers with optimal treatment of any factors contributing to poor control.⁴

Patients also classify as severe when attempts at reducing treatment dosage result in loss of control.⁴ This is a heterogeneous disease that includes different phenotypes based on clinical, functional and inflammatory

parameters and currently, there are only a few biological markers available to identify each phenotype.⁵⁻⁷

The pathophysiology of severe asthma is complex, and as understanding of the disease has developed, the diagnosis and treatment options have evolved. Traditional classification has been replaced by definitions based on groups of observable clinical characteristics (phenotype) or other underlying disease mechanisms (endotype), that allows to optimize care for specific patients, classify them as candidates for specific treatments and provide prognostic implications. Additionally, the nomenclature for response to treatment has also evolved and is still recognized as heterogeneous.⁸

Eosinophilic asthma accounts for 25% of severe asthma cases,^{7,9} it is characterized by the presence of eosinophils in bronchial biopsies and sputum, despite high-dose glucocorticoid therapy, and may present with nasal polyps and chronic rhinosinusitis. Elevated IL-5 production favors eosinophilic inflammation in the absence of the classical allergy-mediated T2 mechanism.^{7,9}



The severity and burden of asthma can be predicted by the presence of an elevated blood eosinophil count, with a risk of hospitalization at least 1.3 times higher in patients with asthma and blood eosinophil counts ≥ 150 cells/ μ L versus patients below this threshold.¹⁰⁻¹³

The exhaled fraction of nitric oxide (FeNO) has an important relationship with the level of eosinophil-mediated inflammation in the airway and the level of interleukin-13, so it could represent a suitable biomarker for monitoring control in asthma.⁸

The first biologic treatment approved for commercialization by Mexico's regulatory institution, COFEPRIS ("Federal Commission for the Protection against Sanitary Risks") was the anti-IgE antibody omalizumab, reserved for patients with asthma caused by a perennial allergen, followed by the approval of mepolizumab, dupilumab, benralizumab and tezepelumab.

Mepolizumab, benralizumab and dupilumab are currently indicated for the eosinophilic phenotype of asthma, with mepolizumab targeting the Th2-pathway cytokines through IL-5, while benralizumab is focused on IL-5 receptors. Dupilumab, also indicated for eosinophilic patients, inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor, whereas tezepelumab is a human monoclonal antibody that blocks the interaction of the thymic stromal lymphopoietin (TSLP) with the heterodimeric TSLP receptor and is indicated in all cases of severe asthma.¹⁴

Benralizumab is a humanized, afucosylated, anti-eosinophil monoclonal antibody (IgG1, kappa). It binds with high affinity and specificity to the alpha subunit of the human interleukin 5 receptor (IL-5R α). This receptor is specifically expressed on the surface of eosinophils and basophils, has a high affinity for Fc γ RIII receptors on immune effector cells such as natural killer lymphocytes (NK cells), promotes eosinophil and basophil apoptosis by enhancing antibody-dependent cell-mediated cytotoxicity (ADCC), which reduces eosinophilic inflammation.¹⁵

Prognostic factors for response to biologic therapy remain a controversial subject. Furthermore, a distinction is currently being made between responders and super-responder patients.¹⁵ Aspects that can de-

fine super-responder status include: reduction in oral corticosteroid utilization, reduction or elimination of exacerbations, and subjective patient perception; an additional element is a variation in cellularity and respiratory function test results.¹⁶

The present study evaluated the type and intensity of response to treatment and identified responders and super-responders among patients with severe uncontrolled eosinophilic asthma treated with benralizumab in Mexican healthcare institutions.

METHODS

A longitudinal observational, prospective, multicenter, analytical study was conducted in Mexico with data from three hospitals: Mexico's Social Security Institute's High Specialty Medical Unit No. 1, Bajío National Medical Center Specialties Hospital; Regional General Hospital Lic. Ignacio García Tellez T-1 Mexican Social Security Institute in Mérida, Yucatán; and the Medical Specialties Unit of the Ministry of National Defense in Mexico City, with approval by the ethics and research committee granted in May 2022 and registrational approval from CONBIOETICA number 11 CEI D03 2018060.

