









Therapeutic Effects of Benralizumab Assessed in Patients with Severe Eosinophilic Asthma: Real-Life Evaluation Correlated with Allergic and Non-Allergic Phenotype Expression

This article was published in the following Dove Press journal:
Journal of Asthma and Allergy

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Background: Benralizumab can be utilized as add-on biological treatment of severe eosinophilic asthma. However, so far only a few real-life studies have been published with regard to the use of this anti-IL-5 receptor humanized monoclonal antibody.

Objective: The primary aim of this multicenter observational investigation has been to assess the therapeutic effects of benralizumab in patients with severe uncontrolled, corticosteroid refractory eosinophilic asthma. The secondary objective was to evaluate the efficacy of benralizumab with regard to positive or negative skin prick test (SPT).

Methods: Clinical, functional, and laboratory parameters were evaluated in order to verify the therapeutic actions of benralizumab in atopic and non atopic subjects with difficult-to-treat eosinophilic asthma. Moreover, a comparative evaluation was carried out in relation to the presence or absence of SPT positivity.

Results: After 6 months of add-on biological therapy with benralizumab, our 111 patients experienced a marked improvement of their severe eosinophilic asthma, expressed by significant changes in asthma exacerbation rate, prednisone intake, daily use of short-acting β_2 -adrenergic agonists (SABA), asthma control test (ACT) score, asthma quality of life questionnaire (AQLQ) score (56 patients), forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), blood eosinophil count, blood basophil count (59 patients), and fractional exhaled nitric oxide (FeNO) levels (39 patients). In addition, significantly more effective outcomes were detected in patients with positive SPT, when compared to subjects with negative SPT, only in regard to asthma exacerbation number, ACT score, and daily SABA utilization. No significant correlation was found between serum IgE concentrations and each of all measured parameters.

Conclusion and Clinical Relevance: Taken together, the results of this real-world study indicate that in both allergic and non-allergic subjects benralizumab can be used as a valuable pharmacotherapeutic option for add-on biological therapy of severe eosinophilic asthma, regardless of SPT positivity or negativity.

Keywords: severe eosinophilic asthma, allergic and non-allergic phenotypes, asthma exacerbations, IL-5 receptor, benralizumab

Introduction

Over 300 million people worldwide suffer from asthma, a chronic respiratory disorder commonly shaped by variable airflow limitation and airway hyperresponsiveness, underpinned by predominant inflammatory features consisting of several

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phenotypes.¹⁻⁷ Among the latter, bronchial eosinophilia characterizes many forms of both allergic and non-allergic asthma, and high eosinophil numbers can be detected in blood and induced sputum from patients experiencing recurrent disease exacerbations and severe bronchoconstriction.⁸ Airway eosinophilic infiltration is indeed highly frequent in severe asthma, which is often associated with an inflammatory trait driven by a type-2 (T2-high) immune response sustained by key pathogenic roles played by T helper 2 (Th2) lymphocytes and group 2 innate lymphoid cells (ILC2).⁹⁻¹² Either atopic or non atopic phenotypes of asthma can be characterized by eosinophilic inflammation,¹³ which is usually sensitive to corticosteroid therapy. However, severe eosinophilic asthma can be resistant to inhaled corticosteroids (ICS) and also to oral corticosteroids (OCS) because of different mechanisms including an up-regulation of the dysfunctional β isoform of glucocorticoid receptor, a p38 MAPK (mitogen-activated protein kinase)-dependent inactivation of glucocorticoid receptor, and an impairment of histone deacetylase function.¹⁴⁻¹⁶

For patients expressing T2-high phenotypes/endotypes of severe asthma, the step 5 of current GINA (Global Initiative for Asthma) guidelines recommends a maximal medical treatment.¹⁷ The latter consists of high doses of ICS/LABA (long-acting β_2 -adrenergic agonists) combinations, inhaled tiotropium and eventually an oral leukotriene inhibitor, as well as an add-on biological therapy.¹⁷ Licensed monoclonal antibodies indicated for biological treatment of severe asthma include anti-IgE omalizumab, anti-IL-5 mepolizumab and reslizumab, IL-5 receptor (IL-5R) antagonist benralizumab, and dual IL-4/IL-13 receptor blocker dupilumab.¹⁸⁻²⁶ In this regard it is noteworthy that many severe asthmatic patients can be responsive to different biologic therapies,²⁷ thereby committing physicians to a complex pharmacologic choice. Within such a context, the therapeutic effectiveness of omalizumab in eosinophilic allergic asthma has been convincingly demonstrated along the last two decades by both randomized controlled studies and real-world experiences.^{18,19} Moreover, some post hoc evaluations of recent Phase 3 trials,²⁸⁻³⁰ and also a few real-life observations referring to relatively small numbers of patients with severe asthma,³¹⁻³⁸ suggest that mepolizumab, benralizumab and dupilumab can be very effective in both allergic and non-allergic asthma.

