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Original article

Real-Life effects of benralizumab on exacerbation number and lung hyperinflation in atopic patients with severe eosinophilic asthma

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ABSTRACT

Background: The humanized monoclonal antibody benralizumab targets the α subunit of the interleukin-5 (IL-5) receptor and the FcγRIIIa receptor expressed by natural killer cells. Through this dual mechanism of action, benralizumab neutralizes the pro-eosinophil functions of IL-5 and promotes eosinophil apoptosis.
Objectives and methods: The present real-life study aimed to evaluate, in 22 allergic patients with severe eosinophilic asthma, the effects of benralizumab on asthma exacerbations and lung hyperinflation.
Results: In this regard here we show that, after 24 weeks of add-on treatment, benralizumab completely depleted peripheral blood eosinophils (from 810 to 0 cells/μL; $p < 0.0001$), and significantly decreased both asthma exacerbation number (from 4 to 0; $p < 0.0001$) and residual volume (from 2720 to 2300 mL; $p < 0.01$). Moreover, at the same time point (24 weeks) benralizumab also increased pre-bronchodilator FEV_1 (from 1295 to 1985 mL; $p < 0.0001$), FVC (from 2390 to 2974 mL; $p < 0.0001$), FEF_{25-75} (from 0.6 to 1.42 L/sec; $p < 0.0001$), IC (from 1940 to 2460 mL; not significant), and ACT score (from 14.73 to 22.95; $p < 0.0001$), as well as reduced prednisone intake (from 25 to 0 mg; $p < 0.0001$).
Conclusion: In conclusion, our results suggest that via its anti-eosinophil actions benralizumab improved airflow limitation, lung hyperinflation, and respiratory symptoms, as well as lowered asthma exacerbation rate and abrogated OCS consumption in most patients.

1. Introduction

Asthma is a widespread and heterogeneous respiratory disease, characterized by variable airflow limitation expressing as different phenotypes driven by complex pathobiologic mechanisms (endotypes) [1–4].In particular, bronchial eosinophilia occurs in the majority of patients with either allergic or non allergic asthma, and elevated numbers of sputum/blood eosinophils are frequently concomitant with recurrent disease exacerbations and severe airflow limitation [5]. Indeed, in severe asthma airways are often featured by a predominant eosinophilic inflammation, triggered by type-2 (T2) cellular responses involving T helper 2 (Th2) lymphocytes and group 2 innate lymphoid cells (ILC2) [6–9].The secretory pattern of these cells includes several cytokines such as interleukins (IL)-4, 5, 9 and 13, that induce immunoglobulin E (IgE) synthesis, eosinophilic inflammation, mast cell development and bronchial hyperresponsiveness, respectively [10]. Hence, it is quite common that eosinophilic phenotypes coexist with an overproduction of IgE, defined as atopy [11–13].

Most allergic eosinophilic patients achieve a good asthma control upon treatment with inhaled corticosteroids (ICS), eventually integrated by the addition of long-acting β_2-adrenergic agonists (LABA) and systemic allergen-specific immunotherapy [14,15]. However, a relatively small percentage of eosinophilic asthmatic patients are inadequately controlled, and experience a poor response to both ICS and oral corticosteroids (OCS) [7,16].This therapeutic failure can be caused by several underlying mechanisms, including a huge secretion of IL-5 and IL-13, a down-regulation of histone deacetylases, an overexpression of the dysfunctional β isoform of the glucocorticoid receptor (GR), and/

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or a GR impairment due to phosphorylation catalyzed by p38 mitogen-activated protein kinase [17–19]. Therefore, in order to pursuing a satisfactory control of difficult-to-treat asthma, current guidelines recommend an add-on biological therapy with one of the following monoclonal antibodies: (i) omalizumab (anti-IgE); (ii) mepolizumab or reslizumab (anti-IL-5); (iii) benralizumab (IL-5 receptor blocker); (iiii) dupilumab (dual IL-4/IL-13 receptor antagonist) [20–29].

