

Real-life rapidity of benralizumab effects in patients with severe allergic eosinophilic asthma: Assessment of blood eosinophils, symptom control, lung function and oral corticosteroid intake after the first drug dose

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ABSTRACT

Benralizumab is a humanized monoclonal antibody which binds to the α subunit of the interleukin-5 (IL-5) receptor and to the Fc γ RIIIa receptor expressed by natural killer cells, thus suppressing the pro-eosinophil actions of IL-5 and triggering eosinophil apoptosis via the very effective mechanism of antibody-dependent cell-mediated cytotoxicity (ADCC). Because of its recent approval and introduction in clinical practice for the add-on biological therapy of severe eosinophilic asthma, real-life investigations are still lacking. In this regard, our present real-life study refers to 13 patients with severe allergic eosinophilic asthma, currently under treatment with benralizumab at the Respiratory Unit of "Magna Græcia" University Hospital located in Catanzaro, Italy.

Already 4 weeks after the first subcutaneous injection of benralizumab at the dosage of 30 mg, blood eosinophil count rapidly dropped down from 814.7 ± 292.3 cells/ μ L to 51.3 ± 97.5 cells/ μ L ($p < 0.0001$). This relevant hematologic change was associated with quick and significant increases in asthma control test (ACT) score (from 15.31 ± 2.78 to 21.15 ± 3.58 ; $p < 0.0001$), pre-bronchodilator forced expiratory volume in 1 s (FEV₁) (from 1441 ± 757.9 mL to 1887 ± 837.3 mL; $p < 0.001$), and morning peak expiratory flow (PEF) (from 4.21 ± 2.20 to 5.33 ± 1.99 L/sec; $p < 0.01$). Furthermore, the marked improvement in global health status experienced by our patients allowed them to progressively lower and then completely interrupt, within 4 weeks, their daily intake of oral corticosteroids (OCS), which thereby fell from 15.58 ± 8.30 to 0 mg ($p < 0.0001$) of prednisone.

Therefore, such preliminary results suggest that in patients with severe allergic eosinophilic asthma benralizumab can exert, within a real-life context, a very rapid and effective therapeutic action, already detectable 4 weeks after the first drug administration.

1. Introduction

Asthma is a largely diffuse chronic obstructive airway disease, portrayed by a variable and often reversible airflow limitation, which affects more than 300 million people worldwide [1,2]. Although the great majority of patients with asthma are well controlled by standard treatments including inhaled corticosteroids (ICS) and long-acting β_2 -adrenergic agonists (LABA), about 5–10% of asthmatic subjects experience the most severe disease forms, thus requiring further therapies such as leukotriene modifiers, tiotropium, oral corticosteroids (OCS), and eventually biological drugs [3–6]. In this regard, the recently

updated GINA (Global Initiative for Asthma) guidelines consider at step 5 an additional treatment consisting of a biological drug, to be selected on the basis of patient phenotype/endotype among either *anti*-IgE, *anti*-IL-5, *anti*-IL-5 receptor, or *anti*-IL-4 receptor monoclonal antibodies [7]. These drugs are mainly directed against molecular targets involved in the pathobiology of type 2 eosinophilic airway inflammation [8,9], which characterizes a large percentage of patients with severe asthma [10,11].

The most important cytokine implicated in the pathophysiology of eosinophilic asthma is interleukin-5 (IL-5), which is produced in high amounts by T helper-2 (Th2) lymphocytes and group 2 innate lymphoid

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cells (ILC2) [12–14]. Indeed, IL-5 plays a central role in differentiation, survival, recruitment and activation of eosinophils [15,16]. Type 2 asthmatic airway inflammation is generally susceptible to treatment with ICS [17], that are potent triggers of the apoptotic death of eosinophils [18]. Nevertheless, severe eosinophilic asthma is frequently refractory to both ICS and OCS, probably because of an excessive release into the airways of IL-5, which can thus overwhelm the anti-eosinophil therapeutic properties of corticosteroids [19]. Hence, IL-5 is a highly relevant target for add-on biological therapies of corticosteroid-resistant type 2 severe asthma, and several monoclonal antibodies have been developed that target either this cytokine (mepolizumab, reslizumab) or its receptor (benralizumab) [20–25].

