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Severe asthma and long-term Benralizumab effectiveness in real-life

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Abstract. – OBJECTIVE: Long-term efficacy of Benralizumab in real life is not clearly known. We assessed the long-term effectiveness persistence to anti-IL-5R treatment in a group of severe eosinophilic asthmatics.

PATIENTS AND METHODS: We retrospectively analyzed 95 individuals affected by severe asthma (36 males - 37.9%; mean age 58.1 ± 12.2) treated with Benralizumab (mean time 19.7 ± 7.2 months, range 12-35). Outcomes were evaluated at the beginning and at the end of patients' treatment periods.

RESULTS: Mean baseline blood eosinophils were 897.5 ± 720.1 cells/μL (11 ± 5.6%) decreasing to 7.4 ± 20.6 cells/μL (0.97 ± 0.26%; $p < 0.0001$) after Benralizumab. FENO likewise decreased from 63.9 ± 68.4 to 28.4 ± 23.6 ppb, while FEV_1% significantly improved ($p < 0.0001$). Mean FEF_{25-75} also increased from 45.8 ± 24.6% to 60.7 ± 24.6%, whereas RAW dropped from 202.15 ± 109.6% to 135.2 ± 54.75% ($p < 0.0001$). Also, lung volumes greatly decreased. ACT/ACQ significantly improved, while exacerbations number fell from 4.1 ± 2.4, before anti-IL-5R, to 0.33 ± 0.77, after treatment ($p < 0.0001$). Rhinitis severity levels and SNOT-22 also changed favorably. Patients that took long-term OCs were 71.6% before treatment, decreasing to 23.2% after Benralizumab ($p < 0.0001$), with an OCs dose reduction from 14.8 ± 8.9 to 1.45 ± 2.8 mg/day ($p < 0.0001$). 51.6% of subjects used SABA as needed before Benralizumab, falling to 4.2% after treatment. Several patients showed a reduction of ICS doses, SA-

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BA use and maintenance therapy step-down. Clinical/biological response with anti-IL-5R remained constant or even improved in terms of exacerbations or maintenance therapy reductions over time. On the contrary, FEF_{25-75}% improvement slowed down in the long-term. No relationship was found between baseline blood eosinophil number and therapeutic response.

CONCLUSIONS: Long-term Benralizumab effectiveness persistence in all outcomes in real life was confirmed.

Key Words:
Benralizumab, Severe asthma, Real-life, Lung function, Small airways, Symptoms, Oral corticosteroids, Long-term, Effectiveness.

Introduction

Asthmatics with uncontrolled symptoms and frequent exacerbations requiring systemic corticosteroids treatment, despite high doses of ICS, bronchodilators and antileukotrienes (step 5 of GINA guidelines), are considered affected by an asthma phenotype defined as "severe"[1,2].

Based on the major immune-inflammatory pathway involved, type-2 high, type-2 low and mixed endotypes are described for severe asthma. T2-high asthma is mainly divided into allergic and eosinophilic phenotypes[3] for which, nowadays, we have several biological treatments available in Italy. Omalizumab is indicated for severe allergic asthma, while Mepolizumab, Benralizumab and Dupilumab are recommended for severe eosinophilic asthma.

Based on blood eosinophil cut-offs ≥ 150/300 cells/μL, 61%/41%, respectively, all severe asthmatics had an eosinophilic phenotype[4]. Benralizumab has been available in Italy for about 3 years for severe eosinophilic asthma as an add-on therapy for patients whose disease is still uncontrolled despite a maximal treatment as required by step 5 of GINA guidelines[1,2]. Benralizumab is a monoclonal antibody against interleukin-5 receptor α (anti-IL5R) that depletes eosinophils by an antibody-dependent cell-mediated cytotoxicity, for patients with severe, uncontrolled asthma with eosinophilia. It is indicated when the blood eosinophil count at treatment initiation is ≥ 300 cells/μL or ≥ 150 cells/μL for patients with a frequent or prolonged therapy of oral corticosteroids (OCs)[5]. The recommended dose is 30 mg subcutaneously every 4 weeks for the first 3 months and then every 8 weeks thereafter. All major clinical trials[5-8] have demonstrated Benralizumab remarkable efficacy in improving lung function, symptoms and in significantly reducing exacerbations and OCs use. Its effectiveness is confirmed in the short term (6-12 months) by several real-life studies[9-16], some of which indicate that Benralizumab is also effective in chronic rhinosinusitis and nasal polyposis, although this efficacy was evaluated only in a short period of treatment with anti-IL-5R[12,16-20]. Although some trials[21,22] indicate that Benralizumab effectiveness remains unaffected over the long term, little is known, however, about the persistence of efficacy in the long term of anti-IL-5R in real-life. Furthermore, few studies[11,13,16,23] have also investigated a possible anti-IL-5R effectiveness on small airways. FEF_{25-75} and lung volumes, indicators of the small airway obstruction, improved after 6-12 months of Benralizumab therapy. However, we do not know whether its efficacy on the small airways remains unchanged over time. On the basis of this premise, we wanted to verify the persistence of Benralizumab long-term effectiveness in real life on all clinical, functional and therapeutic aspects in a group of patients with severe eosinophilic asthma responsive to treatment with anti-IL5R.