Among the molecular targets of currently available biological drugs for severe asthma, IL-5 represents the key cytokine responsible for maturation, chemotaxis, degranulation and survival of eosinophils [30]. IL-5 exerts its pro-eosinophil functions by interacting with the α subunit of the IL-5 receptor (IL-5Rα), which can be occupied and blocked by the humanized IgG1k monoclonal antibody benralizumab [27,28,31]. In particular, the variable Fab fragments of benralizumab bind to cell membrane of eosinophils, basophils and ILC2 at level of their IL-5Rα [27,28,31,32], thus preventing its interaction with IL-5. Furthermore, the Fc constant region of benralizumab ligates the FcγRIIIa receptor present on the surface of natural killer (NK) cells, thereby stimulating the release of high amounts of perforin and granzyme B, which trigger eosinophil apoptosis through a mechanism known as antibody-dependent cell mediated cytotoxicity (ADCC) [27,28,31].

In regard to the clinical and functional effects of benralizumab, the phase 3 randomized controlled trials SIROCCO and CALIMA have shown that this IL-5Rα antagonist decreased the number of yearly exacerbations of severe eosinophilic asthma, and also concomitantly improved asthma symptom control and airflow limitation [33,34]. These therapeutic actions of benralizumab appear to be tightly linked, because in severe asthma there is a close relationship between disease exacerbations and bronchial obstruction. In fact, more severe is airflow limitation and the consequent lung hyperinflation, higher is the rate and worse the severity of asthma exacerbations [35]. On the other hand, by worsening airway inflammation and remodeling, recurrent exacerbations expedite the progressive decline of lung function in severe asthmatic patients [35,36]. Indeed, differently from mild-to-moderate asthma, severe disease can be often characterized by relevant air trapping, detectable as a marked increase in residual volume (RV) [37]. Interestingly, the phase 3b SOLANA trial has recently shown that benralizumab decreased RV and total lung capacity (TLC), and simultaneously increased inspiratory capacity (IC) [38], thereby deflating the hyperinflated lungs of patients with severe eosinophilic asthma. Furthermore, it was also previously observed that benralizumab is able to improve many aspects of severe eosinophilic asthma in both atopic and non atopic patients [39–41].

On the basis of the above considerations, the present single centre observational study aimed to assess, in real-world practice, the effects of benralizumab on asthma exacerbations and lung hyperinflation. To our knowledge there is currently a lack of published real-life reports about such crucial therapeutic effects of benralizumab, regarding allergic subjects with severe eosinophilic asthma.

2. Patients and methods

2.1. Study design and endpoints

This was a real-life, single-center study that included atopic patients suffering from severe persistent eosinophilic asthma, treated with benralizumab. These subjects were evaluated at the Respiratory Unit of "Magna Græcia" University Hospital located in Catanzaro, Italy. All enrolled patients met the European Respiratory Society (ERS)/American Thoracic Society (ATS) criteria that define severe uncontrolled asthma [16]. Spirometry was performed according to ATS/ERS guidelines [42] at baseline, as well as 4 and 24 weeks after the first injection of benralizumab, respectively. Benralizumab was prescribed in conformity with existing eligibility indications, and it was administered subcutaneously at the dosage of 30 mg every 4 weeks for the first three times, and every 8 weeks thereafter.

The main aims of this observational study were to evaluate in a real-life setting the effects of benralizumab on clinical, functional, and laboratory parameters in patients with severe eosinophilic asthma. Asthma control test (ACT) score, forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), residual volume (RV), inspiratory capacity (IC), forced mid-expiratory flow between 25 % and 75 % of FVC (FEF_{25-75}), and blood eosinophil count were assessed at baseline, as well as 4 and 24 weeks after the first injection of benralizumab. Spirometry and body plethysmography were performed by Master Screen Pulmonary Function Testing System and Master Screen Body (Jaeger, Germany). The number of exacerbations occurring within the previous 6 months and the daily intake (mg) of prednisone were recorded at baseline, and 24 weeks after the first dose of benralizumab. We also evaluated drug safety and tolerability during the first two hours after benralizumab administration, as well as through a once-weekly telephone call, investigating if patients had experienced pyrexia, headache or anaphylaxis, and also asking to refer if any worsening of health condition had happened.

This observational investigation met the standards of Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki. All recruited patients signed a written informed consent. Our study was also carried out in agreement to what decided by the local Ethical Committee of Calabria Region (Catanzaro, Italy; document n. 113 – 16th April 2020).