In particular, benralizumab is a humanized IgG1k monoclonal antibody which exerts powerful anti-eosinophil effects, due to a dual mechanism of action [26–29]. Namely, benralizumab utilizes its variable Fab fragments to specifically interact with the α subunit of the IL-5 receptor (IL-5R α), located on the surface of eosinophils, basophils and ILC2 [26–30]; as a consequence of such a benralizumab-operated occupancy of IL-5R α , this receptor component becomes unavailable for binding to the endogenous ligand IL-5. On the other hand, via its Fc constant portion benralizumab makes contact with the Fc γ RIIIa receptor expressed by macrophages and natural killer (NK) cells, thus eliciting the release of large quantities of granzyme B and perforin, that induce eosinophil death by implementing the apoptotic mechanism named antibody-dependent cell mediated cytotoxicity (ADCC) [26–29].

The phase 3 randomized controlled studies CALIMA and SIROCCO demonstrated that benralizumab lowered the annual rate of severe eosinophilic asthma exacerbations and also increased the forced expiratory volume in 1 s (FEV₁), as well as improved the control of asthma symptoms [31,32]. Moreover, the ZONDA trial showed that benralizumab significantly reduced the daily OCS intake [33]. Furthermore, the BORA study documented that benralizumab was characterized by a good long-term profile of safety and tolerability [34]. It is also noticeable that benralizumab seems to be equally effective in both allergic and non-allergic severe eosinophilic asthma [35]; indeed, it has been shown that the therapeutic actions of this biologic drug occur independently of atopy and serum IgE levels.

Some of the above mentioned pivotal trials have been essential for approval of benralizumab as add-on treatment of severe eosinophilic asthma by both US-based Food and Drug Administration (FDA) and European Medicine Agency (EMA). However, because of the very recent introduction of benralizumab in clinical practice, real-life studies are still lacking. Therefore, the aim of the present single centre observational study has been to evaluate in a real-life setting, in OCS-dependent patients with severe allergic eosinophilic asthma, the rapidity of the therapeutic effects of benralizumab already detectable 4 weeks after the first drug injection with regard to blood eosinophil count, symptom control, lung function and OCS intake.

2. Patients and methods

In this real-life, single centre study 13 OCS-dependent outpatients with severe allergic eosinophilic asthma were evaluated at the Respiratory Unit of “Magna Græcia” University Hospital of Catanzaro, Italy. These patients complained of persistent respiratory symptoms, though they were on regular treatment with high dosages of ICS/LABA combinations, and also received a nearly continuous OCS therapy. At baseline, all enrolled subjects had more than 300 eosinophils/ μ L of peripheral blood. They were characterized by a severe, reversible air-flow limitation, and all of them were atopic thus displaying positive skin prick tests for perennial and seasonal aeroallergens. The main features of the 13 recruited patients are summarized in Table 1.

Treatment with 30 mg benralizumab was prescribed according to a regimen schedule consisting of a single subcutaneous injection, to be administered at intervals of 4 weeks for the first three times, and every 8 weeks thereafter. Immediately before and 4 weeks after the first

Table 1
Baseline patient characteristics.