The study included data from patients who were evaluated and managed between August 2022 (treatment start date) to September 2023 and treated with 30mg of benralizumab every 4 weeks for 3 doses and subsequently every 8 weeks up to 12 months.¹⁸

We excluded data from patients who did not meet the diagnosis of severe uncontrolled asthma, patients where a comorbidity was identified as the underlying cause for the lack of control during follow-up, and those who received treatment with a monoclonal antibody other than benralizumab.

In addition to demographic data, patient records had to include at least the pre-benralizumab and 12-month follow-up assessments and the following evaluations: a) Asthma Control Test (ACT) C, QualityMetric Incorporated and Asthma Control Questionnaire (ACQ) b) Asthma Quality of Life Questionnaire (AQLQ) mini-test score¹⁹ c) Blood eosinophils cells per microliter of blood d) exhaled fraction of nitric oxide ppb (FeNO ppb), to determine the difference before and after treatment.

Response to treatment with benralizumab was defined as: reduction of exacerbations by at least 20%, ACT score increase ≥ 3 points as cut-off point for >18 years and/or increase in $FEV_1 \geq 500$ ml in spirometry.²⁰

For the assessment of eosinophilic inflammation, we evaluated FeNO reduction compared to basal evaluation, evaluating response as a reduction $\geq 20\%$ when basal was ≥ 50 ppb, and ≥ 10 ppb when basal FeNO was <50 ppb. For peripheral blood eosinophil counts, a 50% decrease from baseline was considered as a good response to treatment.^{8,21,22}

A descriptive statistical analysis was performed using measures of central tendency and dispersion, quantitative variables were expressed as mean and standard deviation in variables with normal distribution or medians and interquartile range (25th-75th percentile) in for non-normal distribution, qualitative variables were described in frequencies and percentages. For the before and after comparison analysis, the Wilcoxon test was used on quantitative variables and the McNemar test for GINA classification steps ≤ 3 or ≥ 3 at 12 months. Responders were those who met at least 3 criteria of the international definition (2 major and 1 minor). The major criteria were: elimination of exacerbations, improvement in control questionnaires (difference in ACQ ≥ 1 point or ACT ≥ 3 points), withdrawal of maintenance oral steroid. And the minor criteria were: reduction of exacerbations by 75%, asthma well controlled by ACT or ACQ questionnaires, increase in $FEV_1 \geq 500$ ml. Super-responders were defined ad hoc as those patients who were able to stop oral corticosteroids use and presented with a 75% reduction in exacerbations, as well as disease control assessed by ACT (≥ 6 points)²³.

Microsoft Excel 2016 was used for data input, and the statistical analysis was performed using the R program. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 28 clinical records of patients with an established diagnosis of severe uncontrolled eosinophilic asthma were included. Table 1 displays the general characteristics of the sample, with a 64% ($n = 18$) of women and an average age of 52 years ($SD = 13.8$), 74 kg weight ($SD=13.8$), and a BMI of 29.9 ($SD=6.21$). For

the case of comorbidities, 75% of patients had allergic rhinitis ($n=21$), eleven patients had chronic perennial rhino conjunctivitis (CPRC; 39%). A total of 7% ($n=2$) were registered as smokers. Regarding occupation, 29% ($n = 8$) of patients reported having a paid job, 21% ($n=6$) were paid professionals, while 39% ($n = 11$) were stay-at-home spouses and 3 did not indicate an occupation. **Table 1**

All 28 patients were diagnosed with uncontrolled asthma at the start of the observation period. By the end of the 12 months of treatment, 82.1% of patients were adequately controlled (**Table 2**). Regarding improvement parameters, 75% ($n = 21$) presented a complete elimination of exacerbations, 89% ($n = 25$) showed improvement in ACT, 79% ($n = 22$) discontinued maintenance corticosteroids, 75% ($n = 21$) had a 75% reduction in exacerbations, while 82% ($n = 23$) reached good asthma control and 64% ($n = 18$) presented increased FEV_1 values over 500ml compared to baseline.

There was a statistically significant decrease in serum eosinophils, with a mean at baseline of 640 cells/ μ L compared to 98 cells/ μ L at 12 months ($p < 0.05$), rep-

Table 1. Baseline demographic and clinical characteristics.

