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ORIGINAL RESEARCH

# Reliability, Satisfaction and Effectiveness of Benralizumab Home Self-Administration in Patients with Severe Eosinophilic Asthma in Real-World Practice: The Auto-Benra Study

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**Introduction:** The increase in drugs available for severe uncontrolled asthma and the lifestyle of these patients make it necessary to implement self-administration programs of these therapies at home. Benralizumab, a monoclonal antibody targeting IL5R, was authorized in Spain for poorly controlled severe eosinophilic asthma. The possibility of administration at home was approved in March 2020 in Spain. The aim of the Auto-Benra study was to evaluate the usability and satisfaction of the benralizumab prefilled syringe and autoinjector and assessing the effectivity of these devices in uncontrolled severe eosinophilic asthma (SEA) in home-self administration.

**Methods:** This is a retrospective, observational multicenter study uncontrolled SEA patients treated with benralizumab at least with 3 doses self-administered at home before April 30, 2021. Reliability and satisfaction with benralizumab at home were evaluated with subcutaneous administration assessment questionnaire (SQAAQ) and visual analogic scales (VAS). Effectiveness was evaluated in all patients with asthma control test (ACT), Mini Asthma Quality of Life Questionnaire (MiniAQLQ), annual exacerbation rate, oral corticosteroid treatment (OCS) and asthma-related hospitalizations and emergency visits.

**Results:** Fifty-four patients across 9 hospitals in Spain were included. The mean SQAAQ score was 6.89 (±0.16) points. Patients and their caregivers and doctors report excellent satisfaction by VAS, with no differences between benralizumab devices used (prefilled syringe and autoinjector). Severe exacerbation rate decreased by 65% ($p = 0.0007$) after benralizumab treatment. ACT score improved on average 6.27 ± 5.35 points ($p < 0.0001$) and the mean MiniAQLQ increased up to 1.58 ± 1.47 points ($p < 0.0001$). Twenty-four patients were OCS-dependent and at the end of study 14 patients get complete OCS withdrawal.

**Conclusion:** AUTO-BENRA study supports the use of benralizumab at home given the excellent results of satisfaction and usability by patients and their caregivers.

**Keywords:** benralizumab, severe eosinophilic asthma, self-administration, severe asthma, eosinophilic asthma



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## Introduction

Advances in the knowledge of the physiopathological mechanisms of severe asthma has allowed the development of specific biological therapies for patients with poor control despite optimized maintenance treatment. Benralizumab was recent marketing approval in Spain in January 2019 for uncontrolled severe eosinophilic asthma (SEA). It is a humanized monoclonal antibody that specifically binds to the alpha subunit of the interleukin (IL)-5 receptor, present in the surface of eosinophils and basophils, inducing an antibody-dependent cell-mediated apoptosis by natural-killer (NK) and other cells.[1] Its efficacy and safety have been proved in some clinical trials.[2–6]

Home self-administration of biological therapies has shown to increase health-related quality of life (HRQoL), decreasing costs through a substantial reduction of visits to specialized clinics, and avoiding travelling long distances to the clinic.[7–10] Furthermore, the use of autoinjectors positively correlates with medication adherence, which is known to be lower in patients with chronic diseases.[11] There are two main types of devices for self-administration therapy: the pre-filled syringe and the autoinjector. In this sense, benralizumab has been evaluated for home self-administration in three studies; GREGALE, to confirm the functionality and correct performance of the pre-filled syringe when used at home in patients with SEA;[12] AMES, to check pharmacokinetic parameters between the benralizumab pre-filled syringe and the auto-injector system.[13] Finally, the GRECO study to verify that the auto-injector was completely reliable and easy to use self-administered.[14] According to these data, Spanish regulatory entities allowed the home-self-use with a pre-filled syringe or single-use autoinjector of benralizumab in March 2020.[15] Moreover, self-administration has become vitally important due to the COVID 19 pandemic, in a scenario in which hospital visits could increase the health risk in certain situations. Several national societies, such as the British Thoracic Society (BTS) and the Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC), recommend to promote the home self-administration versus hospital administration during the pandemic.[16,17] Furthermore, maintaining the biological therapy in patients with severe asthma is important to keep the disease control and may also be useful to mitigate the clinical course of COVID-19 based on the current and initial evidence.[18,19]