Age (years)	56.85 $\pm$ 10.05
Sex (M/F)	4/9
Weight (kg)	67.54 $\pm$ 14.45
Height (cm)	164.7 $\pm$ 12.41
FEV ₁ (mL)	1441 $\pm$ 757.9
FEV ₁ (% predicted)	48.08 $\pm$ 17.37
FEV ₁ /FVC (%)	57.33 $\pm$ 10.63
Atopy (yes/no)	13/0
Nasal polyposis (yes/no)	9/4
Blood eosinophils (cells/ μ L)	814.7 $\pm$ 292.3

benralizumab dose, the following haematological, clinical, functional, and pharmacotherapeutic parameters were recorded and comparatively evaluated: blood eosinophil count, asthma control test (ACT) score, pre-bronchodilator FEV₁, morning peak expiratory flow (PEF), and prednisone daily intake. Moreover, all enrolled patients were carefully checked in order to timely detect the eventual onset of side effects and adverse events.

This observational investigation was carried out according to the standards of Good Clinical Practice (GCP) and to the principles of the Declaration of Helsinki. The study was approved by the local ethics committee, and all recruited patients gave their written informed consent.

3. Statistical analysis

All data are expressed as mean $\pm$ standard deviation (SD). Statistical analysis of the results was performed by Student's *t*-test for paired data. A *p* value lower than 0.05 was considered to be significant.

4. Results

Four weeks after the first subcutaneous injection of benralizumab, blood eosinophil numbers significantly decreased to 51.3 $\pm$ 97.5 cells/ μ L with respect to the baseline count of 814.7 $\pm$ 292.3 cells/ μ L (*p* < 0.0001) (Fig. 1). All 13 atopic patients with severe and OCS-dependent eosinophilic asthma reported a marked reduction of daily symptoms and nocturnal awakenings due their disease. In particular, between baseline and the 4th week the ACT score increased from 15.31 $\pm$ 2.78 to 21.15 $\pm$ 3.58 (*p* < 0.0001) (Fig. 2). Such haematological and clinical changes were associated with a remarkable improvement of lung function. Indeed, pre-bronchodilator FEV₁ enhanced from 1441 $\pm$ 757.9 mL (baseline) to 1887 $\pm$ 837.3 mL after 4 weeks (*p* < 0.001) (Fig. 3). Similarly, when compared to the baseline measurement of 4.21 $\pm$ 2.20 L/sec, morning PEF value rose to

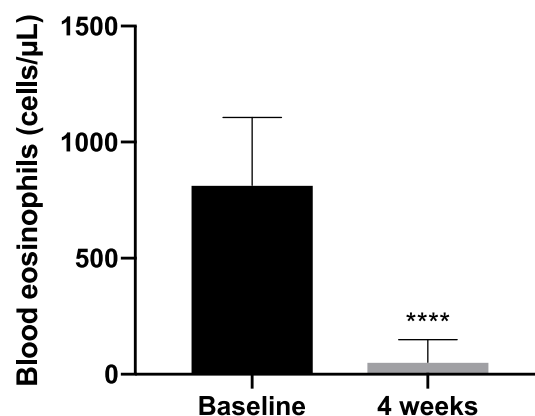


Fig. 1. Effect of benralizumab on blood eosinophil counts. Mean eosinophil numbers, counted at baseline and 4 weeks after the first drug dose. *****p* < 0.0001.

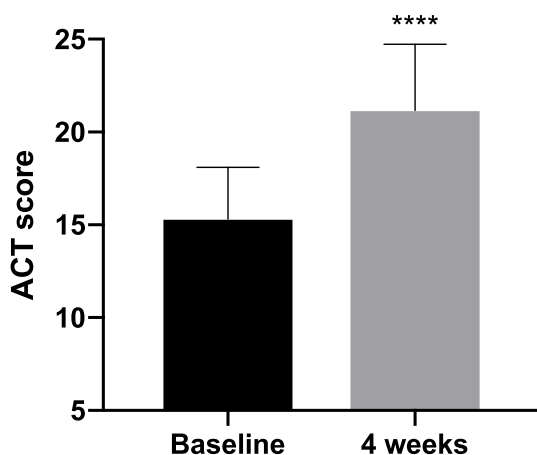


Fig. 2. Effect of benralizumab on ACT score. Mean ACT values, recorded at baseline and 4 weeks after the first drug dose. **** $p < 0.0001$.

