Clinical Study Report Synopsis	
Drug Substance	Benralizumab
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Observational Retrospective Study to Characterise Patients Receiving Benralizumab in the Framework of an Individualized Access Program in Spain

Study dates: First subject enrolled: 13 January 2020
Last subject last visit: 08 May 2020

Phase of development: Therapeutic use (IV)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

One country (Spain) and 20 centres participated in the study:

- Hospital Universitario Basurto
- Hospital Clinic i Provincial
- Hospital Universitario San Cecilio
- Complejo Asistencial Universitario de Salamanca
- Hospital Universitario 12 de Octubre
- Hospital Universitario Virgen de la Victoria
- Hospital Universitario Central de Asturias
- Hospital Universitario del Vinalopó
- Hospital Universitario de Guadalajara
- Hospital Universitario Puerta de Hierro
- Hospital Universitario Doctor Peset
- Hospital General de Requena
- Hospital de Sagunto
- Hospital Universitario Lucus Augusti
- Hospital de la Santa Creu i Sant Pau
- Hospital Universitario de Fuenlabrada
- Complejo Hospitalario Universitario de A Coruña
- Hospital General de la Santísima Trinidad
- Fundación Jiménez Díaz
- Hospital Universitario Marqués de Valdecilla

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To describe the demographic and baseline characteristics in patients with severe eosinophilic asthma who participated in the individualized access program approved in Spain and received at least one dose of benralizumab.	• Demographics (age, sex, body mass index (BMI), smoking status) • Baseline characteristics: – Age at onset of asthma diagnosis – Comorbidities – Severe exacerbations in past 12 months – Healthcare resources utilization: emergency room visits, hospitalizations, unscheduled visits – Patient Reported Outcomes: ACT, miniAQLQ – Blood eosinophils count • Maintenance asthma treatment • Prior biological treatment (type and generic name, dose, duration of treatment) and the reasons for switching.
Secondary	
• To describe clinical outcomes in severe eosinophilic asthma patients that received at least three doses of benralizumab in the individualized access program.	• Change from baseline and percentage of responders to PROs (ACT and miniAQLQ) • Severe exacerbations, number and severity • Change from baseline in blood eosinophils count • Healthcare resources utilization: emergency room visits, hospitalizations, unscheduled visits • Lung function change (FEV1, FEV1/FVC) versus baseline, if available • In those patients using OCS at baseline: OCS dose reduction • Visual Analogue Scale (VAS) to report the investigator's perception of overall clinical improvement • Adherence and persistence to benralizumab treatment

Study design

Observational, retrospective study in adults (≥18 years) with severe asthma (maintenance treatment with high dose inhaled corticosteroids combined with long-acting agonist β2) and eosinophilic phenotype, who at the discretion of the investigators were candidates to receive benralizumab in the individualized access program approved by national health authorities

(AEMPS). The data was collected retrospectively from the medical records in accordance with the usual clinical practice of each study site. The data of each patient was included in the eCRF by the investigator after the patient signed the informed consent.

Target subject population and sample size

The study population included all patients who received at least one dose of benralizumab in individualized access program approved by the AEMPS. The maximum number of patients expected to meet the inclusion criteria was 45. Final sample size was 27 patients.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

FASENRA (benralizumab) 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen. Administered in a real-world setting.

Duration of treatment

Treatment exposure in the study was restricted to the period between March of 2018 and December 31st of 2018, when the individualised access programme to benralizumab was open in Spain. The exposure duration to the drug was individual for each patient and includes the period from the index date to the end of the individualized access program.

Statistical methods

For continuous variables, descriptive statistics (n, mean, and standard deviation [SD]) are provided. For categorical variables, absolute frequency and valid percentages (i.e., excluding missing data) are provided. Patient demographic and clinical characteristics were summarised using descriptive statistics. Exacerbation rates in the year prior to treatment were expressed per patient-year and calculated before and after benralizumab treatment initiation as the number of episodes divided by time of exposure. Background controller treatment was also described and summarised using descriptive statistics (mean, SD, n, and valid percentage). For the comparison of the same measurement at two different times, either paired T-test or Wilcoxon was used, depending on the sample distribution. Statistical significance was set at $p < 0.05$.