Likewise, there are scarcely some data regarding the patients and doctors 'satisfaction with the therapy and particularly, nothing has been reported for benralizumab in SEA in real-life conditions. Patients´ satisfaction has been assessed in some few previous monoclonal antibodies like ixekizumab and galcanezumab.[20,21] Both studies used the subcutaneous administration assessment questionnaire (SQAAQ) to explore the satisfaction, the patient's abilities and confidence in the device. Considering the absence of published evidence, the main objective of this study was to characterize the patient's and the doctor's satisfaction with the self-administration of benralizumab, moreover measuring usability of benralizumab devices for SEA in real-world setting. In addition, as secondary objectives, an analysis of the effectiveness of benralizumab in patients treated at home was carried out.

## Materials and Methods

### Objectives, Study Population and Study Design

AUTO-BENRA study was a retrospective multicenter study conducted at 9 hospitals in Spain with patients with uncontrolled SEA treated with benralizumab at home-use administration. The primary endpoint was to assess patient satisfaction and reliability with the self-administered treatment through the completion of SQAAQ after 3 doses of benralizumab self-administered by the patient of his/her caregiver.

The secondary endpoint was to measure the effectiveness of benralizumab with these devices in self-administration at home.

The study enrolled patients over 18 years of age, with SEA according to the Spanish Guidelines for Asthma Management (GEMA 5.0) criteria, being treated with benralizumab according to its approved indication in Spain, who had received at least three doses of self-administered benralizumab at home before April 30, 2021.[22] The recruitment period ended on October 1, 2021. Exclusion criteria was limited just to the incapacity to understand the informed consent, refusal to sign it and/or if the patient or their caregivers had insufficient intellectual capacity to understand the SQAAQ.

## Variables Related to Satisfaction a Reliability

SQAAQ is a novel 12-item (see Figure 1), self-administered questionnaire that has not yet been psychometrically validated. The SQAAQ items assess ease of use of the device and patient/caregiver confidence. Each item was answered on a 7-point Likert scale ranging from "strongly disagree" to "strongly agree". Moreover, satisfaction with the home-use treatment was also measured with a classic visual analog scale (VAS) where it could be answered with a number from 1 to 10 where 0 was not satisfied and 10 was completely satisfied. This VAS was used to assess satisfaction not only with the device but also with the health results (Global VAS) for both the patient and doctor. VAS has not been measured to validate SQAAQ. The concordance of the results between physician/patients VAS and SQAAQ was evaluated.

SQAAQ scores were registered after the third self-administration of benralizumab. We collected the patient's VAS for global satisfaction with benralizumab treatment, as well as VAS for the patients´ and doctors´ satisfaction with the self-administration regimen at home. The scale ranged from 0 (completely unsatisfied) to 10 (completely satisfied). Any errors in the self-administration at the different doses, adverse events that might have arisen, and possible mistakes in the manufacture were registered. Patients received a prefilled syringe or autoinjector depending on the availability of each of the devices in each center. Patients fulfilled the questionnaires themselves during each scheduled visit to the specialized centers, according to routine clinical practice.

## Clinical-Demographics and Effectiveness Variables

Social-demographic data (race, sex, date of birth, educational level) and clinical outcomes (year of onset of asthma, body mass index, asthma phenotype, concomitant rhinosinusal pathology, comorbidities, tolerance to non-steroidal anti-inflammatory drugs, allergic sensitizations, and previous biological treatment for asthma) were assessed for each patient. We also collected pre- and post-treatment data [counts of eosinophils in absolute value per microliter (μL) in peripheral blood (the closest data after the third self-administration of benralizumab)]; absolute and percentage values concerning the predicted values of the FVC, FEV1 and the FEV1/FVC ratio; self-reported Spanish version of asthma control test (ACT) and Spanish Mini Asthma Quality of Life Questionnaire (MiniAQLQ) scores; number of moderate (add-on or increase up inhaled medications) to severe exacerbations (those that had required systemic corticosteroids at least 3 days