On the basis of the above considerations, the aim of this real-world multicenter, observational investigation,

has been to assess in more than 100 subjects with severe eosinophilic asthma the effects of a 24-week add-on treatment with benralizumab. In particular, the rationale underlying our study refers to the comparative evaluation of benralizumab efficacy in allergic and non-allergic patients, an important aspect which has not been thoroughly addressed by previous trials.

Patients and Methods

Study Design and Patient Enrollment

In 111 patients with severe eosinophilic asthma, a multicenter, real-life study was carried out to evaluate the therapeutic effects of benralizumab, also in relation to allergic/non-allergic phenotype expression. Utilizing a common database regarding severe asthmatic outpatients referring in the last two years to 12 specialized asthma centers located in Southern Italy, the 111 enrolled subjects were consecutively selected on the basis of their treatment with benralizumab. When considering the total number of patients included within this database, the most frequently used drug for add-on biological therapy of severe asthma was omalizumab, followed by mepolizumab and benralizumab.

More than 18 yrs old adult patients, suffering from severe persistent eosinophilic asthma, were recruited. They were on treatment with high dosages of ICS-LABA associations, eventually integrated by the addition of inhaled long-acting muscarinic antagonists (LAMA), and/or leukotriene inhibitors. In particular, 85 out of the 111 enrolled patients were using LAMA. Moreover, most of these subjects required recurrent courses of OCS therapy, comprehensively lasting at least 6 months/year. However, despite such strong treatments, asthma symptoms and disease exacerbations were very frequent. Indeed, these patients experienced a median number of 4 exacerbations during the 6 months before the first benralizumab administration, and 72% of recruited subjects were on maintenance therapy with OCS. In regard to ongoing corticosteroid treatment, we carefully verified that all patients were characterized by a high adherence to both ICS and OCS intake during the 6 months prior to the initiation of benralizumab therapy, as well as throughout the 6 months following the first injection of this biologic drug.

Skin prick test (SPT) positivity and negativity were considered in order to identify either allergic or non-allergic patients. SPT was judged as positive when the

wheel area was equal to or larger than that one caused by histamine. Higher than 100 UI/mL levels of serum IgE were indicative of an atopic trait.^{39,40} All subjects satisfied the diagnostic criteria of severe uncontrolled asthma, jointly established by the European Respiratory Society (ERS) and the American Thoracic Society (ATS).⁴¹ The involved asthma centers used a shared database to collect clinical, functional, and biological data. Smoking habit and comorbidities, such as gastro-esophageal reflux disease (GERD), nasal polyposis, bronchiectasis, osteoporosis, anxiety, atopic dermatitis, and obstructive sleep apnea syndrome (OSAS), were investigated prior to beginning add-on therapy with benralizumab. Spirometry was carried out following ATS/ERS guidelines⁴² at baseline, 1 month, 3 months and 6 months after the first dose of benralizumab. Nasal polyposis was detected by nasal endoscopy and/or computerized tomography of paranasal sinuses. Benralizumab was prescribed according to currently used eligibility criteria. In particular, this biological drug was injected subcutaneously at the dosage of 30 mg every 4 weeks for the first three times, and then every 8 weeks.

This observational study satisfied the standards of Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki. In addition, informed consent was obtained from all patients. Our investigation was also conducted according to what stated by the local Ethical Committee of Calabria Region (Catanzaro, Italy; document n. 113–16th April, 2020).

Outcomes and Measurements

The main aim of this real-life experience was to verify the efficacy of benralizumab in routine clinical practice. Asthma exacerbation rate and daily OCS consumption were assessed at baseline and 6 months after the first benralizumab administration. SABA use, asthma control test (ACT) score, asthma quality of life questionnaire (AQLQ) score, forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), blood eosinophil numbers, blood basophil counts, and exhaled fraction of nitric oxide (FeNO) levels were measured at baseline, 1 month, 3 months and 6 months after the first benralizumab injection.

The secondary goal was to evaluate the efficacy of benralizumab in relation to SPT positivity or negativity. Moreover, after 6 months of additional therapy with benralizumab, we analyzed the eventual correlation occurring between baseline serum IgE concentrations and the

recorded modifications referring to exacerbation rate, daily prednisone consumption, short-acting β_2 -adrenergic agonist (SABA) use, ACT score, AQLQ score, FEV₁, FVC, blood eosinophil numbers, blood basophil counts, and FeNO levels.

For two hours after benralizumab injection, patients were accurately monitored, because of the possible onset of side effects and adverse reactions. Furthermore, the eventual previous occurrence of unwanted drug effects was investigated each time every patient underwent benralizumab administration.