2.2. Patient characteristics

We recruited allergic subjects aged more than 18 years, suffering from severe eosinophilic asthma. At baseline, all participants were characterized by eosinophil levels in peripheral blood of at least 300 cells/μL. The enrolled asthmatic patients needed high dosages of ICS/LABA combinations, associated with long-acting muscarinic antagonists (LAMA). Moreover, all patients required a permanent or near continuous OCS intake. Nevertheless, they reported recurrent symptoms during both day and night, complicated by frequent asthma exacerbations.

22 patients (13 females and 9 males) were enrolled. They were characterized by a mean age of 58.50 ± 10.55 years and a mean BMI of 25.67 ± 4.079 Kg/m^2. Median baseline blood eosinophil count was 810.0 (IQR: 507.5 − 1123) cells/μL. Mean FEV_1 was 51.68 ± 14.09 % of predicted value. All subjects had positive skin prick tests for perennial and seasonal aeroallergens. The main characteristics of the 22 included subjects are summarized in Table 1.

2.3. Statistical analysis

Statistical analysis was performed using Prism Version 8.2.1 (GraphPad Software Inc., San Diego, California, US). Data were expressed as mean ± standard deviation (SD) if normally distributed, otherwise as median values with interquartile range (IQR). The

Table 1
Baseline patient characteristics.

Age (years)	58.5 ± 10.55
Sex (M/F)	9/13
Weight (Kg)	69.86 ± 13.52
Height (cm)	164.9 ± 10.14
BMI (Kg/m^2)	25.67 ± 4.079
FEV_1 (mL)	1295 (940 − 1798)
FEV_1 (% predicted)	51.68 ± 14.09
FEV_1/FVC (%)	56.32 ± 9.826
Blood eosinophils (cells/μL)	810 (507.5 − 1123)
Atopy (yes/no)	22/0
Nasal polyposis (yes/no)	10/12
Smokers (yes/no)	9/13

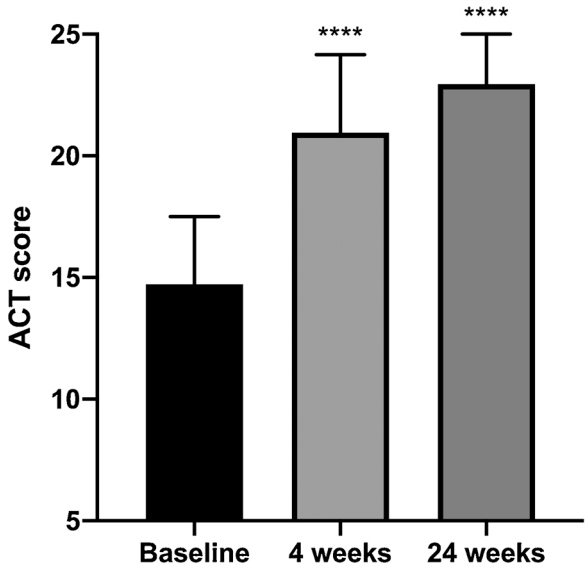

Fig. 1. Effect of benralizumab on ACT score. With respect to baseline, ACT score significantly increased at both study time points, namely 4 and 24 weeks after the first benralizumab dose (**** $p < 0.0001$).

Anderson-Darling test was applied to investigate if data were normally distributed. Student t test, Mann-Whitney U test, Dunnett's multiple comparison test and Friedman test were used to compare variables, when appropriate. A p value lower than 0.05 was considered to be statistically significant.