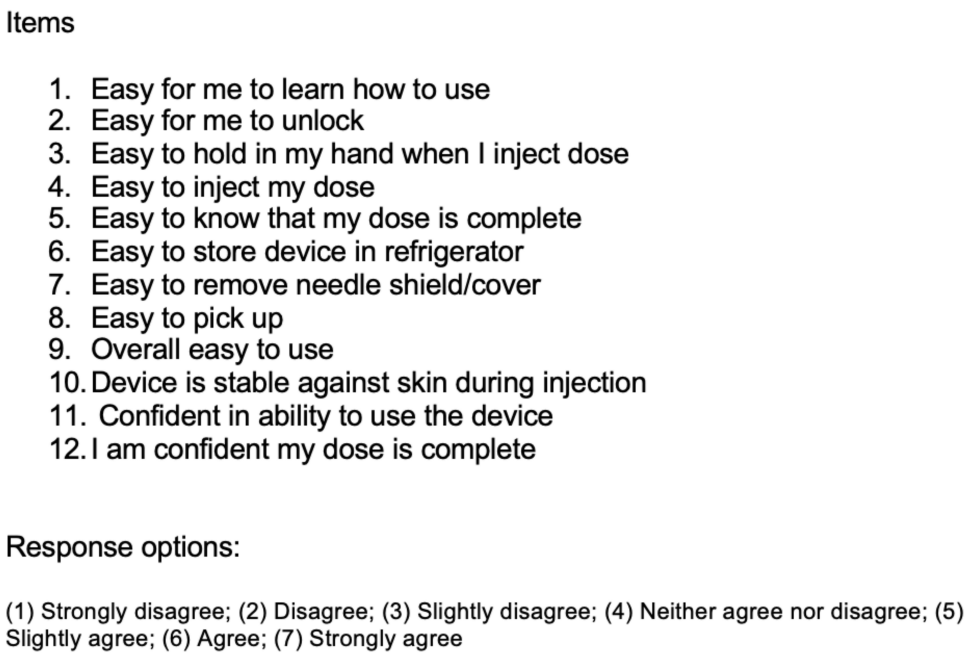


**Figure 1** Subcutaneous administration assessment questionnaire (SQAAQ).

**Notes**: Adapted from Callis Duffin K, Bukhalo M, Bobonich MA, et al. Usability of a novel disposable autoinjector device for ixekizumab: results from a qualitative study and an open-label clinical trial, including patient-reported experience. *Med Devices (Auckl)*. 2016;9:361–369.[20] Copyright © 2016 Callis Duffin et al. Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/).

or increasing the dose if patients already received them).[23–25] Exacerbations that required hospitalization or emergency care attention were also collected. All post-treatment outcomes were collected at least after 6 months of treatment. In prednisone-dependent patients, the dose of prednisone recorded was the closest one to the study enrollment.

## Database and Ethics

An encoded computerized database, specifically designed for this purpose, was compiled from patients' medical records and interviews.The ethics committee for research with medicinal products at Hospital Universitario 12 de Octubre approved the study protocol and assigned the code 21/031 to the project. With this approval, the rest of the participating centers presented at the rest of the ethics committees where they also approved the protocol. This study was performed in accordance with the Declaration of Helsinki.

## Statistical Analysis

The characteristics of the patients and all the results were presented using descriptive statistics. Continuous variables were defined by mean, standard deviation, median, interquartile range, minimum and maximum. The categorical variables were described as absolute and relative frequency. In both cases, the number of observations and missing data will be specified. The assumptions of the normal distribution were evaluated using the Shapiro–Wilk test or the Kolmogorov–Smirnov test. The evolution of change from pre to post was calculated using the t-student related sample test, the non-parametric Mann–Whitney-Wilcoxon *U*-test. McNemar's exact test or Cochran's q test, depending on the nature of the variables.

The concordance index will be calculated to obtain the proportion of agreement observed between the global VAS results, per patient, and doctors. The discrepancies of the VAS values were evaluated with the differences of means and statistically significant differences were evaluated through the symmetry test and Pearson's correlation coefficient. All estimates were accompanied by the 95% confidence interval. All statistical analyses will be performed using Stata version 16 for Windows. The level of significance used was 5% ($\alpha = 0.05$).