Patients and Methods

This observational multicenter retrospective study considered 95 severe asthmatics who had been treated with Benralizumab for more than 12 months. All recruited patients were considered responsive to treatment, as after 6 months they had shown a good response to Benralizumab, in accordance with the guidelines which suggest re-evaluating the patient after 3-6 months of biological treatment to assess its efficacy[2]. All centers shared a common database reporting the clinical, functional and biological characteristics of the enrolled patients. All subjects had a severe asthma diagnosis fulfilling all the diagnostic criteria established by guidelines[1]. They had been poorly controlled even while using high ICS doses, long-acting bronchodilators, anti-leukotrienes (montelukast) and/or OCs, which made it necessary to add Benralizumab, as recommended by steps 5 of GINA asthma guidelines[1]. All patients had to be adherent to inhaled treatments and had to use devices correctly. Benralizumab was prescribed

to subjects that showed a peripheral blood eosinophil count above 300/μL and more than 150/μL in patients continuously or frequently treated with OCs before the first Benralizumab injection. All the included subjects received 30 mg of anti-IL-5R subcutaneously every 4 weeks for the first 3 months and then every 8 weeks thereafter. Information concerning allergic sensitization (*Dermatofagoides pteronissinus* and *D. farinae,* Grass mix*,* Parietaria*, Olea europaea, Cupressus sempervirens, Betula pendula, Alternaria tenuis, Aspergillus f.* and dog-cat dander, and others), IgE serum values, blood eosinophil counts, the presence of rhinitis, sinusitis, nasal polyposis, and/or other comorbidities (systemic hypertension, chronic heart disease, diabetes, osteoporosis, gastro-esophageal reflux, COPD, obesity, others), age, smoking habits and body mass index (BMI) were required for each patient. Furthermore, asthma onset age and treatment period were also recorded. Lung function variables (FEV_1%, FEF_{25-75}%, RV%, TLC%, Raw%), Asthma Control Test (ACT), asthma control questionnaire (ACQ), blood eosinophil counts, fractional exhaled nitric oxide (FENO) and number of moderate/severe exacerbations (that required at least 3 days of OCs treatment) were evaluated at the time of Benralizumab prescription and at the end of each patient's treatment period. Rhinitis severity level (according to ARIA guidelines)[24] and Sinonasal Outcome Test 22 (SNOT-22) were measured before and after treatment in some patients. ICS doses, OCs use/doses, SABA usage as rescue medication, Montelukast and other inhaled drugs taken, plus their step-downs/step-ups, were also considered. The daily dosage of Beclomethasone dipropionate or the equivalent dose of other inhaled corticosteroids (ICS) (Fluticasone, Budesonide or others) were expressed as low (≤ 500 mcg), medium (500-1,000 mcg) or high (≥ 1,000 mcg), according to GINA classification of ICS dose equivalence[1]. Doses of ICS and OCs were evaluated at the time of initial and last check required by the protocol (at least 12 months or more). SABA use (number of times a week) in the month before starting Benralizumab and during the 30 days before the end of each patient's anti-IL5R treatment period was also considered. Furthermore, we also investigated whether there was a relationship between the treatment period and the various outcomes, as well as between blood eosinophil counts measured at baseline and clinical/biological/functional responses. Only standard techniques were used to measure lung function variables, while small-airway disease parameters (e.g., oscillometry or washout-techniques) were not assessed, as only few centers had these techniques which, however, are not usually measured in clinical practice.

Statistical Analysis

Continuous variables were expressed as means and standard deviations (SD). Categorical variables were considered as number of cases and percentages. Comparisons of continuous variables were performed by using the paired *t*-test or the Wilcoxon Signed-Rank test in order to assess the difference between "before" and "after" treatment. Categorical variable frequencies were compared by Chi-square test or Fisher's exact test as appropriate. As already said, we wanted to evaluate whether Benralizumab therapy period and blood eosinophil count at baseline (before anti-IL-5R) could influence the response to treatment, i.e., whether a longer therapy time or a higher number of circulating eosinophils at baseline could correspond to a greater functional/clinical/biological benefit. To verify the association between the response to treatment (in terms of outcome changes: post-treatment – pre-treatment) and months of therapy with Benralizumab, multivariate regression models were used, corrected for the subjects' individual characteristics (listed in Table I). In case the response to treatment was measured with continuous variables, linear regression models were used, while with nominal variables, logistic regression models were applied: one model for each response variable. The same procedure was employed to verify the association between response to treatment and number of pre-treatment blood eosinophils. p-value < 0.05 was considered to indicate the significance of the results.

Results

This study included 95 severe asthmatics (36 males - 37.9%; mean age 58.1 ± 12.2) treated with Benralizumab for a mean time of 19.7 ± 7.2 months (range 12-35 months). All patients' baseline characteristics are reported in Table I. No safety concerns were noted with the use of Benralizumab. Until the end of the observation period of each patient there was no switch to another biologic or dropped out from the study.

Table I. Characteristics of 95 patients treated with Benralizumab for more than one year.