Statistical Analysis

Prism Version 8.2.1 (GraphPad Software Inc., San Diego, California) was used to statistically analyze study results. Median values with interquartile range (IQR) were used to express skewed data distributions, while normally distributed data were expressed as mean \pm standard deviation (SD). In consideration of data normality, parametric or non-parametric tests were chosen. The normal distribution of data was assessed by using Anderson-Darling test and Kolmogorov–Smirnov test. When appropriate, variable comparisons were performed using Student *t*-test or Mann–Whitney *U*-test. The latter statistical test was also utilized for the secondary study outcome, referring to the comparative evaluation of benralizumab efficacy in patients with either positive or negative SPT. Fisher exact test was applied to compare categorical variables. The association between baseline serum IgE concentrations and changes in clinical, functional and laboratory parameters was investigated using linear regression analysis. Spearman's rank correlation coefficient was assessed. When appropriate, post hoc power analysis was carried out. Statistical significance was set at a threshold of *p* value <0.05.

Results

Patient Features

Overall, 111 participants (71 females and 40 males) were enrolled in this observational study. The median (IQR) age of our study population was 56 (43–65) years, and the median (IQR) disease duration was 18 years (10–30). Median (IQR) baseline FEV₁ was 61% (49.75–74.25) of predicted value. Median (IQR) body mass index (BMI) was 26.17 (23.14–28.13). Median (IQR) blood eosinophil number was 740.0 cells/ μ L (200.0–1097), and median (IQR) blood basophil count was 44.0 cells/ μ L (30.0–86.0). Sixty

(54.1%) patients were SPT positive, 32 (28.8%) subjects were smokers or former smokers, 55 (49.5%) had gastroesophageal reflux disease (GERD), 51 (45.9%) suffered from nasal polyposis, 27 (24.3%) had osteoporosis, 21 (18.9%) complained of anxiety, 13 (11.7%) had atopic dermatitis, and 11 (9.9%) suffered from obstructive sleep apnea syndrome (OSAS). Moreover, the presence of bronchiectasis was evidenced in 27 (24.3%) participants. No patient was previously treated with other biologics.

Baseline patient features also characterized on the basis of SPT positivity or negativity, are summarized in Table 1. At baseline, no difference was found between SPT positive and negative patients with regard to AQLQ and ACT scores. No significant difference was detected with regard to either allergic or non-allergic trait, except for disease duration, which resulted to be longer in allergic patients ($p < 0.001$), and atopic dermatitis, that was more common among allergic subjects ($p < 0.01$); p values relate to SPT negative versus SPT positive patients. Furthermore, we found that 46 subjects were allergic to dust mites, 38 to pollens, and 20 to pet dander; 32 patients were allergic to more than one aeroallergen. In addition, in 39 (35.1%) out of the 111 enrolled subjects we measured FeNO, whose baseline median level was 48 parts per billion (ppb) (35–67).

Efficacy of Benralizumab in the Whole Population

In comparison to the 6-month period preceding the first benralizumab administration, asthma exacerbation rate sharply dropped from 4 (3–6) to 0 (0–0) after six months of anti-IL-5R α therapy ($p < 0.0001$) (Figure 1A). This remarkable therapeutic outcome made it possible to lower OCS consumption from 5 mg (0–12.5) to 0 mg (0–0) ($p < 0.0001$) (Figure 1B). Moreover, with respect to baseline, after 6 months of benralizumab treatment the percentage of subjects needing a daily prednisone intake decreased from 72% to 20%. Otherwise, no change in ICS dosage was detected throughout the study period (data not shown). Daily SABA inhalations, used as needed rescue medications, decreased from 2 (1–4) to 0 (0–0) ($p < 0.0001$) after 1 month, as well as after 3 and 6 months (Figure 1C).

Six months after add-on therapy with benralizumab, ACT score enhanced from a baseline value of 13.31 (\pm 3.961) to 21.88 (\pm 2.835) ($p < 0.0001$). This result was already relevant after 1 month, when ACT score was 19.05 (\pm 4.334) ($p < 0.0001$), and after 3 months, when ACT score was 21.09 (\pm 3.250) ($p < 0.0001$) (Figure

1D). In 56 out of 111 patients, AQLQ score was also examined; it increased from a baseline value of 3.0 (2.09–4.0), to 4.35 (3.625–6.39) ($p < 0.001$), 5.075 (4.8–7.0) ($p < 0.0001$), and 6.0 (5.0–7.0) ($p < 0.0001$), after 1 month, 3 months and 6 months of treatment with benralizumab, respectively (Figure 1E). These important clinical findings were paralleled by significant improvements in lung function measures. In this regard, in comparison to baseline, FEV₁ rose from 1.57 L (1.23–2.15) to 1.96 L (1.60–2.42) ($p < 0.0001$), 2.09 L (1.70–2.53) ($p < 0.0001$), and 2.10 L (1.70–2.53) ($p < 0.0001$), after 1 month, 3 months and 6 months, respectively (Figure 1F). FVC increased from a baseline value of 2.47 L (2.145–3.055) to 2.76 L (2.375–3.125) ($p < 0.001$) after 1 month, to 2.94 L (2.44–3.415) ($p < 0.0001$) after 3 months, and to 2.91 L (2.42–3.43) ($p < 0.0001$) after 6 months of benralizumab treatment (Figure 1G).