# Results

## Patient Population

Fifty-four patients were recruited in AUTO-BENRA Study. The baseline demographic and clinical characteristics of patients are summarized in Table 1. Median time under benralizumab treatment was 11[7–29] months. Nine patients completed less than 6 months for the evaluation of SQAAQ and VAS Scales, because they switched treatment from other biological drug with similar profile for self-administration or doctors decided to accelerate the training time due the COVID-19 pandemic situation. However, even in these patients, at least the first dose was administered in the hospital to monitor possible adverse events.

Mean age of patients was 57.3[±9.97] years, mostly women (62.96%). Thirty-one patients had been previously treated with other biological drugs for severe asthma, suspended due to lack of efficacy, adverse events, or avoiding of intravenous administration of reslizumab due to the COVID-19 pandemic. Four patients had received 3 biologics sequentially (omalizumab, mepolizumab, and reslizumab), another 4 patients had previously received 2 (omalizumab and mepolizumab), 13 patients had exclusively received omalizumab prior to benralizumab, 7 patients only mepolizumab and, finally, 5 patients only reslizumab. The most frequent recorded comorbidity was gastroesophageal reflux (59.3%) and chronic rhinosinusitis with polyposis (46.3%) and 70.4% were atopic. At baseline, mean (SD) blood eosinophil count was 742.04 ±441.73 cells/μL. A 50.9% of the patients used the pre-filled syringe for home self-administration and 49.1% for the autoinjector. Adherence to asthma maintenance treatments was high, with an average score in the inhaler adherence test (TAI) of 49.8 out of 50 points and a 92.6% mean withdrawal at the pharmacy office for inhalers, according to the pharmacy refill data from the National Spanish Health System.

## SQAAQ and VAS Results

The mean SQAAQ score was 6.89 (±0.16) points. Patients and their caregivers report excellent satisfaction, safety with the device, and ability to administer medication at home with the devices offered. The question with the worst average

**Table 1** Baseline Demographic and Clinical Characteristics of AUTO-BENRA Study

| Demographics Characteristics | | N Missed |
|---|---|---|
| Age y, mean±SD | 57.31±9.97 | |
| Female, n (%) | 34 (62.96%) | |
| Educational level | | |
| High school n (%) | 9 (18.75%) | |
| Vocational training n (%) | 14 (29.17%) | |
| Secondary education n (%) | 17 (35.41%) | |
| Primary education n (%) | 8 (16.67%) | |
| BMI mean±SD | 28.04±4.62 | 1 |
| Current/ex- smoker >10p/year n (%) | 9 (16.7%) | |
| **Comorbidities** | | |
| GERD n (%) | 32 (59.26%) | |
| OSAS (%) | 5 (9.26%) | |
| Mental disorders n (%) | 13 (24.07%) | |
| Bronchiectasis n (%) | 11 (20.37%) | |
| Nasal polyps n (%) | 25 (26.3%) | |
| AERD n (%) | 16 (30.7%) | |
| Aeroallergen's sensitization-atopy n (%) | 38 (70.37%) | |
| **Biomarkers** | | |
| Total IgE KU/L mean ±SD | 554.21±1337.22 | |
| Eosinophils Cells /microliter ±SD | 742.04±441.73 | |
| **Clinical Characteristics** | | |
| Prednisone-dependent patients n (%) | 24(44.4%) | |
| Severe exacerbation rate Exacerbations/ year ±SD | | |
| $FEV_1$ percentage mean ±SD | 68.82±15.92% | 2 |
| ACT points mean±SD | 14.10±4.41 | 2 |
| MiniAQLQ mean ±SD | 3.99±1.30 | 26 |

**Abbreviations**: BMI, body mass index; GERD, gastroesophageal reflux disease; OSAS, obstructive sleep apnea syndrome; AERD, aspirin-exacerbated respiratory disease; $FEV_1$, forced expiratory volume in first second; ACT, asthma control test; MiniAQLQ, reduced version of asthma quality of life questionnaire.