Study population

Table 1: Baseline patient characteristics

Parameter	N = 27
Age (years), Mean (SD)	49.8 (12.7)
Women, n (%)	14 (51.9)
BMI, Mean (SD)	28.4 (5.9)

Parameter	**N = 27**
Smoking, n (%)	
Non-smoker	19 (70.4)
Former smoker	8 (29.6)
Age at diagnosis (years), Mean (SD)[a]	30.2 (12.2)
Time since diagnosis (years), Mean (SD)	19.2 (13.8)
Asthma phenotype, n (%)	
Eosinophilic	24 (88.9)
Atopic	3 (11.1)
Pre-BD FEV_1, Mean (SD)[b]	
mL	1,813.3 (480.8)
%	62.1 (14.6)
Post-BD FEV_1, Mean (SD)[b]	
mL	1,989.3 (819.7)
%	65.7 (20.5)
ACT[c]	
Mean (SD)	14 (6.1)
Controlled asthma (ACT≥20), n (%)	6 (22.2)
miniAQLQ, Mean (SD)	3.4 (0.7)
FeNO (ppb), Mean (SD)[d]	76.2 (56.5)
Blood eosinophil count (cells/µL), Mean (SD)[a]	371.9 (315.5)
< 300 cells/µL, n (%)	11 (40.7)
≥ 300 cells/µL, n (%)	15 (55.6)
Total IgE (IU/ml), Mean (SD)[b]	593.1 (1,054.5)
Asthma-treatment in the previous year, n (%)	
ICS + LABA	27 (100)
OCS	24 (88.9)
LAMA	22 (81.5)
LTRA	17 (63)
ICS	8 (29.6)
Macrolides	6 (22.2)
Theophylline	1 (3.7)
LABA	1 (3.7)
Biologic agent	
Mepolizumab (anti-IL5)	24 (88.9)
Reslizumab (anti-IL5)	3 (11.1)
Omalizumab (anti-IgE)	2 (7.4)
Oral prednisone dose (mg/day), Mean (SD)	20.3 (20.1)
Inhaled budesonide (in combination) dose (µg/ day), Mean (SD)	305 (60.2)

Parameter	N = 27
Duration of prior biologic therapy (days), Mean (SD)	
Duration of prior mepolizumab therapy[a]	250.8 (167.6)
Duration of prior reslizumab therapy	150.7 (58.4)
Duration of prior omalizumab therapy	77 (107.5)
Time since prior biologic therapy (days), Mean (SD)[a]	121.4 (110.7)

Abbreviations: ACT= Asthma Control Test; AQLQ= Asthma Quality of Life Questionnaire; BD = Bronchodilator; BMI= Body mass index; FeNO= Fractional exhaled nitric oxide; FEV_1= Forced expiratory volume in 1 s; ICS= Inhaled corticosteroids; IL-5= Interleukin 5; IU= International units; LABA= Long acting β2-agonists; LAMA= Long acting muscarinic antagonists; LTRA= Leukotriene receptor antagonists; µL= microlitre; mL= millilitre; OCS= Oral corticosteroids; ppb= Parts per billion; SD= Standard deviation; SPT= Skin prick test.

[a]Data unknown in 1 case (3.7%)
[b]Data unknown in 6 cases (22.2%)
[c]Data unknown in 2 cases (7.4%)
[d]Data unknown in 8 cases (29.6%)

Summary of results

Clinical, functional, and laboratory data of patients at baseline

A total of 27 severe asthma patients were evaluated, 88.9% (n=24) had eosinophilic asthma and 11.1% (n=3) also had atopic features. Mean (SD) time since diagnosis was 19.2 (13.8) years. At baseline, mean (SD) blood eosinophil count was 371.9 (315.5) cells/µL and 55.6% (n=15) had ≥300 cells/µL; mean (SD) ACT score was 14 (6.1) with a total of 21 patients (77.8%) with uncontrolled asthma (ACT score < 20).

All patients were treated with high-dose ICS plus LABA and 24 (88.9%) had been treated with OCS as maintenance treatment prior to benralizumab initiation. Oral prednisone (equivalent) mean (SD) dose was 20.3 (20.1) mg/day. All patients had failed or were intolerant to prior treatment with anti-IL5 or anti IgE treatment: 24 (88.9%) had been previously treated with mepolizumab; 3 (11.1%) with reslizumab and 2 (7.4%) with omalizumab before being switched to benralizumab.