3. Results

After 4 weeks of treatment with benralizumab, ACT score significantly increased from a baseline value of 14.73 ± 2.781–20.95 ± 3.199 ($p < 0.0001$) (Fig. 1). Moreover, 24 weeks after the first benralizumab dose this score reached a mean value of 22.95 ± 2.214 ($p < 0.0001$) (Fig. 1). Such an impressive clinical result was associated with a significant improvement in lung function. In fact, pre-bronchodilator FEV_1 increased from a baseline value of 1295 (940 − 1798) mL to 1800 (1260–2303) mL after 4 weeks of add-on treatment with benralizumab ($p < 0.05$), and reached the median value of 1985 (1703–2515) mL at the 24th week of therapy ($p < 0.0001$) (Fig. 2). Furthermore, FVC mean value significantly increased, with respect to baseline, from 2390 ± 807.9 mL to 2799 ± 907.1 mL ($p < 0.001$) after 4 weeks, and to 2974 ± 871.3 mL ($p < 0.0001$) after 24 weeks (Fig. 3), respectively. Add-on treatment with benralizumab had a considerable impact on lung hyperinflation caused by airway obstruction. Indeed, 24 weeks after the first injection of benralizumab RV median value significantly decreased from 2720 (2560–3180) mL to 2300 (1910–2810) mL ($p < 0.01$) (Fig. 4); this remarkable functional effect was already detectable at the 4th week of therapy, when RV lowered to 2450 (1990–2800) mL ($p < 0.05$) (Fig. 4). RV reduction was associated with a concomitant increase of IC, that in comparison to the baseline measurement of 1940 (1630–2520) mL enhanced to 2470 (2015–2950) mL after 4 weeks ($p < 0.05$), and to 2460 (2065–2855) mL after 24 weeks, though this latter result did not reach the threshold of statistical significance (Fig. 5). These marked effects on lung hyperinflation were paralleled by a significant improvement of small airway obstruction. Indeed, FEF_{25-75} median value increased from baseline 0.6000 (0.3800–1.150) L/sec to 1.420 (0.9650–2.245) L/sec at the 24th week of treatment ($p < 0.0001$) (Fig. 6); also this functional outcome was already evident after just 4 weeks, when FEF_{25-75} resulted to be 1.085 (0.6325–1.918) L/sec ($p < 0.05$) (Fig. 6).

With regard to the hematological effects of benralizumab, 24 weeks after the first injection the median blood eosinophil count fell from 810.0 (507.5 − 1123) cells/μL to 0.000 (0.000 − 0.000) cells/μL ($p < 0.0001$) (Fig. 7); however, this result was already detectable at the 4th week of treatment, when benralizumab zeroed the median eosinophil number (IQR: 0.000–2.500) cells/μL ($p < 0.0001$) (Fig. 7).

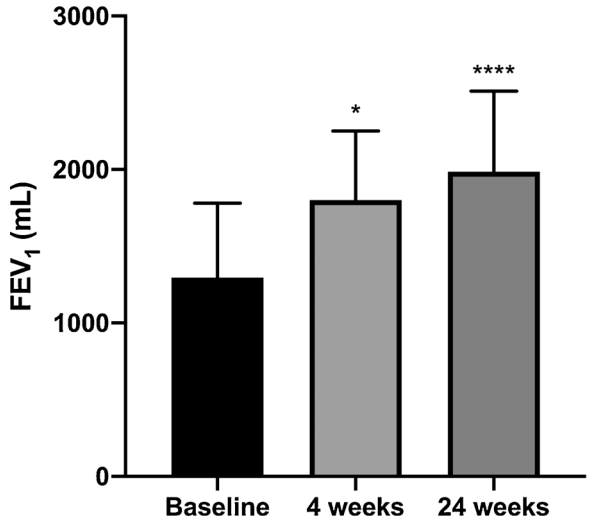

Fig. 2. Effect of benralizumab on pre-bronchodilator FEV_1. With respect to baseline spirometry showed significant FEV_1 increases, recorded at the 4th and 24th week after the first drug injection (* $p < 0.05$; **** $p < 0.0001$).

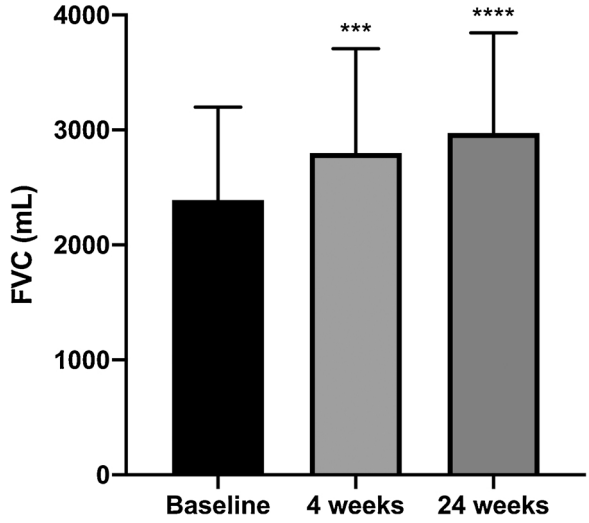

Fig. 3. Effect of benralizumab on FVC. With respect to baseline spirometry showed significant FVC increases, recorded at the 4th and 24th week after the first benralizumab dose (*** $p < 0.001$; **** $p < 0.0001$).