score was the one related to the storage conditions of the device (question 6, average score of 6.81 points) and the best-scored question was question 9, related to the opinion of the general ease of use of the device with a score of 6.96 points. The mean VAS score for home administration was 9.40 points by the patient and 9.45 by the doctor. The VAS on global satisfaction with benralizumab treatment was 9.40 points. The concordance between the perception of the doctor and the patient about the treatment was measured with a spearman coefficient of 0.648 indicating a good positive correlation ($p < 0.0001$). There were no statistical differences between prefilled syringe and autoinjector (see Table 2). There were no errors recorded during the study, nor in the application of the medication by the patient or their caregivers, nor in any manufacturing errors.

## Effectiveness Variables

Regarding the effectiveness variables, the annualized rate of exacerbations (see Figure 2) decreased by 63%, reducing from 3.67±3.32 to 1.36±3.19 exacerbations per year ($p = 0.0008$), severe exacerbations, decreased by 65% ($p = 0.0007$) exacerbations a year. A 91.2% ($p < 0.0001$) reduction was observed in exacerbations attended at emergency department. At the beginning of the study, 52 (96.3%) patients had experienced at least one exacerbation, and at the end of the study 38 (73.1%) patients were free of exacerbations. Only 2 patients enrolled in the AUTO-BENRA study had been admitted to the hospital for an asthma attack at baseline, and no one until the study ended. Regarding asthma control, median ACT score improved on average 6.27±5.35 points ($p <0.0001$, N missed 2 patients) and the median MiniAQLQ raised 1.58±1.47 points ($p <0.0001$ N missed 17 patients). Only 3 patients had >20 points in ACT (cut-off to consider good

**Table 2** Summary of SQAAQ and VAS Score

| | Total | | Prefilled Syringe | | | Autoinjector | | p-value |
|---|---|---|---|---|---|---|---|---|
| | N= 54 | N missed | N=27 | | Nmiss | N=26 | N missed | |
| Device | | 0 | | | | | | |
| Prefilled syringe | 27 (50.94%) | | | | | | | |
| Autoinjector | 26 (49.06%) | | | | | | | |
| Global VAS patient | 9.37 (0.99) | 1 | 9.38 (0.64) | 26 | 1 | 9.35 (1.26) | 0 | 0.89 |
| Patient VAS | 9.38 (1.03) | 1 | 9.50 (0.86) | 26 | 1 | 9.27 (1.19) | 0 | 0.43 |
| Physician VAS | 9.44 (0.92) | 1 | 9.58 (0.58) | 26 | 1 | 9.31 (1.16) | 0 | 0.29 |
| Average 12-SQAAQ | 6.89 (0.16) | 0 | 6.90 (0.16) | 27 | 0 | 6.89 (0.16) | 0 | 0.87 |

asthma control) before benralizumab, and after benralizumab 37 patients had >20 points. Regarding lung function, FEV1 improved by 320.77±458.74 mL on average (p <0.0001, N missed 2 patients), and an improvement of 13.82 ±15.92% (p < 0.0001) was observed. The FVC improved on average by 239.61±495.62 mL (p = 0.0010) and 9.43 ±19.45% in percentage value (p = 0.0011). Twenty-four patients (44.4%) were on maintenance systemic corticosteroids with a mean dose of 16.7 mg prednisone per day. At the end of the study, 14 patients (58.3%) achieved complete withdrawal and of the 10 patients undergoing treatment, the average dose downed to 7.38 mg of prednisone daily. Eosinophils decreased a 99.4% (p < 0.0001), drooped to 3.82 eosinophils per microliter to the end of the study. The device complaints or malfunctions in the study were low. No discontinuation due to adverse effects was reported by the investigators.

## Discussion

Although home self-administration has become a frequent option for most biological treatments, there is an increasing need to verify satisfaction, usability, and reliability with this treatment in patients with SEA to ensure good adherence and good health outcomes.