	Patients treated with Benralizumab
Age	58.1 ± 12.2
Sex (M/F)	36/59 (37.9/62.1%)
Smokers	4 (4.3%)
Ex-Smokers	27 (28.7%)
BMI	26.49 ± 4.16
Age of asthma onset (yrs)	36.1 ± 14.5
FEV_1% pre-Benralizumab	74.1 ± 24.9
FEV_1/FVC pre-Benralizumab	65.8 ± 12.4
Aspirin intolerance/allergy	9 (9.5%)
House dust mite	29 (30.5%)
Pollens	32 (33.7%)
Moulds	6 (6.3%)
Cat/dog dander	11 (11.6%)
Food allergy	4 (4.2%)
Drug allergy	16 (16.8%)
Rhinitis	46 (48.4%)
Sinusitis	36 (37.9%)
Nasal Polyposis	39 (41.1%)
Hypertension	19 (20.2%)
Chronic Heart Disease	5 (5.3%)
Gastro-esophageal reflux	33 (35.1%)
Diabetes	4 (4.3%)
Osteoporosis	8 (8.5%)
Obesity	18 (18.9%)
COPD	2 (2.1%)
Autoimmune/allergic disease	25 (26.6%)
Anxious/depressive disease	28 (29.5%)
Other comorbidities	27 (29%)
Total serum IgE UI/ml	452.16 ± 730.89
Blood eosinophils (n°/mm^3)	897.5 ± 720.1
Months of Benralizumab treatment	19.7 ± 7.2
Previous treatment with other biologics	20 (21%)
N° of patients treated for 12 months	33 (34.7%)
N° of patients treated for 13-24 months	34 (35.8%)
N° of patients treated for > 24 months	28 (29.5%)

Lung Function Results

Lung function after the biological therapy improved significantly (Figure 1). Mean FEV_1 before Benralizumab was 74.1 ± 24.9% (2.03 ± 0.79 L), whereas it was 87.9 ± 20.8% (2.4 ± 0.78 L) after treatment (Figure 1A; $p < 0.0001$). Pre-treatment mean FEF_{25-75} was 45.8 ± 24.6% (1.07 ± 0.76 L/s), while it was 60.7 ± 24.6% (1.58 ± 0.92 L/sec) at the end of therapy (Figure 1B; $p < 0.0001$). When we measured lung volumes, RV and TLC pre-treatment mean values were 126.9 ± 49.6% (2.58 ± 1.13 L) and 105.7 ± 22.4% (5.9 ± 1.38 L) respectively, whereas after Benralizumab they were 111.5 ± 41.7% (2.35 ± 1 L) (Figure 1C; $p = 0.020$) and 101.9 ± 18.4% (5.76 ± 1.33 L) (Figure 1D; $p = 0.051$). Values of airway resistance (RAW) were 202.15 ± 109.6% (2.14 ± 3.3 kPa*s/l) before treatment and 135.2 ± 54.75% (0.93 ± 0.9 kPa*s/l) after about 20 months of Benralizumab (Figure 1E; $p < 0.0001$).

Clinical Outcome Changes

Benralizumab also led to a significant improvement in ACT (mean pre: 15.2 ± 4.1; mean post: 21.9 ± 3; $p < 0.0001$; Figure 2A) and ACQ (mean pre: 3.3 ± 1.07; mean post: 1.03 ± 0.92; $p < 0.0001$; Figure 2B). An important exacerbation reduction was also observed, which dropped from 4.1 ± 2.4, observed before Benralizumab, to 0.33 ± 0.77 after treatment (Figure 2C; $p < 0.0001$). Nasal symptoms also significantly rose. SNOT-22 score improved from 47.2 ± 22.9 to 28 ± 21.1 (Figure 2D; $p < 0.0001$). Subjects with or without intermittent and moderate/severe rhinitis were 23.9%, 30.4% and 45.7% before Benralizumab, whereas they amounted to 37%, 39.1% and 23.9% respectively after treatment (Figure 2E; $p = 0.08$).

Biomarkers Results

Pre-treatment total IgE values were similar to measurements made after therapy (495 ± 906.4 *vs.*