Characteristics	
Gender n (%)	Population (n=28)
Women	18 (64.3)
Men	10 (35.7)
Age (years) mean (SD)	52.4 (13.8)
Weight (kg) mean (SD)	73.6 (13.8)
Height (m) mean (SD)	1.58 (0.10)
BMI (kg/m ²) mean (SD)	29.9 (6.2)
Comorbidities n (%)	
Allergic rhinitis n (%)	21 (75.0)
Chronic perennial rhino conjunctivitis n (%)	11 (39.3)
Aspirin-Exacerbated Respiratory Disease n (%)	7 (25.0)
Former smokers n (%)	2 (7.1)
Eosinophil count mean (SD)	640.2 (392.1)
ACT mean (SD)	9.86 (4.4)
AQLQ mean (SD)	2.95 (1.5)
ACQ mean (SD)	2.30 (1.2)

SD: Standard deviation; kg: Kilograms; m²: square meter.

representing an 85% reduction in absolute values. The change in ACT score at 12 months was roughly 10.8, [95%CI (8.91/12.73)]. **Table 3**

The mean difference in all variables excluding FeNO, were statistically significant (**Figure 1A**). The eosinophil count showed an average reduction of 542 cell/ μ L (**Figure 1B**); while FEV₁ showed an increase of 470 ml (**Figure 1C**); the number of hospitalizations was reduced by 0.43, and steroid cycles showed a reduction of 2.43 cycles. On the subject of test scores, ACT scores showed an increase of 10.8 points (**Figure 1D**); while ACQ showed an average reduction of 1.35 points (**Figure 1E**); and the mini-AQLQ presented an increase of 2 points.

Table 2. Evaluation of asthma control parameters at 12 months after the start of the treatment.

Improvement parameters	n = 28
Complete exacerbations elimination	21 (75.0%)
ACT improvement (≥ 6 points)	25 (89.3%)
Maintenance OCS interruption	22 (78.6%)
Steroid cycles interruption	22 (78.6%)
Super-responders	18 (64.3%)
75% exacerbations reduction	21 (75.0%)
Well-controlled asthma (ACT >20 points)	23 (82.1%)
FEV ₁ (Change from baseline) >500 mL	18 (64.3%)

ACT: asthma control test; OCS: oral corticosteroids; FEV₁: forced expiratory volume in 1 second.

A total of 82% (n = 23) of patients achieved disease control by the end of the follow-up period (p<0.001). The analysis based on GINA steps, showed that 86% (n = 24) of patients moved from steps 4 and 5 to step 3 at 12 months of treatment (p<0.001).

Amongst responders to benralizumab, nearly 4 out of 5 patients (78%) were able to stop oral corticosteroids use, presented with a 75% reduction of exacerbations and classified as controlled through their ACT scores.

The treatment response level analysis showed 82% of patients classified as responders and 64% would be classified as super-responders after 12 months of treatment with benralizumab (**Figure 2**).

No adverse events or treatment discontinuations were reported during the follow-up period.

Fig 2. Patients by level of response at 12-months follow-up.

DISCUSSION

The present study allowed us to confirm the effectiveness of benralizumab treatment in patients with severe eosinophilic asthma. With an 82% of responders, including a 64% of super-responders, our analysis coincides with the 63% reported by Miralles *et al*, providing further evidence on the effect of the IL-5R α -tar-

Table 3. Mean differences for clinical and quality of life variables.

Parameter	Difference Basal vs 12 m	95%CI		t	p
		Ci _{lower}	Ci _{upper}		
FeNO (ppb)	-15.1	1.2	-31.5	-1.9	0.068
Blood eosinophils (cells/ μ L)	-542.4	-390.2	-694.7	-7.3	<0.001
FEV ₁ (ml)	470.0	710	230.0	4.0	<0.001
FEV ₁ (%)	0.2	0.3	0.1	3.9	0.001
Moderate to severe exacerbations (n)	-2.6	-2.0	-3.1	-9.9	<0.001
Hospitalization (n)	-0.4	-0.1	-0.8	-2.5	0.020
Steroid cycle (n)	-2.4	-2.0	-3.0	-10.1	<0.001
ACT (points)	10.8	12.7	8.9	11.6	<0.001
ACQ (points)	-1.4	-0.6	-2.1	-3.7	0.001
Mini AQLQ (points)	2.0	3.0	1.0	4.2	<0.000

FeNO: exhaled fraction of nitric oxide; ppb= Parts per billion; cel/ μ L= Cells per microliter ml= milliliters; FEV₁: forced expiratory volume in 1 second; ACT: asthma control test; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire.