The AUTO-BENRA study emerged to objectively confirm the good perception of most patients and physicians regarding satisfaction with benralizumab when administered at home. These results demonstrate the great satisfaction, usability, and reliability that patients report through the SQAAQ of the different devices in which benralizumab is

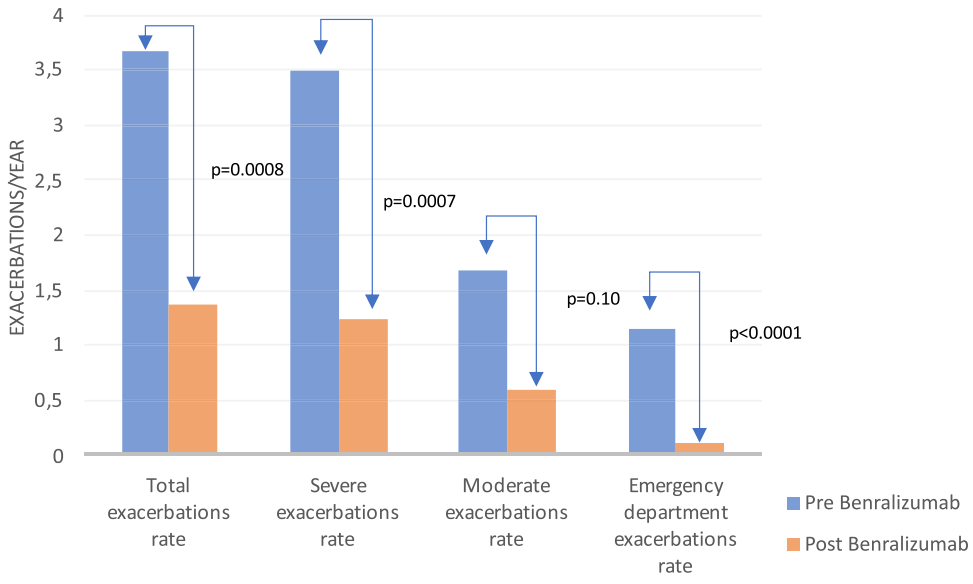


**Figure 2** Improvement on subtypes of exacerbations rate after benralizumab.

presented, wherein a generalized way the average score achieved in each question is close to the maximum, 7 points (totally agree) within 162 administered doses.

Our results are coincident with previous publications, although for different drug and diseases. We have evaluated the SQAAQ scores after 3 doses. We truly believe this evaluation adds robustness to our results. Similar to the ixekizumab trial, the study tried to assess the ease of use and confidence by using an injection device at weeks 0, 4, and 8. For ixekizumab at the first use, 95% of subjects either agreed or strongly agreed that the device was "overall easy to use", and they felt "confident the dose was complete" according to the SQAAQ.[20] Concordantly to our study, continued experience with the self-administration over the course of the trial offered an extremely high proportion of patients or caregivers agreeing or strongly agreeing with each item of the SQAAQ, even in issues in which clinicians are not directly involved, like the storage conditions of the device, the worst average score in our study. For galcanezumab prefilled syringe and autoinjector study, which analyzed patients with at least one administration, most patients had positive responses to the SQAAQ.[21] A possible weakness in our study could be that SQAAQ has not been validated in Spanish and it is not a validated measure. However, it helps providing insight into the patient-reported experiences using both devices, syringe and autoinjector. Furthermore, we have confirmed the SQAAQ results, through providing another usability and satisfaction measure, the global VAS for benralizumab treatment and a patients' VAS for home-us of benralizumab, which has resulted also positively correlated with the opinion of doctors.