All patients reported a considerable decrease in asthma exacerbation rate. After 24 weeks of biological therapy with benralizumab, the number of exacerbations experienced in the previous 6 months decreased from 4.000 (2.750–7.000) to 0.000 (0.000–1.000) ($p < 0.0001$) (Fig. 8). This stunning therapeutic effect made it possible to progressively taper, and afterwards to definitely stop OCS administration in 18 patients; the remaining 4 patients consistently reduced their OCS consumption. In particular, when compared to baseline, daily prednisone intake dropped from 25.00 (12.50–25.00) mg/day to 0.000 (0.000 − 0.000) mg/day ($p < 0.0001$) (Fig. 9).

With regard to the adverse events, benralizumab was characterized by a very acceptable safety and tolerability profile. In fact, no severe adverse event occurred, and only three patients referred mild fever and chills, that spontaneously disappeared without requiring any pharmacologic treatment.

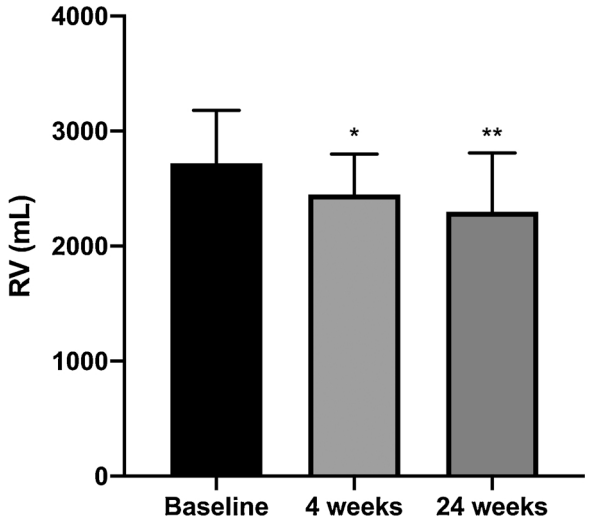

Fig. 4. Effect of benralizumab on RV. With respect to baseline, body plethysmography showed significant RV decreases, measured at the 4th and 24th week after the first drug dose (* $p < 0.05$; ** $p < 0.01$).

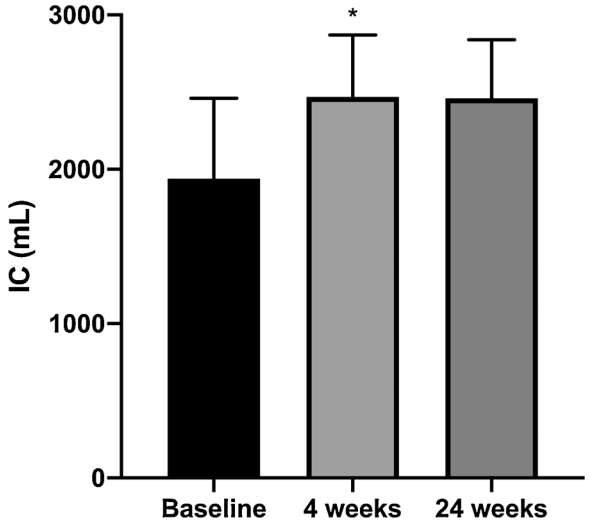

Fig. 5. Effect of benralizumab on IC. IC changes with respect to baseline were assessed 4 and 24 weeks after the first drug injection (* $p < 0.05$).