When considering the therapeutic impact on laboratory parameters, it is noteworthy that after 1 month benralizumab zeroed blood eosinophil number, which fell from 740 cells/ μ L (490–1097) to 0 cells/ μ L (0–0) ($p < 0.0001$); this result was maintained also after 3 months and 6 months of treatment, respectively (Figure 1H). In 59 out of 111 patients, we also quantified blood basophil number, thus showing that cell count decreased from baseline 46 cells/ μ L (30–90) to 6 cells/ μ L (0–20) ($p < 0.0001$) after 1 month, and to 0 cells/ μ L (0–10) ($p < 0.0001$) after 3 months as well as after 6 months, respectively (Figure 1I).

In 39 out of 111 patients, FeNO was also measured at baseline and after 1 month, 3 months, and 6 months of anti-IL-5R α therapy. FeNO levels diminished from baseline values of 48 parts per billion (ppb) (35–67) to 34 ppb (18–55) ($p < 0.01$) after 1 month, to 30 ppb (15–48) ($p < 0.0001$) after 3 months, and to 25 ppb (15–41) ($p < 0.0001$) after 6 months, respectively (Figure 1J).

Comparative Evaluation in Relation to Allergic and Non-Allergic Traits

About the effects of a 6-month treatment with benralizumab on clinical, functional and laboratory indices with respect to baseline, we found some differences between SPT negative and positive patients. The reduction of asthma exacerbation number amounted to –3 (–5 to –1) in SPT negative patients, and –5 (–7 to –3) in SPT positive subjects, respectively ($p < 0.01$) (Figure 2A). In comparison to baseline, the observed increases in ACT score were 5 points (4–9) and 9.5 points (6–13) in patients

with negative and positive SPT, respectively ($p < 0.01$) (Figure 2D). Moreover, we detected a decrease in daily SABA use, quantified as -1 inhalations (-3 to 0) in SPT negative group, and -2 inhalations (-4 to -1) in SPT positive group ($p < 0.05$), respectively (Figure 2C).

By contrast with the above findings, the following results were not significantly different between the two patient subgroups. Indeed, the decreases of daily OCS intake were -5 mg (-10 to 0) in patients with negative SPT, and -5 mg (-12.5 to -0) in subjects with positive SPT, respectively ($p = 0.3192$) (Figure 2B). AQLQ score increased by 2.5 points ($1-3.44$) in SPT negative group, and by 2.43 points ($1.6-4$) in SPT positive group ($p = 0.4845$) (Figure 2E). With respect to baseline, FEV₁ increments were 0.43 L ($0.1625-0.7275$) in patients with negative SPT, and 0.36 L ($0.0675-0.9625$) in subjects with positive SPT ($p = 0.697$) (Figure 2F). FVC increases were 0.17 L ($0.01-0.57$) in SPT negative group and 0.34 L ($0.06-0.7$) in SPT positive group ($p = 0.7589$) (Figure 2G). In addition, the decreases in blood eosinophil numbers were -740 cells/ μ L (-1100 to -520) in patients with negative SPT, and -700 cells/ μ L (-1010 to -452.5) in

subjects with positive SPT ($p = 0.6403$) (Figure 2H). The decrements of blood basophil count were -40 cells/ μ L (-60 to -20) in SPT negative group, and -44 cells/ μ L (-85 to -10) in SPT positive group ($p = 0.9243$) (Figure 2I). Moreover, FeNO level variations were -26 ppb (-37.3 to -15) in patients with negative SPT, and -17 ppb (-33 to 1) in subjects with positive SPT, respectively ($p = 0.2026$) (Figure 2J).

Lastly, we observed no significant correlation between serum IgE concentrations and the 6-month modifications elicited by benralizumab with regard to the following results, including asthma exacerbation reduction ($r = -0.05876$; $p = 0.591$) (Figure 3A), OCS intake decrease ($r = -0.06656$; $p = 0.5575$) (Figure 3B), decrement of daily SABA inhalation number ($r = -0.1706$; $p = 0.1302$) (Figure 3C), ACT score increment ($r = 0.168$; $p = 0.122$) (Figure 3D), AQLQ score improvement ($r = 0.1388$; $p = 0.3263$) (Figure 3E), FEV₁ enhancement ($r = 0.06749$; $p = 0.5571$) (Figure 3F), FVC increase ($r = 0.03773$; $p = 0.7496$) (Figure 3G), blood eosinophil decrease ($r = 0.1448$; $p = 0.1808$) (Figure 3H), blood basophil