Most of the patients had ≥1 asthma-related comorbidity (74.1%; n=20). The most frequent were allergic rhinitis (44.4%), nasal polyps (40.7%), gastroesophageal reflux disease (40.7%), and chronic rhinosinusitis (37%).

Clinical variables assessed after benralizumab treatment initiation

Of the 27 patients evaluated at baseline, 70.4% (n=19) received at least three doses of benralizumab in the EAP and were evaluated at follow-up. 11.1% (n=3) received two doses and 18.5% (n=5) received a single dose. The mean (SD) time between the first and the last dosage in those patients was 5 (2.1) months. 89.5% (n=17) of the patients continued treatment with

benralizumab after the EAP had been completed and following the approval and marketing authorisation of benralizumab in Spain.

Asthma control and quality of life

Mean (SD) blood eosinophil counts decreased from 490 (353.9) at baseline to 0.8 (2.8) cells/µl after treatment (p=0.002).

According to data from the 19 patients that received at least the first three doses, pre-bronchodilator (pre-BD) and post-bronchodilator (post-BD) lung function showed no apparent difference after benralizumab treatment initiation compared with baseline. However, 9 (60%) out of 15 patients had a clinically meaningful increase in FEV_1 of 230 mL.

Patients showed improvement in asthma control based on the ACT score after benralizumab treatment compared with baseline [14.8 (6.8) vs. 18.1 (6.3); p=0.079]. The point estimate difference between the last monitoring value and baseline was 3.3 (6.8), which is numerically larger than the minimal clinically important difference (MCID) (increase of ≥3 units). Additionally, 60% (n=9) of the patients with ACT score recorded at baseline and after treatment initiation (n=15) achieved a clinically significant response (ACT score difference ≥3).

A significant reduction in the proportion of patients (88.9% [n=24]) receiving OCS at baseline vs. 78.9% (n=15) after treatment initiation with benralizumab was observed and 31.6% (n=6) had an overall OCS dose reduction ≥ 50%.

Regarding QoL, although not numerical difference (p=0.236), a MCID (score difference ≥ 0.5) in miniAQLQ of 1.2 (1.9) was observed vs. baseline.

Exacerbations and asthma-related healthcare resources use

A reduction in the annualized exacerbation rate was observed between the year prior to treatment initiation and the time following benralizumab initiation [4.4 (2.9) vs. 1.9 (1.2) respectively]. The difference in the annual severe exacerbation rate was 2.12 (95%CI: 0.99-3.24) (i.e., 3.89 before treatment vs. 1.77 after treatment initiation, nominal p=0.002). A total of 10 patients did not report exacerbations during follow-up after benralizumab treatment initiation (11.1% of patients before treatment vs. 52.6% during follow-up). In contrast, 71.5% (n=22) of patients before treatment had ≥ 2 exacerbations in the previous year vs. 21.1% (n=4) after benralizumab treatment initiation.

Regarding asthma-related healthcare resources use, most of the patients had ≥1 non-scheduled primary care and specialist visits in the year prior to benralizumab treatment (55.6% and 59.3%, respectively). In contrast, after benralizumab treatment initiation, the mean (SD) number of non-scheduled visits to primary care and specialists registered a reduction from 3.7 (3.9) to 1 (0), and from 3.8 (3.3) to 1.6 (0.9), respectively. The observed differences during follow-up in the

annual rate of non-scheduled visits to primary care and specialist were 2.28 (95%CI: 1.55-3.01; p<0.001) and 1.47 (95%CI: 0.65-2.30; p=0.004), respectively. Also, the difference in annual rate of asthma-related ED visits was nominally statistically significant: 1.18 (95%CI: 0.51-1.85; p=0.007).

Conclusion(s)

In line with the results obtained in previous studies, benralizumab reduced eosinophilic count and exacerbation rate, as well as healthcare resource use derived from the management of asthma patients. Asthma control improved after starting treatment with benralizumab, reaching a considerable percentage of patients with maximum control of their disease.

Lung function remained similar to levels prior to the start of treatment and showed no significant improvement.

The results from the ORBE study demonstrate for the first time the effectiveness of benralizumab in an observational study following conditions of usual clinical practice in Spain, adding a lot of value to the results that had already been obtained in clinical trials.