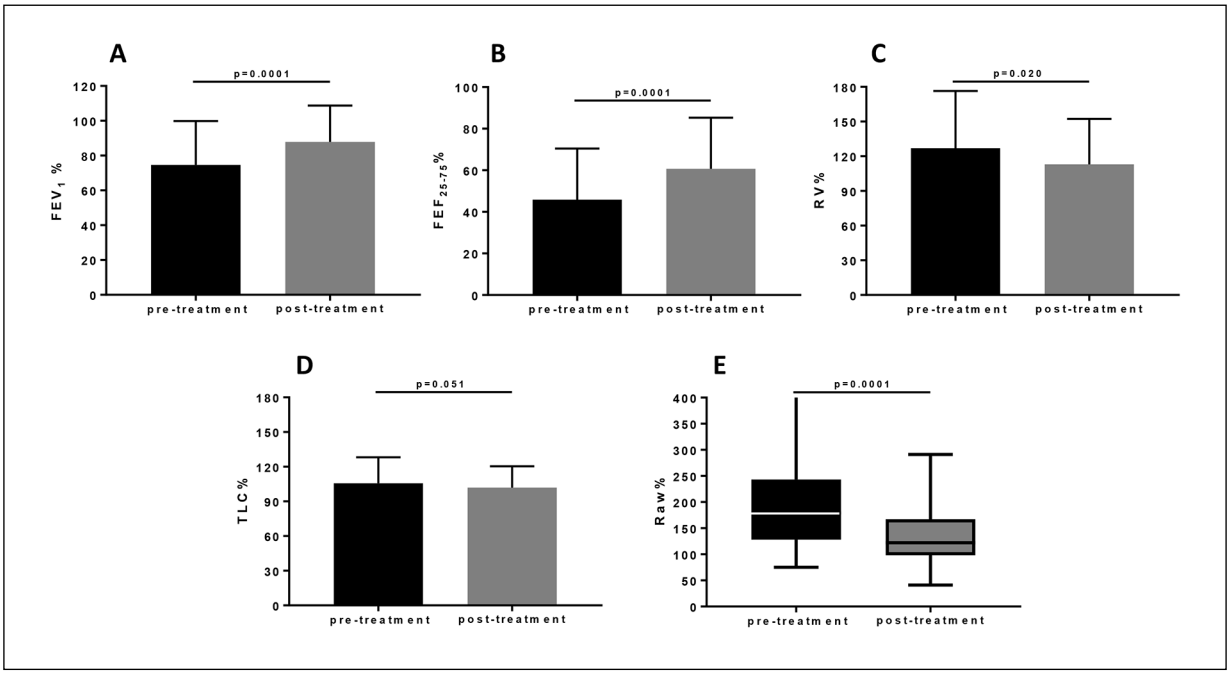

Figure 1. FEV_1% (**A**), FEF_{25-75}% (**B**), RV% (**C**), TLC% (**D**) and Raw% (**E**) measured before (pre-treatment) and after (post-treatment) at least 12 months of Benralizumab therapy.

453.4 ± 863.5 UI/ml; Figure 3A; $p = 0.158$). Mean baseline blood eosinophil level was 897.5 ± 720.1/μL (11 ± 5.6%) decreasing to 7.4 ± 20.6/μL (0.97 ± 0.26%) after Benralizumab (Figure 3B; $p < 0.0001$). Mean FENO level likewise decreased from 63.9 ± 68.4 to 28.4 ± 23.6 ppb (Figure 3/C; $p < 0.0001$).

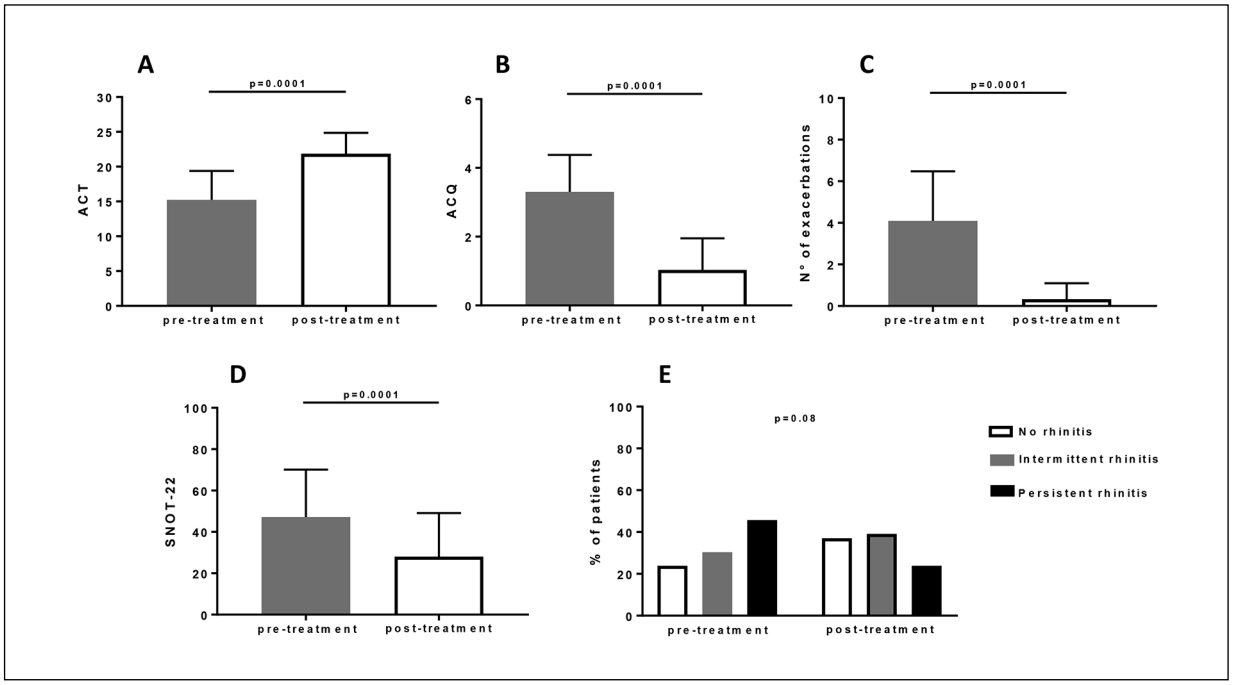

Figure 2. ACT (**A**), ACQ (**B**) rates, number of exacerbations (**C**), SNOT-22 score (**D**) and number of subjects with no/intermittent/persistent rhinitis (**E**) observed before (pre-treatment) and after (post-treatment) Benralizumab therapy.