Regarding the effectiveness of benralizumab, its efficacy has been widely demonstrated in pivotal clinical trials. Benralizumab reduced exacerbations in CALIMA (56 weeks) and SIROCCO (48 weeks) studies by 28% (RR = 0.72; 95% CI 0.54–0.95; p = 0.019) and 51%, respectively (RR = 0.49; 95% CI: 0.37–0.64; p < 0.001) vs placebo. In the SIROCCO study, the rate of exacerbations that led to the hospitalization (secondary variable) was reduced in a 63% (RR = 0.37; 95% CI: 0.20–0.67; p = 0.0010).[2,3] In the ZONDA trial (steroid-dependent patients) the 70% reduction in exacerbations was obtained (RR = 0.30; 95% CI: 0.17–0.53; p < 0.001).[4] AUTO-BENRA study was not placebo controlled. In real-world evidence (RWE), the evidence about effectiveness of benralizumab is limited. There are several case series of patients, but most of them included less than half a hundred patients and only one with 130 (Kavanagh et al).[26–38] In most RWE studies, results in reducing the rate of exacerbations exceed those reported in clinical trials. Similarly, in AUTO-BENRA, data on the reduction in the rate of exacerbations outstrip the reality of clinical trials, achieving a 73.4% reduction in patients with zero exacerbation/year, a rate not communicated in other RWE studies.

In other clinical outcomes, the improvement with benralizumab was again evident. In the RWE groups, where the effect of benralizumab on asthma control measured by ACT has been assessed, improvements of up to 7.1 points (Padilla-Galo et al) and 6 points (Bagnasco et al) have been achieved.[27,29] In our study, we observed an important effect on asthma control with an improvement of almost 7 points in our population, ranging from 14.1± 4.23 points to 20.37 points± 4.41. This implied a significant improvement in asthma-controlled patients in this group. Also, few groups have assessed the effect on quality of life of benralizumab in RWE. Interestingly, the improvement in quality of life, measured by the MiniAQLQ in the AUTO-BENRA study, is the highest recorded in RWE – studies to date and much higher than the 0.5 points considered as clinically relevant.[39] It has been even higher than the 0.89 points reported in Kavanagh et al.[26] Improvement in lung function has been well reported with benralizumab. In tSIROCCO and CALIMA trials, $FEV_1$ improvement was 398 mL vs 239 mL at 48 weeks (p = 0.001) and 330 mL vs 215 mL placebo at 56 weeks (p = 0.01), respectively.[2,3] RWE studies report greater improvements in lung function, measured with spirometry and other techniques like oscillometry.[40] In our study, improvements exceed 320 mL, with improvement considered clinically relevant, as occurs in most RWE studies, where improvements have been observed even above 680 mL.[35] Exacerbations and lung function were evaluated in studies in SEA population with or without CRSwNP, obtaining better results in the subpopulation with CRSwNP.[33,41] CRSwNP population is likely to become a clinical marker of eosinophilic endotype in the Caucasian population, and therefore the response to benralizumab will be better. In our case, the population did not show significant differences in the results with the general population, possibly because the number of patients with CRSwNP was low (24 patients).

One important issue is oral corticosteroids (OCS) sparing rate due to benralizumab. According to clinical trials, benralizumab reduced the median dose reduction of OCS by 75% compared to the basal dose at 28 weeks vs 25%, with placebo (OR 4.12 (95% CI 2.22–7.63) p <0.0017).[4] Withdrawal of OCS with benralizumab was 52% compared to 19%

with placebo (OR 4.19 (1.58–11.12) p=0.002) in patients with a basal prednisone dose ≤12.5 mg/day.[4] In most series of RWE, more than half of the steroid-dependent patients achieve withdrawal, and in some up to 80% of the steroid-dependent population.[33] In our study, we achieved withdrawal in just over half of the patients who were on OCS, and those who could not withdraw them reduced the dose of prednisone by half.

The first limitation of our study could be that SQAAQ has not been validated. Other limitations of our study are the lack of a control group. Furthermore, we only have one recorded measure of FEV1, corticosteroid doses, questionnaires such as the ACT and MiniAQLQ corresponding to the closest date to enrollment.

In conclusion, we report the first study that objectively evaluates satisfaction with home-use of biologic therapy in SEA. We observed how benralizumab home-use represents an important change in their lives, reflected in enormous satisfaction and confidence with the treatment, without losing effectiveness and offering high safety. In times like the current COVID-19 pandemic and patients with specific risks such as infectious or related to hospital displacement, results from this study support that this treatment regimen could be the best choice. However, more studies, probably with a prospective design, could add validation and more data on the satisfaction and usability even cost saving of these devices while maintaining the effectiveness of the drug.

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## Disclosure

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