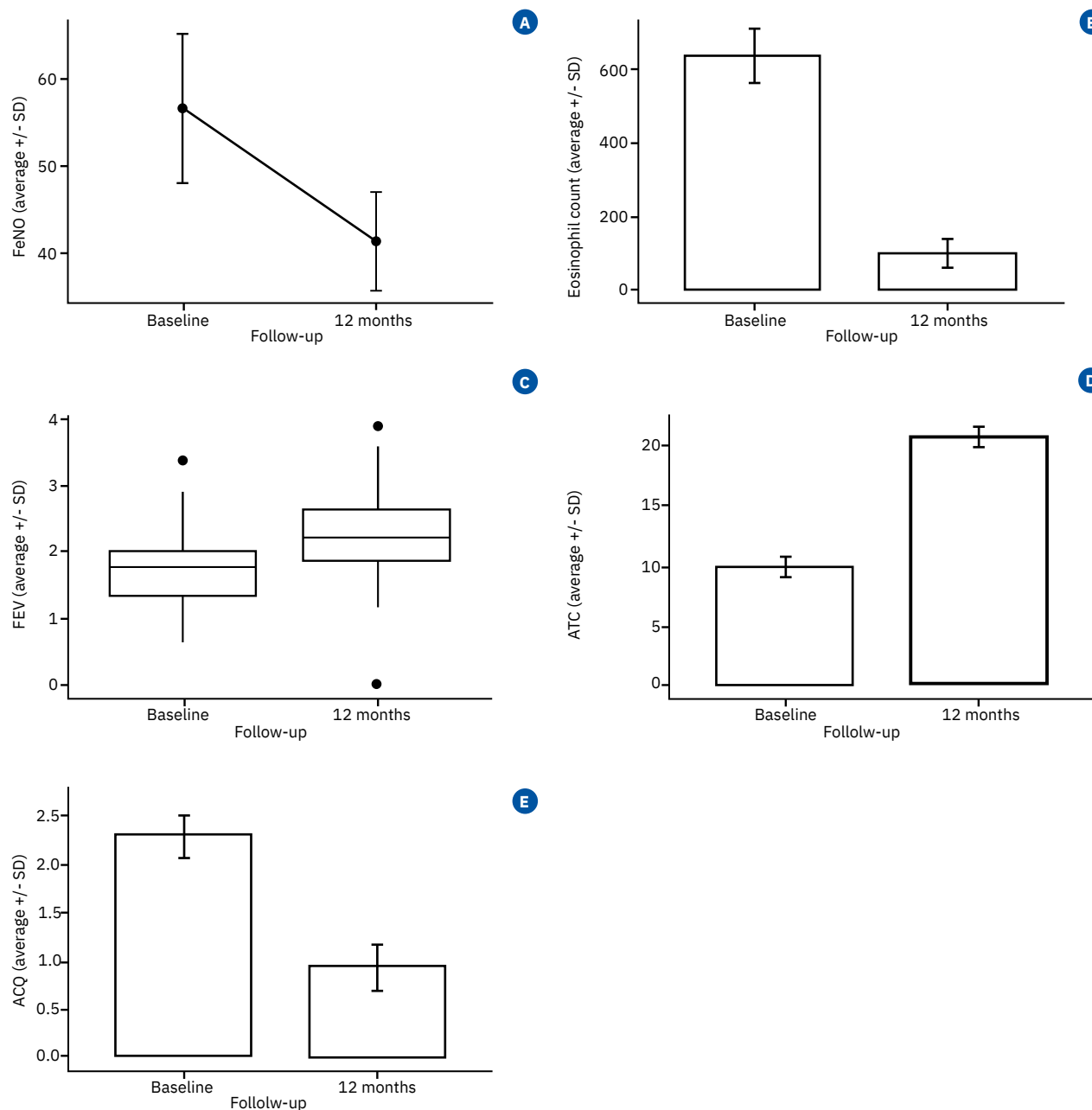


Figure 1. Distribution of FeNO values at baseline and at one-year follow-up. **A)** FeNO; **B)** Eosinophil count; **C)** FEV₁; **D)** ACT score; **E)** ACQ score.