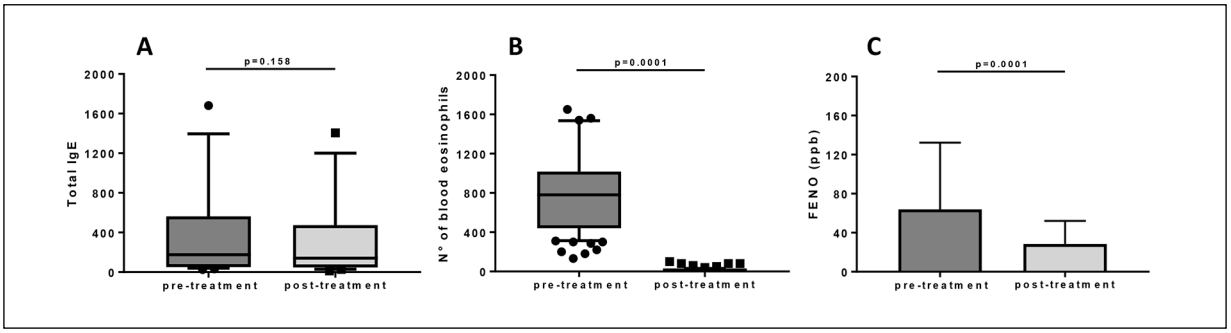

Figure 3. Total IgE (UI/ml) (**A**), blood eosinophils counts (n°/mm^3) (**B**) and FENO values (ppb) (**C**) obtained before (pre-treatment) and after (post-treatment) Benralizumab therapy.

Maintenance Therapy Level and Oral Corticosteroid Use

Overall, a significant ICS dose reduction was observed after almost 20 months of Benralizumab. In fact, 24.5, 47.9 and 27.7% of all patients took low, medium and high ICS doses respectively before treatment, whereas percentages changed to 37.2, 59.6 and 3.2% (Figure 4A; $p < 0.0001$) after anti-IL-5R. Subjects who were taking ICS low/medium doses before Benralizumab were all on OCs treatment; consequently, their doctors decided to reduce the previous high ICS doses (before the study) in order to prevent adverse effects. On the whole, we observed a maintenance treatment step down (ICS dose reduction and/or LABA/LAMA/Montelukast discontinuation) in 66.3% of subjects (Figure 4/B). Patients that took long-term OCs were 71.6% before treatment, decreasing to 23.2% after approximately 2 years of Benralizumab (Figure 4C; $p < 0.0001$). In particular, 48.4% of subjects that took OCs showed an OCs suspension. OCs doses, in patients that took them continuously, dropped from 14.8 ± 8.9 mg/day to 1.45 ± 2.8 mg/day after 20 months of anti-IL-5R treatment (Figure 4D; $p < 0.0001$). One month before beginning Benralizumab, 51.6% of subjects had taken SABA, whereas only 4.2% of them had used SABA one month before the end of each patient's anti-IL-5R treatment period ($p < 0.0001$). Individuals taking SABA reduced the

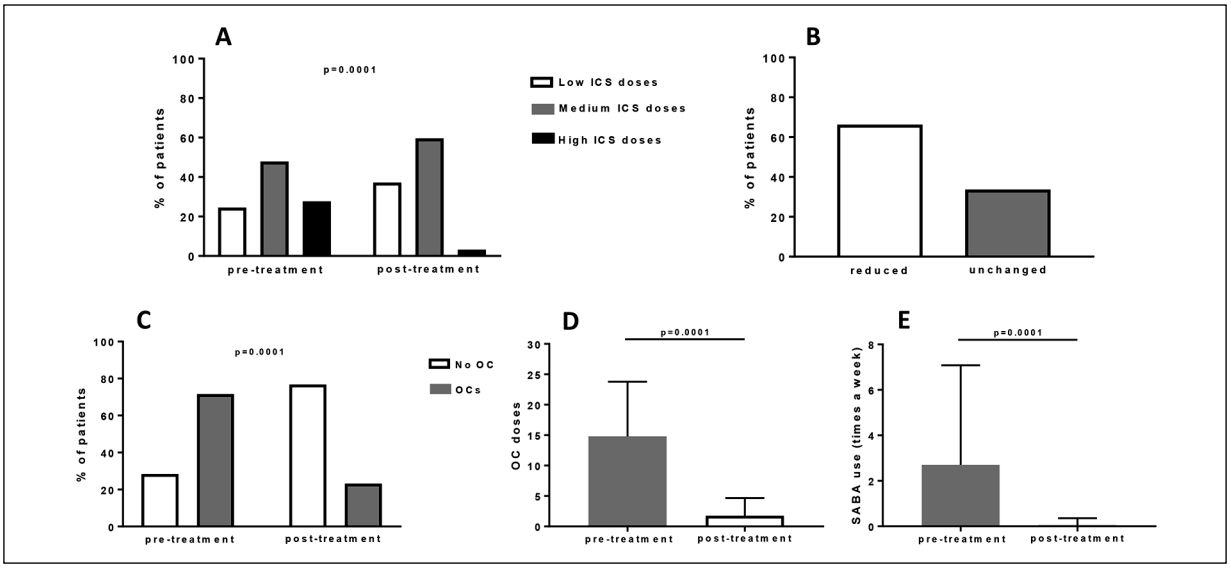

Figure 4. Number of patients with low/medium/high doses of ICS treatment at the beginning and at the end of Benralizumab treatment (**A**). Percentages of patients whose maintenance therapy level was modified after anti-IL5R therapy (**B**). Number of subjects that took OCs (**C**), OCs doses (**D**) and SABA use (**E**) detected before (pre-treatment) and after (post-treatment) Benralizumab.

number of times per week they used it from 2.7 ± 4.4 to 0.05 ± 0.23 (Figure 4E; $p < 0.0001$) after nearly two years of anti-eosinophilic therapy.