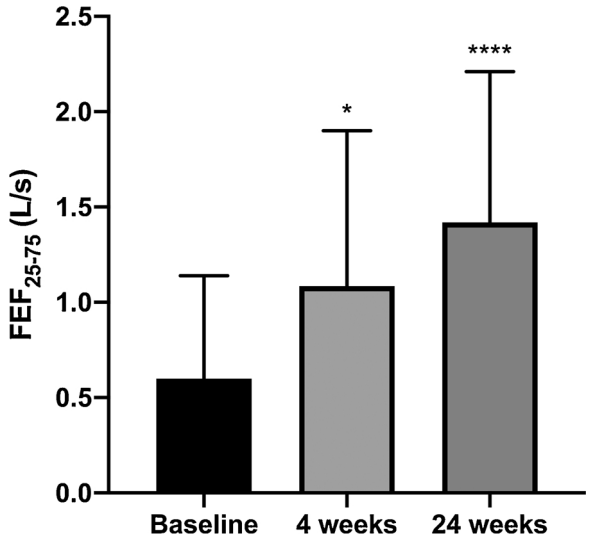

Fig. 6. Effect of benralizumab on FEF_{25-75}. FEF_{25-75} changes with respect to baseline were recorded 4 and 24 weeks after the first drug administration (* $p < 0.05$; **** $p < 0.0001$).

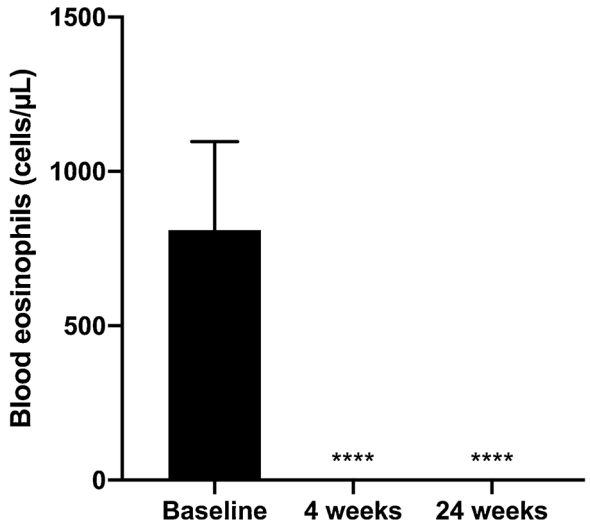

Fig. 7. Effect of benralizumab on blood eosinophil counts. Blood eosinophil counts were analyzed at baseline, as well as 4 and 24 weeks after the first drug dose (**** $p < 0.0001$).

4. Discussion

Within the context of the clinical, functional and hematological findings referring to the present real-life, single-centre observational study, the most relevant therapeutic effect exerted by benralizumab in our allergic patients with severe eosinophilic asthma regards the remarkable decrease in asthma exacerbations after 24 weeks of treatment. This significant reduction widely exceeded the 50 % rate proposed by the British National Institute for Health and Care Excellence (NICE) as a reliable outcome for efficacy validation of a given anti-asthma therapy [43]. The considerable decrement of asthma exacerbations, induced by benralizumab, seems to be tightly linked to the impressive anti-eosinophil action of this drug, which zeroed blood eosinophil counts after only 4 weeks of treatment. Indeed, when blood eosinophil numbers are more than 300–400 cells/µL, patients with asthma carry a higher risk of disease exacerbations [44,45]. Therefore, our results confirm the assumption that keeping blood eosinophil counts at a lower level than 400 cells/µL is crucial to reduce the risk of manifesting two or more annual exacerbations of asthma [46]. We also observed that the stunning protective effect of benralizumab on development of asthma exacerbations made it possible to definitely interrupt OCS intake in most patients, and to achieve a better real-life result than that one reported by ZONDA trial, consisting of a 75 % dosage reduction (vs 25 % obtained with placebo) after 28 weeks of treatment [47].

The positive impact of anti-IL-5Rα therapy on asthma exacerbations was paralleled by another very effective action of benralizumab, resulting in overall improvement of lung function. Also this therapeutic effect probably depends on benralizumab-induced eosinophil depletion, because high blood eosinophil numbers are associated with severe airflow limitation [5]. In particular, with respect to baseline pre-bronchodilator values, benralizumab elicited FEV_1 increases which were higher than 500 mL after 4 weeks of treatment, and reached almost 700 mL after 24 weeks, respectively. Such FEV_1 changes thus largely overcame the highest increments vs placebo measured during SIROCCO, CALIMA, and BISE trials, which consisted of 159 mL, 125 mL, and 80 mL, respectively [33,34,48]. After 4 and 24 weeks of add-on biological treatment with benralizumab, FVC also enhanced of more than 400 mL and 580 mL, respectively. Even more importantly for patients with severe asthma and lung hyperinflation, we also showed