Table I Baseline Patient Features

Characteristics	Total Population N = 111	Negative Skin Prick Test N = 51	Positive Skin Prick Test N = 60	p
Female gender, N (%)	71 (63.96)	33 (64.71)	38 (63.33)	>0.9999
Male gender, N (%)	40 (36.04)	18 (35.29)	22 (36.67)	>0.9999
Age, median values (IQR), years	56.00 (43.00–65.00)	57.00 (49.00–67.00)	51.50 (42.25–62.75)	0.0729
Duration of asthma, median val. (IQR), years	18.0 (10.00–30.00)	14.00 (10.00–21.00)	24.50 (13.00–31.75)	0.0008
FEV₁, median values (IQR), % predicted	61.00 (49.75–74.25)	66.00 (50.00–78.00)	59.00 (48.00–73.00)	0.3367
Blood eosinophils, median v. (IQR), cells/μL	740.0(200.0–1097)	750.0 (550.0–1100)	700.0 (452.5–1010)	0.5987
Blood basophils, median val. (IQR), cells/μL	44.0 (30.00–86.00)	40.00 (20.00–65.00)	46.00 (30.00–90.00)	0.7328
BMI, median values (IQR), kg/m²	26.17 (23.14–28.13)	25.21 (22.84–27.76)	27.02 (23.82–28.82)	0.0846
Smokers, N (%)	32 (28.83)	13 (25.49)	19 (31.67)	0.5321
Gastro-esophageal reflux disease, N (%)	55 (49.55)	24 (47.06)	31 (51.67)	0.7045
Nasal polyposis, N (%)	51 (45.95)	27 (52.94)	24 (40.00)	0.1867
Bronchiectasis, N (%)	27 (24.32)	12 (23.53)	15 (25.00)	>0.9999
Osteoporosis, N (%)	27 (24.32)	12 (23.53)	15 (25.00)	>0.9999
Anxiety, N (%)	21 (18.92)	11 (21.57)	10 (16.67)	0.6289
Atopic dermatitis, N (%)	13 (11.71)	1 (1.96)	12 (20.00)	0.0029
Obstructive sleep apnea syndrome, N (%)	11 (9.91)	3 (5.88)	8 (13.33)	0.2204

Note: Bold entries highlight statistically significant differences between patients with negative SPT versus subjects with positive SPT.

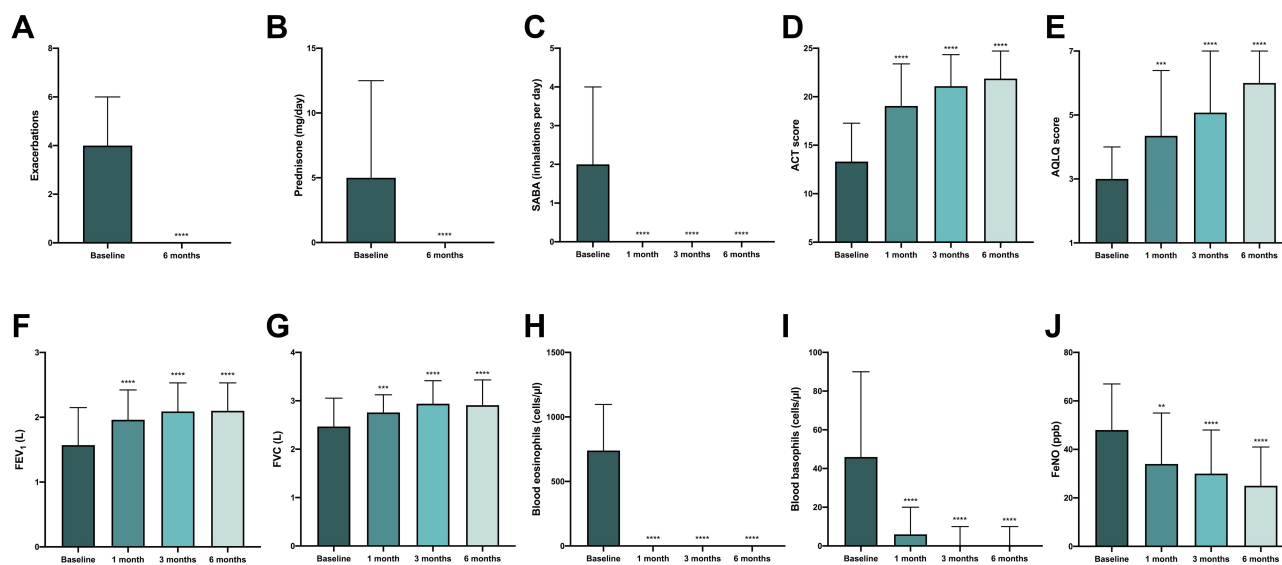


Figure 1 Efficacy of benralizumab in the whole population of patients with severe persistent eosinophilic asthma, with regard to asthma exacerbation rate (A), prednisone intake (B), daily SABA inhalations (C), ACT score (D), AQLQ score (E), FEV₁ (F), FVC (G), blood eosinophil numbers (H), blood basophil count (I), and FeNO levels (J). ACT score values are expressed as mean (\pm SD). All other parameters are expressed as median values (IQR). ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

decrement ($r = 0.06086$; $p = 0.6651$) (Figure 3I), and FeNO level reduction ($r = -0.1717$; $p = 0.3026$) (Figure 3J).