Relationship Between Time of Treatment/Blood Eosinophil Counts and Response to Treatment

Treatment time does not seem to influence the changes obtained after Benralizumab in the various outcomes considered (Table II), except for FEF_{25-75}%, the number of exacerbations and the level of maintenance therapy associated with anti-IL-5R. The change in FEF_{25-75}% was inversely related to the therapy period (β = - 0.583; p = 0.044; Table II). The improvement appeared to slow down with the Benralizumab treatment length. In fact, the increase of FEF_{25-75}% was 25.9 ± 30.4 at 12 months of therapy, 11.4 ± 21.7% after 13-24 months and 5 ± 11.5% after > 25 months of Benralizumab. On the contrary, there was a negative relationship between Benralizumab months of treatment and exacerbation number changes (β = - 0.090; p = 0.007; Table II). In other words, the reduction of exacerbations appears progressive during therapy. Furthermore, treatment length was associated to a higher risk of having a reduced level of maintenance therapy after Benralizumab (OR: 0.911 [0.844-0.983]; p = 0.017; Table II). On the contrary, no relationship was found between the level of circulating eosinophils and the various outcomes considered in the study (Table III). Basically, after Benralizumab, different levels of blood eosinophils at baseline did not differently influence the various outcome improvements.

Discussion

After a mean of 20 months (range 12-35 months) of Benralizumab treatment, an improvement in all outcomes considered (lung function, biological markers, symptoms, OCs/ICS-sparing and therapy level maintenance) was observed in severe eosinophilic asthma. Basically, this study confirms the long-term persistence of Benralizumab efficacy in real life. In fact, we did not observe any relationship between treatment time and most of the outcomes considered, confirming that response with anti-IL-5R remained constant or even improved in terms of exacerbation reduction over time. The other existing real-life studies to date confirmed the effectiveness of such biologic in severe asthma but with results

Table II. Relationships between time of treatment (months) and changes in various outcomes obtained after Benralizumab (post-values – pre-values).

	β	*p*
Δ FEV_1%	-0.191	0.457
Δ FEF_{25-75}%	**-0.583**	**0.044**
Δ VR %	-0.936	0.302
Δ TLC %	-0.521	0.112
Δ RAW %	2.370	0.227
Δ ACT	-0.017	0.769
Δ ACQ	-0.020	0.527
Δ SNOT-22 score	1.095	0.249
Δ of asthma exacerbations	**-0.090**	**0.007**
Δ FENO	0.733	0.700
Δ of SABA use as needed	-0.008	0.899
Δ of blood eosinophils N°	-12.54	0.240
Δ of Oral Corticosteroids doses after B.	0.184	0.428
	OR	*p*
Risk of having rhinitis after B. (*vs.* no rhinitis)	1.020 [0.881-1.181]	0.791
Risk of having a reduced level of maintenance therapy after B. (*vs.* stable level)	**0.911 [0.844-0.983]**	0.017

Linear (β) logistic (OR [95% CI]) regression models were applied for each outcome. Models were adjusted for all confounding factors listed in Table I. The bold highlights the outcomes with statistical significance compared to the other non-significant ones. FEV_1, forced expiratory volume in one second; FEF_{25-75}%, forced expiratory flow at 25-75%; RV, residual volumes; TLC, total lung capacity; Raw, airway resistance; ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; SNOT-22, Sinonasal Outcome Test; SABA, short-acting β2-agonist; ICS, inhaled corticosteroids; OC, oral corticosteroids; FENO, fractional exhaled nitric oxide.

Table III. Relationships between baseline (pre-treatment) blood eosinophil counts and changes in various outcomes obtained after Benralizumab (post-values – pre-values).

	β	*p*
Δ FEV_1%	0.001	0.731
Δ FEF_{25-75}%	0.006	0.104
Δ VR %	0.004	0.683
Δ TLC %	0.0001	0.884
Δ RAW %	-0.015	0.580
Δ ACT	0.001	0.065
Δ ACQ	-0.001	0.061
Δ SNOT-22 score	-0.025	0.137
Δ of asthma exacerbations	-1.95	0.952
Δ FENO	-0.009	0.797
Δ of SABA use as needed	-0.001	0.443
Δ of blood eosinophils N°	**-1.000**	**0.0001**
Δ of Oral Corticosteroids doses after B.	-0.001	0.479
	OR	*p*
Risk of having rhinitis after B. (*vs.* no rhinitis)	0.999 [0.997-1.000]	0.137
Risk of having a reduced level of maintenance therapy after B. *(vs.* stable level)	1.000 [1.000-1.001]	0.327

Linear (β) logistic (OR [95% CI]) regression models were applied for each outcome. Models were adjusted for all confounding factors listed in Table I. The bold highlights the outcomes with statistical significance compared to the other non-significant ones.

limited to only 6-12 months of observation. These results are in line with what was observed in two trials[21,22] conducted for 2 and 5 years, respectively, which confirmed the persistence of a stable efficacy of Benralizumab over the long term.