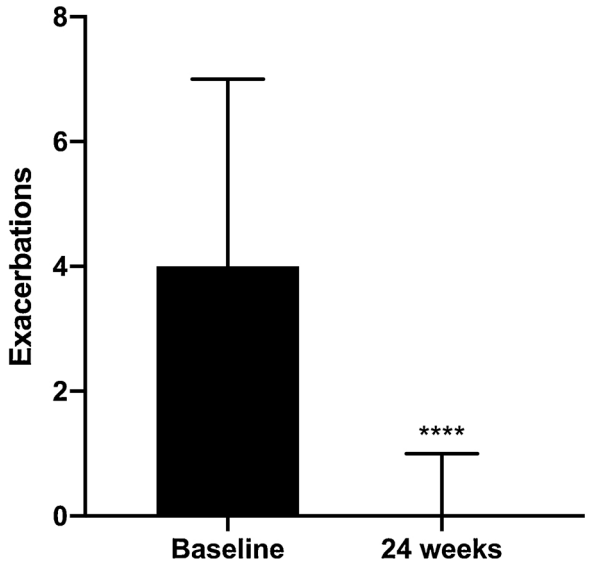

Fig. 8. Effect of benralizumab on asthma exacerbations. Numbers of asthma exacerbations were evaluated during the 24 weeks preceding (baseline) and following the first drug injection, respectively (**** $p < 0.0001$).

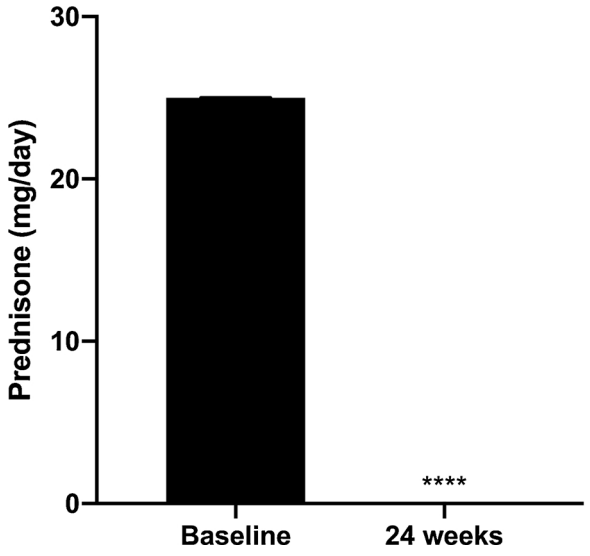

Fig. 9. Effect of benralizumab on prednisone daily intake. Prednisone dosages were recorded at baseline and 24 weeks after the first drug injection (**** $p < 0.0001$).

that in comparison to baseline median values benralizumab induced significant RV decreases which amounted to more than 250 mL and 400 mL at the 4th and 24th week of therapy, respectively. Such a relevant functional effect of benralizumab was confirmed by another index of lung deflation, consisting of a constant trend towards IC improvement, calculated after both 4 and 24 weeks of treatment as higher increases than 500 mL, when compared to baseline. These clinically meaningful reductions of lung hyperinflation are quite concordant with those recently reported by SOLANA trial [38]. The significant deflating effect of benralizumab, exerted on the hyperinflated lungs of our severe asthmatic patients, was likely due to an effective pharmacologic action carried out at level of small airways, leading to a consequent amelioration of expiratory flow and air trapping. In this regard we indeed found that, with respect to baseline, FEF_{25-75} increased by 0.48 L/sec and 0.82 L/sec after 4 and 24 weeks of treatment with benralizumab, respectively.