Safety and Tolerability Profile of Benralizumab

Add-on therapy with benralizumab was well tolerated, and no serious adverse reactions occurred throughout this real-life observational study.

Discussion

The current multicenter observational study further proves, within a real-life setting, that in patients with severe eosinophilic asthma benralizumab exerts very positive therapeutic effects, already documented by randomized clinical trials, such as SIROCCO and CALIMA.^{43,44} Moreover, our present data confirm, in a quite larger number of severe asthmatic subjects, recent findings referring to real-world investigations carried out in relatively few enrolled patients.^{33–38}

In particular, we herein show that the most important result experienced by our patients regarded the marked reduction of asthma exacerbations after 6 months of treatment. Such a relevant anti-asthma action of benralizumab appears to be strictly dependent on eosinophil depletion, which was detected in our patients already after 1 month of treatment. This fast and effective pharmacological activity of benralizumab is likely due to its complex

mechanism of action, consisting not only of IL-5R α blockade operated by Fab fragments but also including eosinophil apoptosis induced by antibody-dependent cell-mediated cytotoxicity (ADCC).^{24,25} With regard to prevention of asthma exacerbations, it is noteworthy that our current study also showed that benralizumab caused a significant decrease of measured levels of FeNO, another important biomarker of type-2 inflammation.⁴⁵ However, we analyzed FeNO levels only in 39 out of 111 patients, and benralizumab action was not sufficient to bring FeNO values below 25 ppb. Therefore, our findings suggest that in order to assess the overall efficacy of biological therapies targeting either IL-5 or IL-5 receptor, monitoring blood eosinophil count is clinically more relevant than measuring FeNO. Nevertheless, FeNO can represent an accessory inflammatory biomarker in these patients. Indeed, though IL-13 is the main cytokine responsible for inducing the synthesis of NO, the latter can be considered as a surrogate for airway eosinophilic inflammation,⁴⁶ which is thus responsive to the inhibitory action of benralizumab.

It is likely that the observed decrease in asthma exacerbation rate was also favored by noticeable improvements in lung function, expressed as significant FEV₁ and FVC increases, which in our real-life context resulted of a greater extent than those reported by the randomized clinical trials SIROCCO, CALIMA and BISE.^{43,44,47} Indeed, worse is the severity of airflow limitation, higher