FEV_1% improvement, after Benralizumab**,** was greater than the one encountered in the main clinical trials. In fact, we found a FEV_1 increase of over 300 ml in real-life after approximately 20 months of treatment *vs.* a FEV_1 variation of 116-159 ml after one year of therapy[8]. This result suggests a possible Benralizumab time-dependent effect on lung function, i.e., a longer treatment time may correspond to a greater FEV_1 increase, suggesting a possible influence of anti-IL-5R on airway remodeling. Lung function improvement may be also secondary to IL-5 induced bronchial hyperresponsiveness reduction. In fact, targeting IL-5 pathway with monoclonal antibodies, in particular with Benralizumab, was an effective strategy to prevent airways hyperreactivity[25] and consequently lead to lung function improvement.

Our study also highlights the long-term Benralizumab efficacy on small airways. In fact, FEF_{25-75}% and RAW% significantly improved after approximately a mean of two years. Lung volumes (RV, TLC) also showed a significant reduction after treatment with anti-IL-5R, thus confirming the improvement of small airway obstruction with its consequent lung desufflation. Other studies affirmed the improvement of small airway impairment, both in terms of FEF_{25-75}%[13] and in lung volume improvement[11,23], although such results were assessed after a very short treatment.

FEF_{25-75}% and (RAW) are the spirometric variables most commonly cited as indicators of small airway obstruction[26]. Furthermore, small airway impairment might be responsible for long-term persistent asthma and the subsequent risk for poor asthma outcomes, independently of large airway status[27,28]. Our findings suggest a possible anti-inflammatory effect of Benralizumab, particularly addressed in the small airways. In severe asthmatics, a marked reduction in FEF_{25-75}% and RAW% could indicate a greater impairment of the small airways due to a significant inflammation located in that district. Therefore, their considerable impairment may give a specific indication to biological treatments, especially with Benralizumab which might be the most targeted therapy to treat distal lung regions.

Another feature of this study is the evidence of a significantly negative relationship between treatment period and FEF_{25-75}. This means that, according to our study, improvement in small airway obstruction slows down over time. In fact, we observed a greater FEF_{25-75} improvement in the first 12 months, whereas it was lower in the following period of time. Similarly, in other tri-

als[6,8], it was also observed, after an initial significant FEV_1 increase, a reduced lung function improvement after 40-48 months of Benralizumab treatment. We hypothesize an efficacy slowdown over time due to airway remodeling persistence despite treatment. In fact, eosinophilic inflammation markers were associated to lower baseline lung function and lung function decline[29-35]. However, other studies on a larger population are needed to clarify this aspect.

Regarding asthma symptoms, Benralizumab produced a significant ACT score improvement. ACT variations were higher than the accepted minimal clinically important differences of 3 points in real life[36], thus confirming an excellent anti-IL-5R effectiveness on symptoms. ACQ changes were also higher than significant clinical differences of 0.5 points and of what observed in clinical trials[7,8]. The improvement obtained in our study was similar to what observed in other real-life studies after one year of Benralizumab[37]. This means that its induced improvement in symptoms is rapid and appears to remain stable even over 12 months.

In our study, a major exacerbation number reduction (about 90%) was observed after an average of 20 months of anti-IL-5R treatment. This result was similar to what was observed by two other real-life studies[14,15], one after 6 months[14] and the other after 48 weeks of treatment[15]. This suggests that Benralizumab effect on exacerbations is quite rapid and that it lasts over time. In fact, we noted that the exacerbation number reduction is related to treatment duration (a longer duration leads to a greater improvement in terms of exacerbation reduction), likely due to a persistent eosinophil depletion in time. This is in line with a recent study[22] that has observed that among patients with severe, uncontrolled eosinophilic asthma receiving Benralizumab for up to 5 years, long-term blood eosinophil depletion was associated with an asthma exacerbation rate reduction that was steady through a long-term follow-up.

Nasal symptoms also significantly improved with treatment. Although measured on a small number of patients, SNOT-22 score improved significantly. The rhinitis severity level also changed favorably with treatment. Other real-life studies[12,16,20] confirmed a similar significant improvement in SNOT-22. According to our study, such improvement persists unchanged over time. Therefore, Benralizumab could also play a role in allergic/eosinophilic chronic rhinosinusitis. In fact, some trials**,** specifically designed for the study of nasal symptoms in chronic rhinosinusitis with nasal polyps (CRSwNP)**,** showed that Benralizumab, when added to standard-of-care therapy, reduced NPS, nasal blockage, and sense of smell problem compared to placebo in patients with CRSwNP[17-19].

Similarly to other studies[21,22], our research argues that eosinophils depletion is long-lasting. FENO, an airway T2 inflammation marker, also significantly decreased after anti-IL-5R. Such result had already been found by other authors[9-16] in the short time. The eosinophilic asthma phenotype is characterized by high eosinophil levels in induced sputum and peripheral blood and is associated with more frequent symptoms/exacerbations and a greater airflow limitation[38,39]. Failure to reduce eosinophils, even after maximal therapy, could be associated with unstable asthma and a reduced clinical and functional response to treatment[40,41]. Therefore, the eosinophilic airway inflammation reduction is the target that must be achieved to treat the eosinophilic asthma phenotype by using antieosinophilic therapies and, in particular, Benralizumab. This study also highlights that such biological treatment does not appear to affect changes in IgE values. However, the ineffectiveness on IgE does not seem to impact on the response to Benralizumab in any way. This also appears to be confirmed by another study[42] that has highlighted that patients with severe eosinophilic asthma treated with Benralizumab had considerable reductions in exacerbation risk**s**, regardless of IgE concentrations. As follows, it acts at a different level of the asthma inflammatory cascade, exclusively inhibiting/reducing eosinophils. This could suggest the possibility of treating severe asthmatics by combining an anti-IL-5R with an anti-IgE acting on two different sites of the asthmatic inflammatory cascade, which could lead to an additive/synergistic therapeutic effect.