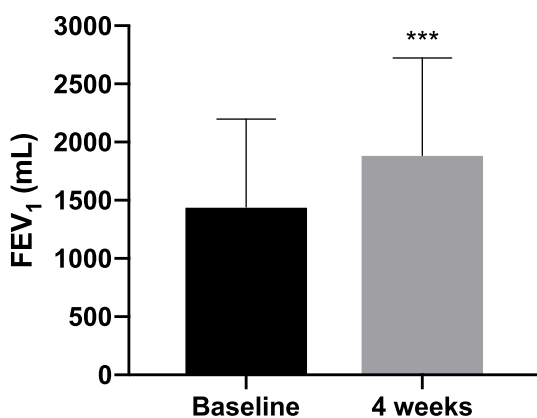


Fig. 3. Effect of benralizumab on pre-bronchodilator FEV₁. Mean FEV₁ values, measured at baseline and 4 weeks after the first drug dose *** $p < 0.001$.

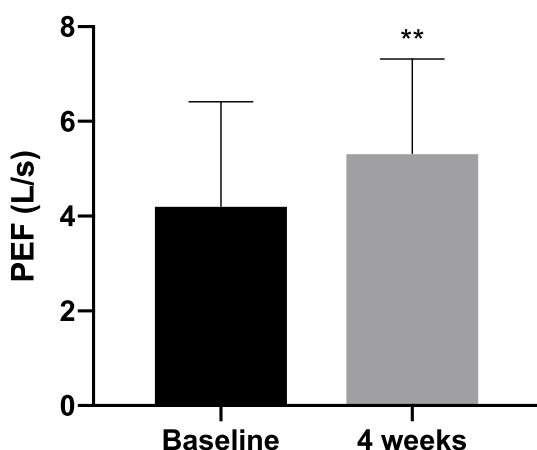


Fig. 4. Effect of benralizumab on morning PEF. Mean PEF values, detected at baseline and 4 weeks after the first drug dose. ** $p < 0.01$.

5.33 $\pm$ 1.99 L/sec at the 4th week ($p < 0.01$) (Fig. 4). Furthermore, as a consequence of the overall improvement in health status rapidly induced by benralizumab, throughout a short period of only 4 weeks prednisone daily intake was tapered, thus quickly and sharply decreasing from the baseline dosage of 15.58 $\pm$ 8.30 mg/day to 0 mg/day ($p < 0.0001$) (Fig. 5). The first subcutaneous injection of benralizumab was well tolerated, and only two subjects experienced a slight fever with chills, which swiftly and spontaneously resolved, without requiring any pharmacologic treatment.

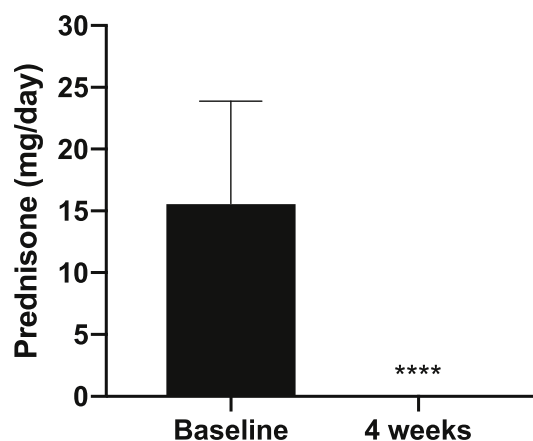


Fig. 5. Effect of benralizumab on OCS consumption. Mean prednisone daily dosages, assessed at baseline and 4 weeks after the first drug injection. **** $p < 0.0001$.