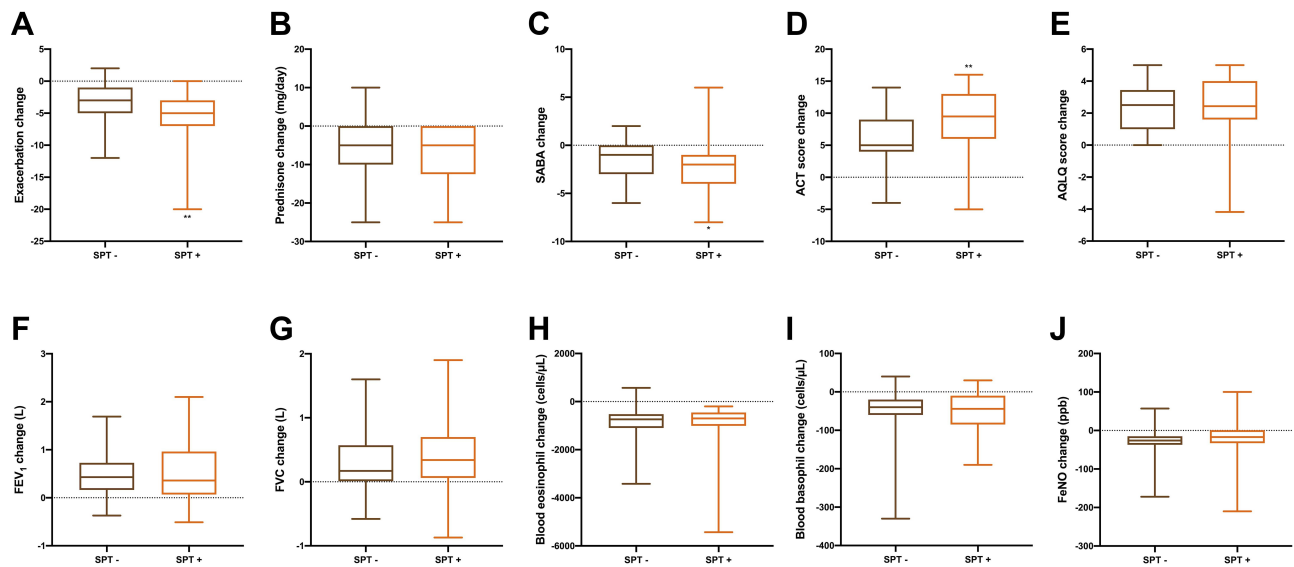


Figure 2 Efficacy of benralizumab in relation to SPT negativity or positivity, with regard to asthma exacerbation rate (A), prednisone intake (B), daily SABA inhalations (C), ACT score (D), AQLQ score (E), FEV₁ (F), FVC (G), blood eosinophil numbers (H), blood basophil count (I), and FeNO levels (J). Boxes display median values and IQR, and whiskers define maximum and minimum. * $p < 0.05$; ** $p < 0.01$.

is the tendency to manifest asthma exacerbations, that in turn promote an acceleration of lung function deterioration.⁴⁸ Therefore, it is reasonable that such a deleterious vicious circle can be effectively interrupted by benralizumab. On the other hand, also benralizumab-induced bronchodilation seems to be dependent on eosinophil depletion because high blood eosinophil counts are associated with severe degrees of bronchial obstruction.⁸ In addition to the eosinophilic inflammatory trait, the atopic status can be another phenotypic feature to be

considered when clinicians decide to prescribe benralizumab. Indeed, our results suggest that benralizumab might be even more effective in improving exacerbation rate, as well as in increasing ACT score and decreasing daily SABA use in SPT positive when compared to SPT negative patients.

Asthma exacerbation zeroing, elicited by benralizumab, made it possible for our patients to drastically lower their OCS intake. This real-life effect resulted to be even greater than that one reported by the authors of the

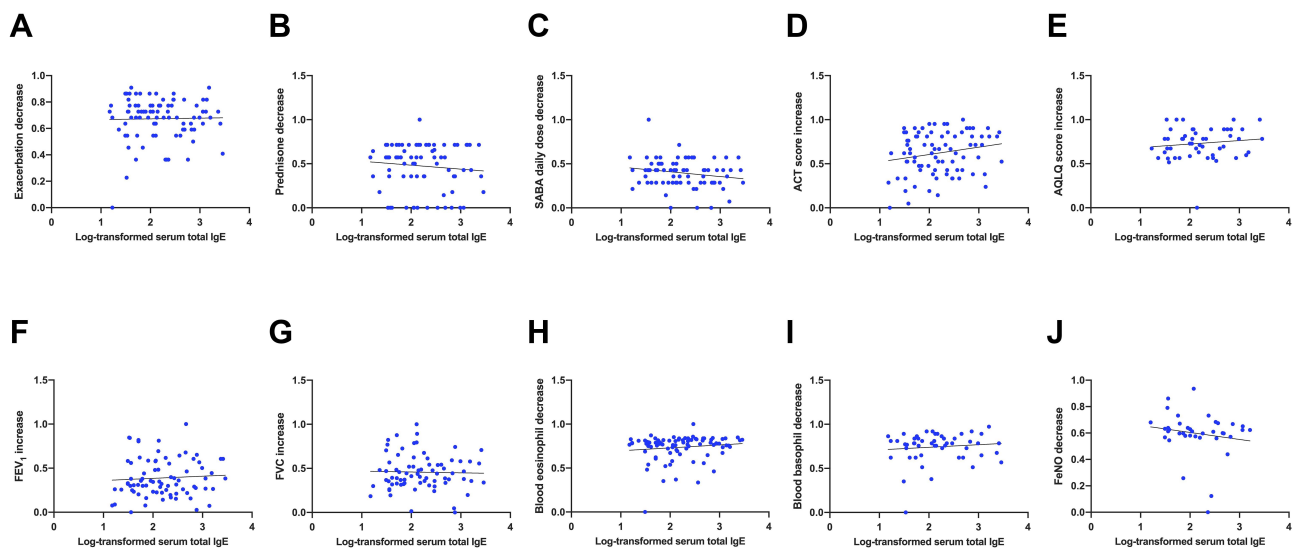


Figure 3 Correlations between serum IgE concentrations, expressed as logarithmic transformation, and 6-month modifications elicited by benralizumab, with regard to asthma exacerbation rate (A), prednisone intake (B), daily SABA inhalations (C), ACT score (D), AQLQ score (E), FEV₁ (F), FVC (G), blood eosinophil numbers (H), blood basophil count (I), and FeNO levels (J).