Our study showed that there was an ICS dose reduction in about 25% of patients after Benralizumab. We also observed that about 35% of patients generally had a reduction in maintenance therapy associated with Benralizumab (ICS, LABA, LAMA, antileukotrienes reduction/discontinuation) after approximately 2 years of biologic therapy. This result had also been observed with Mepolizumab in a previous study[43]. These reductions/suspensions of maintenance therapy did not appear to have had an impact on disease control in our study. Therefore, it can be assumed that in some subjects, if confirmed by studies that specif-

ically analyze this issue, a therapy based mainly on just a biologic therapy may be hypothesized. A reduced use of controller drugs, when effected on a large number of patients, might also have pharmaco-economic repercussions[44]. According to these results, it is possible to hypothesize that therapy with Benralizumab and perhaps also with other biological treatments, could lead to a remission, albeit partial, of the disease.

In addition, a remarkable reduction of SABA use as needed was obtained after Benralizumab (a drop from 51.6 to 4.2%). Such reduction indirectly indicates an improvement in symptoms, in asthma control and a reduced risk of future exacerbations/OCs use. Three or more SABA canisters/year was the cut-off that best predicted an increased risk for asthma-related exacerbations, hospitalization/emergency department/urgent care and use of systemic corticosteroids[45-48]. Therefore, one of the goals of asthma treatment is to get the patient to utilize as little SABA as needed, which can be effectively achieved with Benralizumab.

Our study also showed that this biologic led to an OCs suspension in about 50% of subjects being treated with them. Such result was similar to other studies[11,13,15] that found that 50-60% of patients discontinued OCs treatment. Furthermore, an OCs dose reduction of 90% was observed after Benralizumab, a result similar to what observed by other authors[5,10,13,15]. OCs sparing was also obtained with other biological treatments[10,43]. However, our study confirms that OC sparing is prolonged and does not seem to decrease over time. A recent systematic review[49], investigating the real-world extent and burden of systemic corticosteroids for asthma, showed that oral/systemic corticosteroids are commonly used for asthma control and that both their long-term and repeated short-term use are associated with an increased risk of acute and chronic adverse events. Clinicians have to balance the benefits of corticosteroids use against these risks. Therefore, in the management of severe asthmatics, who take OCs both continuously and for repeated short periods, a biological therapy must always be considered.

As we have already mentioned, treatment length does not appear to influence the response to Benralizumab except for FEF_{25-75}%, exacerbations and level of therapy maintenance when we applied a multivariate analysis adjusted for all confounding factors. This suggests that the clinical/biological response with anti-IL-5R remains constant or even improves in terms of exacerbation reduction over time. This result appears, as already said, to be in line with the outcomes of two trials[21,22] with follow-ups at 2 and 5 years. Significant efficacy was also maintained over time with other biologics (Mepolizumab and Omalizumab)[50-53]. However, as there are no long-term head-to-head comparison studies on the various biologics, it is not possible to establish whether there are any differences in efficacy in the long term. We also found that treatment length was associated to a lower risk of having a reduced level of maintenance therapy. This indicates that, with time, patients undergo a dose reduction/discontinuation of some maintenance therapy drugs associated with Benralizumab, suggesting that maximal maintenance therapy may not be necessary to achieve asthma control lasting over time when using anti-IL-5R.

A recent real-world effectiveness study[15] on Benralizumab highlighted that a higher eosinophil counts as baseline characteristic seems to be associated with a superior response to Benralizumab. On the contrary, we did not find any relationship between the number of blood eosinophils measured before treatment and the therapeutic response to Benralizumab, hypothesizing that, according to our study, anti-IL-5R efficacy is the same, regardless of baseline blood eosinophil levels.

Conclusions

Benralizumab demonstrated long-term effectiveness persistence in improving lung function, asthma/rhinosinusitis symptoms and in reducing exacerbations in real-life settings. It was shown to be particularly effective in improving small airway obstruction, even after a long period of treatment, suggesting that Benralizumab could be especially considered when there is a significant small airway impairment in severe asthma. Furthermore, it confirmed to be highly and persistently effective in OCs/ICS-sparing, in reducing SABA use as needed and, overall, it might also lead to exacerbation reduction and maintenance therapy step-down, which appeared to be also progressive with Benralizumab treatment length thus confirming its prolonged efficacy over time, with possible consequences for costs and adverse pharmacological events. Conversely, the improvement in small airway obstruction seemed to slow down during long-term treat-

ment, probably due to the persistence of airway remodeling despite the biological therapy. Baseline circulating eosinophil levels did not appear to influence the response to anti-IL-5R treatment in real life.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

The study was approved by "Area Vasta Sudest Ethical Committee (C.E.A.S.V.E.), Azienda Ospedaliera Universitaria Senese and Azienda USL Toscana Sud-Est" (Protocol BENRA, No. 12 - 16/02/2021; reference EC: 19117; determination: N° 357, 16/02/2021) and by the Ethics Committees of each participating center.

Informed Consent

Confidentiality of patients' data was totally insured, and informed consent was provided by each participant.

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