Taken together, our results suggest that the improvements of bronchial obstruction and lung hyperinflation, elicited by benralizumab, markedly contributed to its capability of lowering the number of asthma exacerbations. This presumption is supported by the well-known relationships connecting airflow limitation and asthma exacerbations [35,36]. which negatively impact on each other thus nurturing a pathogenic vicious circle that is responsible for the progressive deterioration of pulmonary function in patients with severe asthma. Within such a conceptual context, it is noteworthy that benralizumab can effectively act on eosinophilic inflammation of peripheral airways. In this regard, it is very important to reassert that activated eosinophils densely infiltrate the distal airways of patients with severe asthma [49,50], thus significantly contributing to the pathogenesis of airway hyperresponsiveness, airflow limitation, and air trapping. Blood eosinophil count further increases during life-threatening asthma attacks, and predicts the risk of future disease exacerbations [51]. In addition to crucially participating in inflammatory cell infiltration, at level of small airways of patients with severe asthma eosinophils play a key role also in the induction of structural remodeling [52,53]. which is responsible for fixed bronchial obstruction and lung function decline. Indeed, eosinophils are rich cellular sources of fibrogenic mediators such as transforming growth factor-β (TGF-β), and also implement complex intercellular interactions with mast cells, airway epithelial cells and fibroblasts [53–55]. Overall, these events remarkably contribute to stimulate fibroblast/myofibroblast proliferation and deposition of extracellular matrix proteins, thereby thickening airway walls.

Our present retrospective study thus suggests that, by interfering with the above cellular and molecular mechanisms, benralizumab probably attenuated airway eosinophilic inflammation and bronchial remodeling, thereby decreasing asthma exacerbations and improving airflow limitation and lung hyperinflation. The latter functional improvements likely explain the better symptom control experienced by our patients during add-on anti-IL-5Rα biological therapy. When compared to baseline mean value, ACT score indeed enhanced after 4 and 24 weeks of treatment with benralizumab, and at both time points overcame the critical threshold of 20, indicative of an adequate symptom control [56]. Such improvements were greater than those detected by the authors of SIROCCO and CALIMA phase 3 studies, though they used a different questionnaire, namely the asthma control questionnaire (ACQ)-6 [33,34]. However, in real-life ACT appears to be better practicable because of a higher compliance commonly manifested by outpatients attending routine medical interviews, rather than being enrolled in randomized clinical trials [57].

Interestingly, all 22 patients recruited in this real-world investigation were allergic. Our results confirm the previously reported effectiveness of benralizumab in both atopic and non-atopic subjects with severe eosinophilic asthma [39–41]. It can thus be hypothesized that benralizumab, in addition to exerting a powerful anti-eosinophil action, might also interfere with IgE-dependent immune responses. In this regard, it is noticeable that afucosylation of the Fc constant portion of benralizumab maximizes the ability of this antibody to implement the ADCC mechanism operated by NK cells [27,28,31]. Besides eosinophils, ADCC also targets other IL-5Rα-expressing cells such as basophils [58], whose development and activation are dependent on IL-5 [59]. Benralizumab causes the apoptotic death of basophils [58,60] thereby suppressing a relevant cellular source of IL-4, the key cytokine responsible for Th2 cell differentiation and IgE production [8,10,61]. In addition to inhibiting basophil bioactivity and survival, benralizumab can also affect the functions and viability of IL-5Rα$^+$ ILC2 [32], which synthesize IL-4, IL-5, and IL-13 [62]. Through its pleiotropic mechanisms of action, in subjects with severe atopic asthma benralizumab can thus eventually disrupt the complex network of interacting innate and adaptive immune responses underlying type 2 inflammation [63]. Therefore, on the basis of the reported results it is possible to argue that this anti-IL-5Rα monoclonal antibody could currently represent a valuable therapeutic option for patients with severe allergic eosinophilic asthma, such as those enrolled and monitored in our retrospective

study.

In conclusion, the main limitations of this observational study include the relatively small number of recruited patients and, similar to all real-world investigations, also the lack of a placebo control. However, despite these considerations our results convincingly suggest that by suppressing eosinophilic inflammation benralizumab is able to decrease asthma exacerbations and to concomitantly improve airflow limitation and lung hyperinflation, thus contributing via these effects to relieve respiratory symptoms and OCS dependence. Of course, these real-life preliminary findings need to be further corroborated by pragmatic trials that should be performed in larger groups of allergic patients with severe eosinophilic asthma, characterized by recurrent exacerbations and progressively worsening air trapping.

Authorship contribution

All authors contributed to design and carry out the study protocol, as well as to write the text and draw the figures.

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Declaration of Competing Interest

The authors report no conflict of interest in this work.

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