ZONDA trial.⁴⁹ The OCS sparing action of benralizumab is clinically relevant, given the frequent occurrence of the well-known potential consequences of OCS therapy (diabetes, hypertension, respiratory infections, osteoporosis and bone fracture, cataract and glaucoma, hypothalamic-pituitary-adrenal axis suppression, and decreased growth velocity in children).⁵⁰

In addition to the above-mentioned therapeutic benefits experienced by our patients, benralizumab also improved their quality of life and symptom control, as shown by the significant score increases of AQLQ and ACT, as well as by abrogation of daily SABA assumption. These results, obtained in routine clinical practice, further reinforce the published data referring to SIROCCO and CALIMA phase 3 trials,^{43,44} based on the use of asthma control questionnaire (ACQ)-6 rather than ACT. However, in real-life ACT is perceived by patients as more suitable than ACQ utilized in randomized controlled studies, probably because of a simpler formulation of the various questions.⁵¹ We found that after both 3 and 6 months of treatment with benralizumab, ACT score was higher than 20, which is the reference value considered as indicative of a satisfactory asthma control.⁵²

Overall, our results clearly indicate that benralizumab exerted very positive therapeutic effects in both allergic and non-allergic patients with severe eosinophilic asthma. Such findings confirm previous data coming out of a pooled analysis of SIROCCO and CALIMA trials,²⁹ as well as of some real-life experiences referring to small numbers of patients.^{33,35} In particular, when considering all benralizumab-induced changes, we detected significant differences in asthma exacerbation rate, ACT score, and daily SABA use between non-allergic and allergic subjects, thus showing that the latter ones experienced better improvements. On the contrary, no significant differences between SPT positive and negative patients were found with regard to the other study outcomes, including changes in OCS intake, AQLQ score, FEV₁, FVC, FeNO, and blood eosinophil/basophil counts. Therefore, although ACT improvement was greater in SPT positive versus SPT negative patients, we did not find any difference between these two subgroups with regard to AQLQ. These results suggest that a better symptom control does not necessarily translate into an amelioration of overall quality of life, which likely depends also on other key factors, such as the extent of eosinophilic inflammation, the impairment of respiratory function, and OCS consumption. Indeed, with regard to these three

latter aspects, we did not detect any difference between SPT positive and SPT negative subjects. However, this observation should be further confirmed because AQLQ was investigated in only 56 (50.5%) out of the 111 enrolled patients.

The powerful efficacy of benralizumab as add-on therapy of severe eosinophilic, allergic asthma, could be explained on the basis of potential drug interferences with cellular and molecular mechanisms underlying the atopic trait. In fact, elevated levels of IL-5, mature eosinophils and eosinophil progenitors are present in the induced sputum obtained from atopic asthmatic patients.⁵³ Besides depleting eosinophils, benralizumab can also elicit inhibitory effects on basophils, which express IL-5R α .⁵⁴ Indeed, in the present real-world investigation we analyzed the numbers of blood basophils in 59 (53.2%) out of the enrolled 111 study patients, thereby showing that these cell counts dropped after 1 month of benralizumab treatment, and zeroed after 3 and 6 months, respectively. By triggering the apoptosis of basophils,⁵⁵ benralizumab can eliminate a relevant cellular source of IL-4, the key cytokine responsible for Th2 cell commitment and IgE production.^{12,56} Moreover, benralizumab can also lower the number of other cells expressing IL-5R α and producing Th2 cytokines (IL-4, IL-5, IL-13) such as ILC2,⁵⁷ which play a pivotal role in the complex crosstalk between innate and adaptive immune responses, underpinning the development and amplification of allergic endotypes.⁵⁸ Benralizumab efficacy in atopic patients has also been recently confirmed by a report of our group, regarding the impressive therapeutic actions of this drug at level of upper and lower airways of patients with severe eosinophilic asthma and allergic nasal polyposis.⁵⁹

Finally, we did not observe any correlation between serum IgE concentrations and the real-life positive outcomes detected in our severe asthmatic patients during treatment with benralizumab. Hence, also these findings corroborate the results of recent pooled analyses of SIROCCO and CALIMA trials, which showed that the therapeutic effects of benralizumab were independent of IgE levels and atopic trait in subjects with severe eosinophilic asthma.^{29,60}

In conclusion, despite the typical limitations of real-life studies such as the absence of randomization protocol and placebo control, our multicenter observational investigation clearly indicates that in patients with severe eosinophilic asthma benralizumab was very effective in improving several clinical, functional, and laboratory

parameters. Within such a context, the most relevant achievable outcome of a 6-month benralizumab treatment was the complete prevention of asthma exacerbations. Benralizumab efficacy was evident in both allergic and non-allergic patients. In particular, when compared to subjects with negative SPT, patients with positive SPT experienced significantly better results with regard to changes in exacerbation rate, ACT score and daily SABA use. However, no correlation was found between study outcomes and serum IgE levels. Taken together, these real-world data further confirm that benralizumab can be a valuable therapeutic choice as add-on biological therapy for patients with severe eosinophilic asthma, characterized by either SPT positivity or negativity. SPT positivity could even provide a further clinical advantage with regard to the improvement in asthma control, elicited by benralizumab.

Acknowledgments

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Authorship Contribution

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure

The authors declare that there is no conflict of interest.

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