getting mechanism of action of benralizumab on the decrease in treatment-dependent cellularity reported in the literature.²⁴

Regarding the use of maintenance oral corticosteroids (OCS), our analysis showed a 78.6% of discontinuations in agreement with real-life data studies that report percentages from 50-70%.^{7,24-26}

In this study, 36% of patients were receiving oral corticosteroids (OCS) at baseline. After 12 months, 67% discontinued treatment, highlighting the beneficial impact of biologic therapy in reducing OCS dependence and associated adverse effects.

The change in FEV₁ from baseline to 12-months follow-up in this study was 470 ml, and the percentage of

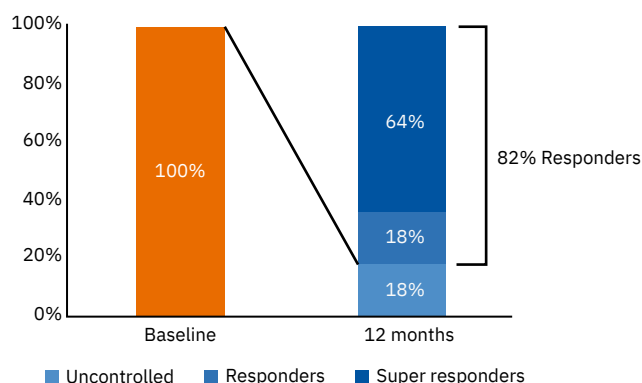


Figure 2. Patients by level of response at 12-months follow-up.

patients with an increase on FEV₁ values at 12 months >500 ml was 64%, in agreement with previous real-world studies published since 2020.^{24,25,27,28}

In our study, treatment impact on patient-reported outcome scores demonstrated an improvement in patient's perception of disease control, which can impact quality of life. ACT scores increased on average 10.8 points and 2 points for the mini AQLQ, while the ACQ showed an average decrease of 1.35 points. Patient-reported outcome evaluations are critical for shared decision making and expectation-setting between clinicians and patients.

Our analysis was performed in patients with severe eosinophilic asthma, treated with benralizumab for 12 months, to determine responders and super-responders, in which it was reported 18.9% of patients who continued with some degree of activity despite showing improvement in some of the evaluated parameters, representing a group of patients that may require further analysis. Taking this into consideration, we consider our results pertinent as they provide a detailed characterization of the effectiveness of benralizumab and different aspects of treatment response, while coinciding with previous randomized clinical trials and real-life data, in line with GINA guidelines.^{7,24-26,29-35}

Limitations of the present study include the prospective single-arm design and the small sample size. We speculate that long-term observations (24 months),

are required not only to accurately assess efficacy, but also to elucidate predictors of response in a real-life study involving patients with diverse backgrounds.

CONCLUSIONS

This is the first study in Mexico to evaluate the subgroup of super-responders to benralizumab who had clinical, laboratory and quality of life improvements.

Benralizumab significantly decreased the annual number of asthma exacerbations, oral corticosteroid usage, total eosinophil count, improved FEV₁ and patient-reported outcomes in ACT, ACQ and mini AQLQ scores. Besides the vast majority were responders and 64% super-responders at 12-months of treatment. Further studies of this type are required to confirm the effectiveness of benralizumab in Mexican population.

STATEMENTS

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Conflict of interest

The author SCR has received speaker fees from Astra-Zeneca, Sanofi, GSK and IPI ASAC Mexico. The author HGF is an analyst at HS Estudios Farmacoeconómicos S.A. de C.V. The author PCLG is an employee of Astra-Zeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Human and animal rights and informed

Consent This article does not contain any studies with human, or animal subjects performed by any of the authors.

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Permissions

All figures and tables are original.

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