5. Discussion

Overall, the hematologic, clinical and functional results regarding the present single centre study strongly indicate that the first injection of benralizumab elicited in our atopic patients with severe eosinophilic asthma very quick and remarkable improvements in symptom control and airflow limitation, thus making it possible a rapid withdrawal of OCS therapy. These findings reinforce, within a real-life context, the data reported by many randomized controlled trials [36,37], and also add further pieces of information.

It is reasonably plausible that such rapid and striking therapeutic effects are mostly attributable to the fast and effective depletion of eosinophils induced by benralizumab via IL-5-receptor blockade and ADCC-mediated apoptosis of these cells [28,29,36]. In particular, we can hypothesize that the eosinophil-depleting action of benralizumab should be limited to pro-inflammatory eosinophils, thereby possibly sparing the lung resident subpopulation of homeostatic anti-inflammatory and anti-allergic eosinophils, which differently from blood and airway pro-inflammatory counterparts, appear to be not really dependent on IL-5, at least in mice [38]. In any case, the prompt and sharp fall of blood eosinophils caused by benralizumab in our patients was associated with a parallel remarkable improvement of their symptom control. Indeed, benralizumab elicited a fast and clinically relevant ACT score increase in all recruited patients, most of whom achieved or even overcame the crucial score threshold of 20, expressive of a satisfactory control of asthma symptoms. This result confirms that, as it was previously shown, there is a significant correlation between blood eosinophil numbers and disease severity [10]. Similar but smaller changes, though detected after a longer evaluation period, were also published by CALIMA and SIROCCO phase 3 trials, which demonstrated a significant decrease of the asthma control questionnaire (ACQ)-6 score [31,32]. However, in the real-world setting of daily clinical practice ACT is probably more easily useable by patients than ACQ, especially with regard to immediate understanding due to a less complicated formulation of key questions [39–41]. Because in asthma high eosinophil counts are also correlated with the severity of airflow limitation [10], concomitantly with the very fast and effective reversal of blood eosinophilia induced by benralizumab, we observed in our patients a significant improvement of lung function. Namely, 4 weeks after the first injection of benralizumab we recorded an impressive mean increase in pre-bronchodilator FEV₁ which exceeded 400 mL, thereby quite largely overcoming the FEV₁ changes reported by CALIMA, SIROCCO and BISE studies [31,32,42,43]. In our patients, benralizumab-dependent FEV₁ elevations were associated with marked enhancements of morning PEF. The latter finding is consistent with the results of a recent comprehensive analysis of the data referring to

CALIMA, SIROCCO and ZONDA trials [44]. This accurate evaluation states that morning PEF levels rapidly increased already within 24 h, and throughout 28 days after the first benralizumab dose [44]. Hence, it can be thoughtfully argued that such a stunning effect of benralizumab on lung function was due to a very quick resolution of bronchial eosinophilic inflammation, leading to a fast enlargement of airway caliber. In fact, we noticed in our patients that higher were baseline blood eosinophil numbers, greater were the increases in both pre-bronchodilator FEV₁ and morning PEF.

Before starting treatment with benralizumab all 13 patients were OCS-dependent because they were taking, continuously or nearly continuously, variable daily dosages of prednisone. The persistence of eosinophilia despite a regular treatment with both ICS and OCS clearly suggests that our patients were refractory to glucocorticoids. In this regard, an excessive IL-5 production can significantly contribute to steroid unresponsiveness [19]. Therefore, it can be inferred that benralizumab-mediated eosinophil apoptosis and neutralization of IL-5 bioactivity made it possible for our patients, within just 4 weeks from the first drug dose, a complete OCS withdrawal. Such a very rapid and powerful OCS-sparing effect of benralizumab resulted to be, in a real-life context, even greater than that one reported by the authors of the phase 3 ZONDA trial [33]. Therefore, our findings further corroborate and emphasize the valuable advantage of using benralizumab as an effective add-on biological therapy of severe asthma. This concept referring to the OCS-spare action of benralizumab, which has been reaffirmed by recent studies [45], is of paramount importance because a large majority of subjects with severe asthma are OCS-dependent [6], thus being exposed to the risk of OCS-induced side effects including iatrogenic osteoporosis, diabetes, arterial hypertension and depression.

Another relevant aspect of the present real-life study regards the atopic status, which characterizes all 13 enrolled patients. Our results are consistent with previous demonstrations of benralizumab effectiveness in both atopic and non-atopic asthmatics [35]. It can thereby be speculated that somehow benralizumab also inhibits immunoglobulin E (IgE)-mediated allergic responses. In this regard, benralizumab probably interferes with the cross-talk between the innate and adaptive branches of the immune system. Indeed, in addition to eosinophils, also basophils and ILC2 express IL-5R α [30,46], and IL-5 contributes to differentiation and activation of these cells. Benralizumab triggers the apoptosis of basophils [47] that are an important cellular source of interleukin-4 (IL-4), whose pivotal functions include induction of Th2 cell commitment and stimulation of IgE synthesis [14,48]. Furthermore, benralizumab has been shown to significantly decrease the number of IL-5R α ⁺ ILC2 [30]. Although ILC2 are commonly believed to produce IL-5 and interleukin-13 (IL-13), but not IL-4, recent experimental evidence suggests that these cells can also synthesize IL-4 and promote IgE production [49,50]. Therefore, by eventually inhibiting the survival and activity of basophils and ILC2, thus potentially impairing Th2 cell differentiation and IgE synthesis, benralizumab could partially suppress the development of IgE-dependent immune responses underlying allergic asthma. On the basis of such considerations, we decided to assign our atopic patients with severe eosinophilic asthma to add-on treatment with benralizumab because they were characterized by one of the following features: a) serum IgE levels higher than 1500 IU/mL, which precluded *anti*-IgE therapy with omalizumab; b) combination of body weight and serum IgE levels which precluded treatment with omalizumab; c) prior unsatisfactory therapeutic response to omalizumab; d) blood eosinophil count of more than 1000 cells/ μ L, even if associated with eligibility to *anti*-IgE treatment.

Finally, it is noteworthy that 9 out of our 13 patients had nasal polyposis, one of the most common comorbidities of severe asthma. Indeed, the presence of nasal polyps in severe asthmatic patients represents a very reliable predictive factor of a successful therapeutic response to add-on treatment with benralizumab [51]. On the other hand, a close similarity characterizes the cellular and molecular

mechanisms underpinning the pathobiology of type 2 inflammation in both asthma and chronic rhinosinusitis with nasal polyps, especially with regard to the allergic phenotypes [52]. Hence, during the follow-up of our patients it will be very interesting to monitor the potential therapeutic effects of benralizumab also on nasal polyps.

In conclusion, our preliminary data referring to add-on biological treatment of severe allergic eosinophilic asthma, obtained within a real-life context, show that benralizumab was able to effectively deplete blood eosinophils, improve symptom control, increase pre-bronchodilator FEV₁ and morning PEF, as well as to allow a complete OCS withdrawal. In particular, the overall magnitude of the therapeutic effects of benralizumab appeared to be much greater than that one reported by placebo-controlled studies. Moreover, benralizumab was also characterized by a good profile of safety and tolerability. Therefore, these observations clearly suggest the opportunity of designing pragmatic trials aimed to further evaluate the efficacy and safety of benralizumab in daily clinical practice.

Autorship contribution

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

Conflicts of interest

Corrado Pelaia, Maria Teresa Busceti, Giuseppe Francesco Rago, Claudia Crimi, and Rosa Terracciano have no conflict of interest.

Alessandro Vatrella has received lecture fees and consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Guidotti-Malesci, Menarini, Mundipharma, Novartis, Sanofi, Zambon.

Girolamo Pelaia has received lecture fees and consultancy fees from Alfasigma, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Guidotti-Malesci, Menarini, Mundipharma, Novartis, Sanofi, Teva, Zambon.

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